Management of Assisted Fertility: review of policies and options

Carried out on behalf of East Midlands ICBs
by Solutions for Public Health

October 2023

This work is based on information and data provided by a number of third parties. While care has been taken in the preparation of the information in this report and every effort has been made to ensure the information is accurate and up-to-date, NHS Solutions for Public Health accepts no responsibility for gaps or limitations in the information.

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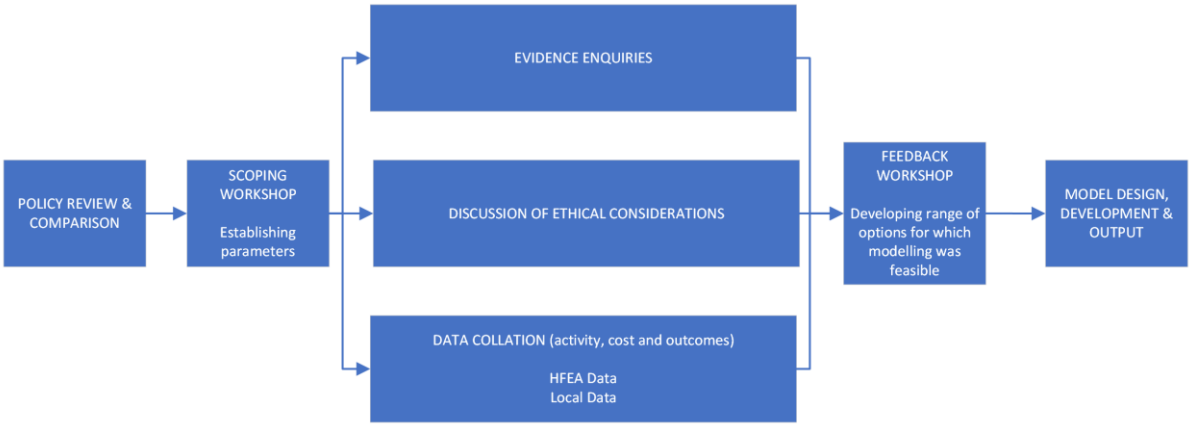
1 EXECUTIVE SUMMARY

1.1 Introduction

Solutions for Public Health (SPH) was commissioned to review existing fertility policies across the five East Midlands ICBs, to provide information to support a collaborative approach to ICB policy making. The work included a comparison of assisted conception policies; evidence enquiries; a discussion of the ethical considerations (for policy areas where evidence is not helpful); collation and analysis of data on activity, costs and outcomes; and modelling of a range of policy scenarios.

Figure 1: Summary of project methodology



1.2 Key model outputs

The modelled scenarios for IVF/ICSI policy provision represent a range of possible policy scearnios in terms of the age and BMI of the patient and the number of IVF/ICSI cycles provided, so as not to prejudge which options may be selected within the East Midlands in future. Table 1 provides the results for a selection of the modelled scenarios for all five East Midlands ICBs combined. Scenarios higher in the table provide more cycles of IVF to more people and more live births, but with lower overall cost effectiveness (higher cost per live birth) and higher overall costs for ICBs. The scenarios range from nearly full NICE guideline implementation to scenarios closer to current policies in East Midlands ICBs (bearing in mind that they do not include all policy criteria due to data constraints). Separate tables for each ICB are provided in the main report.

In making decisions, ICBs need to consider the potential impact of the different scenarios in terms of numbers treated, outcomes and costs, as well as the capacity of local services to deliver higher numbers of assisted fertility treatments at the same or better quality because for fertility treatments in particular, timing of treatments is crucial and waiting lists will have a major impact on quality and outcomes. High quality provision is very important to patients and providers.

Table 1: A selection of modelled scenarios for IVF provision for the five East Midlands ICBs combined

Scenario		Number of women treated	Total number of IVF cycles	Live births (LBs)	Cost	Cost per live birth (LB)	Comments
1	**Close to full NICE guideline implementation**: *BMI 18.5 to <35 kg/m^2 3 IVF cycles for women <40 1 IVF cycle for 40 to 42 year olds No other restrictions	1,680	2,962	872	£10.8 million	£12,356	• Least restrictive • Highest number treated • Most live births • Highest cost • Highest cost per LB
2	**Close to current Bassetlaw policy**: *BMI 18.5 to <35 kg/m^2 3 IVF cycles for women <40 1 IVF cycle for 40 to 42 year olds Other restrictions e.g. re smoking, childlessness, etc.	972	1,712	505	£6.2 million	£12,357	• Highest cost per LB • Similar to NICE for BMI and number of IVF cycles but includes some restrictions
3	**Current Glossop policy**: BMI 18.5 to 30 kg/m^2 3 IVF cycles for women <40 1 IVF cycle for 40 to 42 year olds Other restrictions e.g. re smoking, childlessness, etc.	793	1,369	423	£5.0 million	£11,907	• Similar to NICE and Bassetlaw re number of IVF cycles, but additional BMI criteria and other restrictions
4	**Between Bassetlaw/Glossop and other East Midlands policies, closer to Glossop:** BMI 18.5 to 30 kg/m^2 3 IVF cycles for women ≤37 2 IVF cycles for 38-39 year olds 1 IVF cycle for 40 to 42 year olds Other restrictions e.g. re smoking, childlessness, etc.	793	1,342	421	£4.9 million	£11,671	• Reducing number of IVF cycles (3, 2, 1) with increasing age of woman • Little change in numbers treated, LBs or cost compared to Glossop policy
5	**Between Bassetlaw/Glossop and other East Midlands policies, closer to latter:** BMI 18.5 to 30 kg/m^2 2 IVF cycles for women <40 1 IVF cycle for 40 to 42 year olds Other restrictions e.g. re smoking, childlessness, etc.	793	1,170	382	£4.3 million	£11,289	• Same number of women treated, but 1.3x more LBs, higher cost per LB and 1.5x higher overall cost compared to most current East Midlands policies
6	**Wider BMI criteria than most current East Midlands ICB policies:** 1 IVF cycles for women ≤42 BMI 18.5 to 35 kg/m^2 Other restrictions e.g. re smoking, childlessness, etc.	972	981	335	£3.6 million	£10,698	• Less restrictive BMI criteria than most East Midlands policies except Bassetlaw • Fewer cycles for women <40 than Bassetlaw and Glossop
7	**Close to most current East Midlands ICB policies:** 1 IVF cycles for women ≤42 BMI 18.5 to 30 kg/m^2 Other restrictions e.g. re smoking, childlessness, etc.	793	793	283	£2.9 million	£10,343	• Most current East Midlands policies except more restrictive than Bassetlaw and Glossop
8	**Most restrictive:** BMI 18.5 – 30 kg/m^2 1IVF cycle for women <38 Other restrictions e.g. re smoking, childlessness, etc.	693	693	263	£2.5 million	£9,508	• Most restrictive • Lowest number treated • Lowest live births • Lowest cost • Lowest cost per LB

The model does not take into account maternal or perinatal complications or higher costs of drugs associated with higher BMI. This means that the cost per live birth may be an underestimate, particularly for obese mothers. See main report for model assumptions and limitations. See ethical considerations section for population groups not included.

1.3 Comparison of national and local policies

Current ICB policies differ across several policy areas. Policies for Bassetlaw, and to a lesser extent, Glossop areas are most closely aligned with NICE CG156, whereas the other policies are generally similar to each other and differ from NICE in a number of key areas.

The main differences between policies were in the following areas (see full report for details):

Criteria for access to IVF/ICSI: The majority require the woman's BMI to be between 19 and 30 kg/m^2 and both partners to be non-smoking whereas Bassetlaw only expects the provider to provide advice on BMI and smoking (similar to NICE guideline recommendations).

IVF/ICSI pathway: For women under 40, Bassetlaw and Glossop are in line with the NICE guideline, offering up to three IVF cycles (including privately funded cycles); other policies offer one cycle. Glossop offers IVF with donor oocytes for women aged 40 to 42 with low ovarian reserve, unlike the other policies.

Criteria for access to IUI/DI: Indications for which IUI is offered vary, but most offer IUI where vaginal intercourse is very difficult or not possible including for same-sex relationships, and Glossop includes single women. Age and BMI criteria vary.

IUI/DI pathway: The number of NHS funded IUI cycles varies from one to six, with some policies requiring prior self-funded AI/IUI[1] cycles for some groups. NICE recommends six funded cycles of IUI after the patient has self-funded six cycles of AI.

Social/ethical factors: Most policies require that both partners have no previous children from any relationship (except Glossop; not mentioned by NICE) and will not fund IVF or IUI if either partner has ever been sterilised (except Bassetlaw and Glossop; not mentioned by NICE); for same-sex couples the requirements for proving infertility prior to access to IVF vary (NICE recommend six funded IUI cycles after six unsuccessful cycles of AI); single women are only mentioned by two policies (and not mentioned by NICE). For cryopreservation of gametes and embryos to preserve fertility, all policies include funding for those about to start treatment that permanently affects fertility (as does NICE) although the conditions listed and age criteria and duration of storage vary.

1.4 Evidence enquiries

Evidence enquiries were carried out for the questions agreed at the project scoping workshop, assessing the most relevant studies published after NICE guideline CG156. Unless stated, no relevant studies of safety or cost-effectiveness were identified.

Age and number of IVF cycles

How effectiveness of one full cycle of IVF varies with female age and number of cycles:

All identified studies had limitations in terms of generalisability to the current context and the most useful data for outcomes for the first IVF cycle were those provided by the HFEA following a freedom of information request. These are shown in Table 2. For the second and third cycle, where previous cycle(s) were unsuccessful, the most useful evidence came from a large study in China published in 2022. Because the methodology used by the HFEA and the study from China differed, the live birth rates (LBRs) reported by the Chinese study were slightly higher. The LBRs for the second and third cycle in the East Midlands NHS context were estimated by applying the

[1] NICE guideline CG156 [1] defines intra-uterine insemination (IUI) as a type of artificial insemination (AI). See main report for further details on how these terms are used in this report. DI = donor insemination.

relative differences between LBRs for the second and third cycle compared to the first cycle reported by the Chinese study to the LBRs for the first cycle reported by the HFEA.[2] These estimates are provided in Table 2.

As expected from the published literature, the LBR decreased markedly with increasing female age. LBR also decreased with successive unsuccessful cycles, particularly for a second cycle after a first unsuccessful cycle.

Table 2: Estimated / predicted live birth rates (LBRs) for NHS funded IVF cycles by age group

Patient age	IVF cycles[a]	Live birth occurrences[a]	LBR 1st cycle[a]	LBR 2nd cycle[b]	LBR 3rd cycle[b]
Under 35	3,018	1,220	40%	28%	22%
35-37	1,023	316	31%	19%	17%
38-39	468	111	24%	14%	13%
40-42	353	55	16%	13%	9%
43-44	21	0	0%	n/a	n/a

[a] East Midlands NHS providers, NHS funded IVF cycles, 2016-2018, including patients not registered with East Midlands ICBs. Data provided by HFEA (freedom of information request, received August 2023). (Assumes that all NHS funded IVF in East Midlands is for a first cycle of IVF as most policies only fund 1 cycle).
[b] Estimated using relative difference between LBRs for 2nd and 3rd cycles compared to 1st cycle (where previous cycle(s) were unsuccessful) reported by Wang et al (2022)[3], applied to HFEA data for 1st IVF cycle.
[c] An underestimate because to avoid the risk of patient identification, numbers under 5 in any age group/year were suppressed and counted as zero. In 2017, <5 live births were reported for 43-44 year old NHS-funded patients.

Ovarian response (IVF) – relative value of antral follicle count (AFC) and follicle stimulating hormone (FSH) in predicting IVF outcomes

Relative values of antral follicle count (AFC) and follicle-stimulating hormone (FSH) levels in predicting ovarian response to ovarian stimulation and effectiveness of IVF/ICSI:

The NICE Clinical Guideline (CG156, last updated 2017) recommended that age should be used as the initial predictor of ovarian response to stimulation, followed by either AFC or FSH or AMH (cut-off values were provided by NICE).

Evidence published since the NICE guideline suggests that AFC is a better predictor of low ovarian response to ovarian stimulation than FSH, and one study reported optimal cut-off values by age group for FSH and AFC for the prediction of ovarian response to stimulation in IVF/ICSI. Results relating to prediction of pregnancy rates and LBRs was mixed, although there was some indication that AFC could be a weak predictor of LBRs.

Clinicians have suggested that AMH measurements would be more useful than AFC because AFC is operator dependent, many sonographers are not trained to measure AFC, and the results depend on the timing relative to the menstrual cycle and which follicle size cut-off is used. However, other issues raised by clinicians included that AMH is more costly to measure than AFC (as AFC could be measured during routine ultrasound assessments) and that there is inconsistency across East Midlands providers in machines and reference values used for AMH measurements. Time and resource did not allow further evidence review or evaluation within this project and it is recommended that this is carried out in future.

[2] It was assumed that all NHS funded IVF cycles reported by the HFEA were first cycles, because few current policies allow for more than one NHS funded cycle.
[3] Wang N, Yin X, et al. Cumulative live birth rates over multiple complete cycles of in vitro fertilisation cycles: 10-year cohort study of 20,687 women following freeze-all strategy from one single centre. Archives of gynecology and obstetrics. 2022;305(1):251-9

Obesity / Body Mass index (BMI) (IVF)

Effectiveness of IVF/ICSI for women with a BMI ≥30 compared to a BMI <30 kg/m^2:

The NICE Clinical Guideline CG156 concluded that women who have a BMI ≥30 are likely to have reduced fertility. The current review found that for women with a BMI ≥30, IVF/ICSI was less likely to be effective. The safety of IVF/ICSI (in terms of miscarriage rates) was also lower in women with higher BMIs. For example, one large systematic review reported an odds ratio (OR) for a live birth of 0.81 for women with a BMI ≥30 compared to a BMI of 18.5 to 24.9 and OR of miscarriage of 1.52 for the same comparison (both statistically significant).

Effectiveness of IVF/ICSI where the woman has a BMI ≤19 compared to BMI >19 kg/m^2:

The NICE Clinical Guideline CG156 concluded that for women with a BMI ≤19 with irregular/ceased menstruation, increasing body weight is likely to improve chances of conception. We found limited evidence showing decreased effectiveness of IVF/ICSI in women with a BMI of ≤18.5 compared to women with a BMI of 18.5 to 24.99. The safety of IVF/ICSI for women with a BMI ≤19 is unclear as studies report conflicting results.

Effectiveness of IVF/ICSI where the male partner has a BMI ≥30 compared to BMI <30:

The NICE Clinical Guideline CG156 reported that men with a BMI ≥30 may have reduced fertility. We found no statistically significant evidence of reduced clinical effectiveness of IVF/ICSI when the male partner has a BMI ≥30 compared to BMI <30.

Effectiveness of IVF/ICSI where the male partner has a BMI ≤19 compared to BMI >19:

No evidence was identified.

Betel nut and chewing tobacco (IVF)

The NICE guideline CG156 did not cite any published evidence relating to the use of betel nut or chewing tobacco during IVF. We are unable to draw any conclusions relating to the use of betel nut during IVF treatment as no evidence was identified. We found two recent studies that reported lower quality sperm and embryos in men that used chewing tobacco; no studies were found for chewing tobacco use in the female partner. No data on pregnancy rates or live births was reported.

Cryopreservation of gametes and embryos (IVF)

Effect of duration of cryopreservation on quality of sperm stored for future use in IVF:

The NICE guideline CG156 evidence review concluded that cryopreserved sperm from cancer patients are sufficient for successful IVF or ICSI irrespective of the storage duration. We found one more recent study which supported the NICE conclusion but no studies relating to longer term storage (>10 years).

Effect of duration of cryopreservation on quality of oocytes and embryos stored for future use in IVF:

The NICE guideline CG156 recommended that cryopreserved material for people with cancer who wish to preserve fertility should be stored for an initial period of 10 years but did not cite any published evidence relating to this. No statistical differences were reported in the two studies we found that compared IVF outcomes for different embryo storage durations (>7 years and >10 years respectively). In addition we found studies that reported live births after six and seven years

of oocyte storage and after 6.4 years of embryo storage, but these did not report outcomes by storage duration.

Sterilisation and reversal (IVF and IUI)

The NICE Clinical Guideline CG156 does not include any evidence or recommendations relating to sterilisation and reversal.

Effectiveness of a cycle of IVF following successful reversal of female sterilisation:

From the evidence included in the current review: For women who had had sterilisation reversal and then attempted natural conception, pooled delivery rates ranged from 42% to 68%. Results generally favoured reversal over IVF without reversal, although with the possibility that IVF might have better results for older women. For women who had IVF after sterilisation without reversal vs women undergoing IVF for infertility who had never had a sterilisation, similar outcomes were reported. No evidence relating to IUI was identified.

The study on cost effectiveness concluded that sterilisation reversal was the most cost effective option for younger women, and IVF without reversal was the most cost-effective option for women aged >40 years old.

Effectiveness of a cycle of IVF/IUI following reversal of vasectomy:

From the evidence included in the current review: No statistically significant differences in fertilisation, pregnancy or LBRs were reported between men who had previously had a vasectomy and men with congenital obstruction, all of whom were undergoing a first cycle of IVF/ICSI. No statistically significant differences in cumulative delivery rates were reported after assisted conception in men who had had a vasectomy who went straight to surgical sperm retrieval and IVF/ICSI vs those who had a vasectomy reversal and later had IUI/IVF/ICSI. The majority of pregnancies following vasectomy reversal occurred naturally. No conclusions could be drawn about the effectiveness of IUI following vasectomy reversal.

The study on cost effectiveness concluded that vasectomy reversal was more cost effective than IVF/ICSI without reversal, but the applicability of the results is limited due to allowance for two or four cycles of IVF/ICSI.

Indications for IUI

Effectiveness of IUI compared to IVF for women with unexplained infertility, mild endometriosis or mild male factor infertility:

The NICE Clinical Guideline CG156 recommends IVF for women with unexplained infertility, and states that IUI should not be routinely offered to people with unexplained infertility, mild endometriosis or mild male factor infertility.

For women with unexplained infertility, overall, the evidence identified in the current review supported this recommendation in terms of better outcomes from IVF compared to IUI and no difference in multiple pregnancy rates or ovarian hyperstimulation syndrome (OHSS) rates between stimulated IUI and IVF. There was, however, evidence that stimulated IUI is more cost-effective than IVF.

For mild male factor infertility, no statistically significant difference in pregnancy rates or LBRs between stimulated IUI and IVF, and no significant difference in LBRs between unstimulated IUI and IVF were reported in the evidence identified in the current review.

No relevant studies for patients with mild endometriosis were identified.

Age and effectiveness of IUI

How the clinical effectiveness of one full cycle of IUI varies with age:

NICE guideline CG156 does not include any recommendations relating to IUI and age.

The majority of evidence identified in the current review reported that IUI outcomes were significantly worse in older women (over 38 or 40 years), however no studies reported the specific comparison between women aged 40 to 42 years and those aged 23 to 39 years. Most of the evidence reported no association between male age and IUI outcomes.

Obesity / Body Mass index (BMI) (IUI)

Effectiveness of IUI where the woman has a BMI ≥30 compared to BMI <30 kg/m^2:

The NICE Clinical Guideline CG156 concluded that women who have a BMI ≥30 are likely to have reduced fertility. We found one further cohort study which reported no statistically significant difference in pregnancy rate between women with a BMI ≥30 vs BMI <30.

Effectiveness of IUI where the woman has a BMI ≤19 compared to BMI >19 kg/m^2:

The NICE Clinical Guideline CG156 concluded that for women with a BMI ≤19 with irregular/ceased menstruation, increasing body weight is likely to improve chances of conception. Our review found evidence that women with a BMI ≤18.5 had statistically significantly lower pregnancy and LBRs following IUI than women with a normal BMI.

Effectiveness of IUI where the male partner has a BMI ≥30 compared to BMI <30 kg/m^2:

The NICE Clinical Guideline CG156 reported that men with a BMI ≥30 may have reduced fertility. We found no statistically significant evidence relating to this.

Betel nut and chewing tobacco (IUI)

No relevant evidence was identified.

1.5 Ethical considerations

This review includes a discussion of the ethical considerations around the provision of IVF and IUI for population groups for which evidence is unable to support commissioning considerations and data were not available for their inclusion in the modelled scenarios. The discussion uses the five main principles common to the ethical/decision-making frameworks of all five East Midlands ICBs:

1. Evidence of clinical effectiveness and safety
2. Cost-effectiveness
3. Allocation of resources according to need and/or capacity to benefit
4. Avoiding discrimination except where this is relevant to capacity to benefit
5. Absolute costs, affordability in relation to the overall ICB resources for healthcare, and hence anticipated impact on the rest of the patient population

The population groups and policy criteria covered are:

- Where vaginal intercourse as a means of conception is not possible or very difficult
    - Same-sex female couples

    - Single women
    - Where vaginal intercourse is not possible or is very difficult for physical or psychosexual reasons
    - Transgender (biologically female) individuals (not able to have vaginal intercourse for the purpose of conception e.g. single or female partner)
- Where one or both partners already have a living child
- Where one partner has previously undergone a sterilisation procedure
- NHS-funded gamete and embryo storage, and the duration of storage, for the purpose of preserving fertility

The full ethical discussions are provided in the main report. The following is a summary of key points that arose:

1. ICBs need to decide whether the role of the ICB in allocating resources according to need, is to provide treatment for need resulting only from medical/clinical (physical and psychological) conditions, such as infertility, or whether it includes the provision of support for conception (and to identify infertility) where there is no “clinical” problem. The latter may include single women, same-sex couples and some transgender (biologically female) individuals who have not received treatment that would make them infertile. A similar issue may arise for a woman with endometriosis, or with a demanding career, who, for non-medical reasons, delays having a child and wishes to store gametes or embryos in the interim.

2. Sexual orientation and gender reassignment are both protected characteristics under the Equality Act 2010. Whether not providing a service might be considered discrimination, however, is likely to depend on whether the role of the NHS is to treat clinical conditions (infertility) or to respond to a need for conception that is not associated with a clinical condition (see 1. above).

3. For people who are not able to have vaginal sexual intercourse to conceive because of a clinical condition (physical or psychosexual condition but not infertility), ICBs need to consider whether provision of IUI for these groups is treating a clinical condition and hence part of the role of the NHS, even when there is no indication of infertility.

4. If clinical effectiveness or safety of IUI or IVF for a particular individual is likely to be significantly reduced, not providing treatment in that situation would not be contrary to ICB ethical frameworks because the frameworks allow capacity to benefit to be taken into account when considering possible discrimination. This might apply, for example, to a transgender individual who is on hormone treatments that reduce the likely success rate of assisted conception treatments, or to an individual with certain comorbid conditions, or to an individual who has been previously sterilised.

5. Apart from provision of assisted conception for people with a need in relation to infertility, for couples where one or both partners already has a living child, one of the considerations for commissioners is whether the role of the ICB in allocating resources according to need and capacity to benefit includes provision in relation to a “need” to have a child of one’s own, a “need” for each partner to have a child of their own, or a “need” to have a child / start a family in the current relationship. In other words, whether childlessness of one individual in a couple reflects a need that must be addressed by ICBs.

6. For many of the groups above, it is not possible to estimate the demand that might arise from expansion of assisted conception provision from available data, although trends and private practice data suggest that for some groups (for example same-sex couples and single women), the numbers might be substantial. For other groups, numbers may be relatively small (for example people with certain co-morbid conditions that preclude vaginal sexual intercourse). It is recommended that ICBs carry out further work, such as local population surveys, to better understand the potential demand for fertility services (diagnosis and treatment), and hence potential impact on services (capacity, waiting times, quality, budget), of expanding provision to some of these groups before commissioning policies are changed.

7. The total cost of providing more cycles of IUI or IVF (e.g. three cycles instead of one) will be less than the multiple of the individual cycle cost because not all patients will be eligible for or take up later cycles. For example, the total cost of commissioning a maximum of six cycles of IUI may be in the region of 3.4 times the cost of a single cycle. The effectiveness of an IUI or IVF cycle after a previous unsuccessful cycle may also be reduced, reducing its cost-effectiveness (note that the evidence for this in relation to IUI was not evaluated).

8. There will always be individuals with particular circumstances (exceptions) for whom the ethical considerations discussed do not apply or apply to a lesser extent. It is assumed that exceptional circumstances would be considered by ICBs in the usual way.

1.6 Activity analysis

ICB contract managers provided anonymised patient data for assisted conception activity in 2019/20 to 2022/23. To avoid patient identification the only data provided were ICB, GP practice, year and month of treatment invoice, age group and treatment. Due to information governance concerns, it was not possible to obtain data on ethnicity. Data issues, including missing data and interpretation of ambiguous data, are discussed in the main report.

Total activity across East Midlands ICBs

Across the five ICBs for 2019/20 to 2022/23 (four years) there were nearly four times as many IVF/ICSI cycles provided (2,796) compared to AI/DI/IUI cycles (714). Numbers fell during the 2020/21 Covid-19 pandemic, and have since increased but remain lower than in 2019/20.[4]

Activity by ICB

According to the data received, the main activity for all ICBs was IVF/ICSI, except for Leicester, Leicestershire and Rutland ICB which also reported a large number of AI/DI/IUI cycles and episodes of egg and sperm freezing and storage(Table 3). The rate of IVF/ICSI provision over the four years varied across the ICBs from 2.9 (NHS Lincolnshire ICB) to 4.0 (NHS Derby and Derbyshire ICB) cycles per 1,000 women aged 18 to 42 (Table 4).

[4] This is likely to be due to delays in access to GPs and fertility clinics / waiting times in some ICBs, as a referral from a fertility clinic is needed for accessing IVF (communication from clinician).

Table 3: Number of selected assisted conception treatments across East Midlands ICB registered patients, 2019/20 to 2022/23 combined

ICB	IVF/ICSI	AI/DI/IUI	Egg Freeze / Storage	Sperm Freeze / Storage	Total
NHS Derby and Derbyshire ICB	681	7	22	26	736
NHS Leicester, Leicestershire and Rutland ICB	642	632	91	443	1,808
NHS Lincolnshire ICB	340	67	9	14	430
NHS Northamptonshire ICB	460	8	5	31	504
NHS Nottingham and Nottinghamshire ICB	673	0	45	51	769
Total	**2,796**	**714**	**172**	**565**	**4,247**

See comments in main report regarding data issues.

Table 4: Crude rate of IVF/ICSI per 1,000 women aged 18 to 42 years by ICB (2019/20 to 2022/23 combined)

ICB	IVF/ICSI	AI/DI/IUI	Egg Freeze / Storage	Sperm Freeze / Storage	Female Pop aged 18 to 42
NHS Derby and Derbyshire ICB	4.0	0.0	0.1	0.2	169,269
NHS Leicester, Leicestershire and Rutland ICB	3.2	3.1	0.4	2.2	202,650
NHS Lincolnshire ICB	2.9	0.6	0.1	0.1	116,352
NHS Northamptonshire ICB	3.4	0.1	0.0	0.2	134,653
NHS Nottingham and Nottinghamshire ICB	3.1	0.0	0.2	0.2	218,081
Total	3.3	0.8	0.2	0.7	**841,005**

See comments in main report regarding data issues.

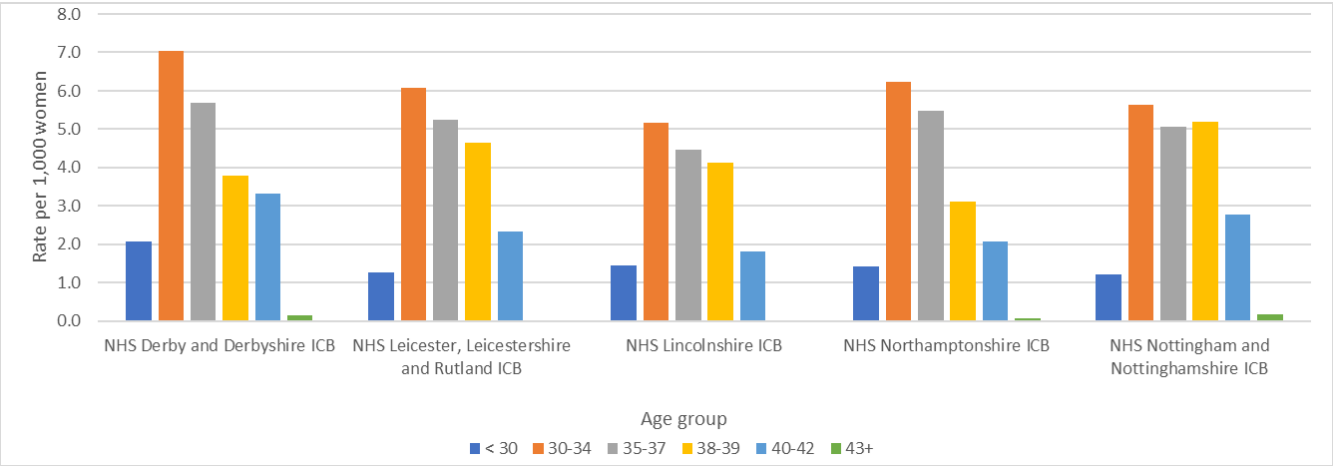
Activity across East Midlands providers

Care Fertility, Nurture and United Hospitals Leicester (UHL) are the main providers of assisted conception treatments in the East Midlands and provided 1,425, 723, and 540 IVF/ICSI cycles respectively over the four years from 2019/20 to 2022/23. A breakdown of provider activity by ICB is provided in the main report.

Activity by age group

For all five ICBs, the largest number of IVF/ICSI cycles and the highest rate per 1,000 women over the 2019/20 to 2022/23 four year period were in the 30-34 year age group, with reducing rates in older age groups (Figure 2).

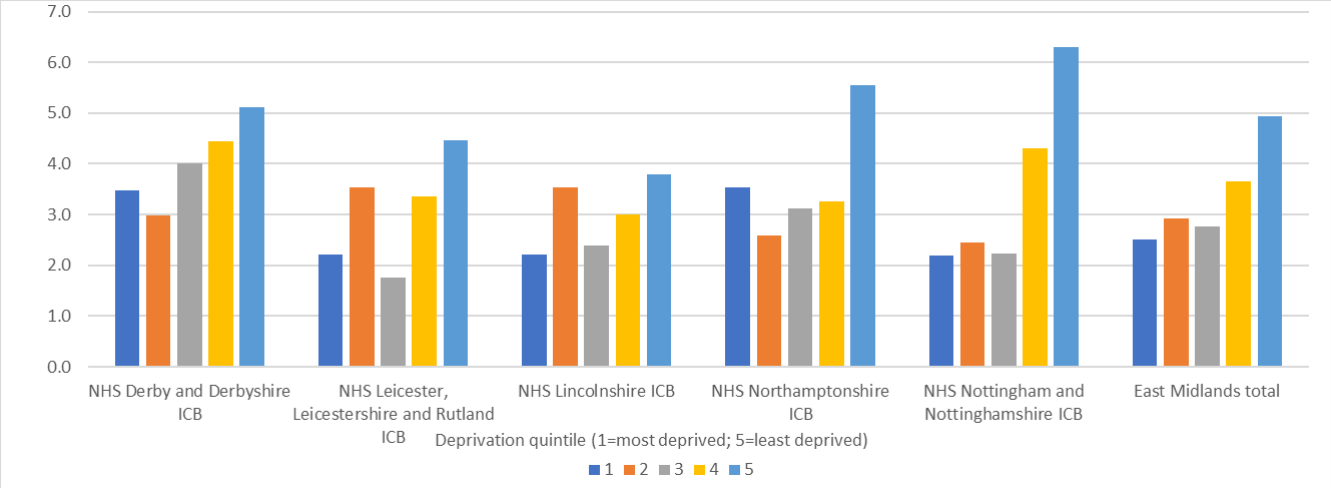
Figure 2: IVF/ICSI age specific rate per 1,000 women (2019/20 to 2022/23 combined)



Activity by deprivation quintile

The number and rate of provision of IVF/ICSI cycles in the four years was lower in all ICBs for women registered with practices in the most deprived GP practice national quintile compared to those in the least deprived quintile (Figure 3). Reasons for this may include factors such as being more likely to have had previous children at a younger age, and higher rates of smoking, obesity and fuel/transport poverty in more deprived groups.

Figure 3: Crude rate of IVF/ICSI cycles (2019/20 to 2022/23 combined) per 1,000 18 to 42 year old female population registered with ICB GP practices in each IMD quintile



Outcomes

Live birth rates for the main East Midlands providers in 2016 to 2018 were received from the HFEA. They are shown in Table 2 above for NHS funded cycles. Except for the under 35 year age group, LBRs were slightly higher for privately funded cycles than for NHS funded cycles.

Miscarriages were the most common adverse event, and the rate tended to increase with increasing age from 3.5% for under 35s to 7.5% for women aged 38 to 39 years.

Cost

Table 5 provides the average annual cost to ICBs of IVF/ICSI and AI/DI/IUI cycles based on the activity data received from contract managers and the contract tariff. The cost per 1,000 women is provided in the main report.

Table 5: Average annual cost of IVF/ICSI and AI/DI/IUI cycles by ICB, 2019/20 to 2022/23

ICB	IVF/ICSI	AI/DI/IUI
NHS Derby and Derbyshire ICB	£637,958	£1,444
NHS Leicester, Leicestershire and Rutland ICB	£597,533	£130,350
NHS Lincolnshire ICB	£311,296	£13,819
NHS Northamptonshire ICB	£413,590	£1,650
NHS Nottingham and Nottinghamshire ICB	£630,466	£0
TOTAL FOR 5 EAST MIDLANDS ICBs	£2,590,841	**£147,263**

Source: Activity data and contract tariff received from contract managers. IVF/ICSI costs assume all reported frozen embryo transfer and luteal support episodes relate to IVF/ICSI cycles and half of the cancelled IVF/ICSI cycles were cancelled after ovarian stimulation and before oocyte retrieval.

1.7 Conclusion

This report and the model outputs support ICB policy considerations by providing an indication of clinical effectiveness, ethical considerations, potential activity, costs and outcomes associated with a range of policy scenarios/options. For some groups (such as single women, same-sex couples and couples where one or both partners already have a child), further data need to be collected to understand potential demand. For all options, there is also a need for public consultation, inequalities impact assessments and financial impact assessments.

2 Introduction and context

Infertility is a recognised medical condition that can occur at any age and for a variety of reasons, such as endometriosis, polycystic ovary syndrome or naturally low ovarian reserve and low sperm count or poor quality sperm. Infertility has been defined as a failure to conceive after regular unprotected sexual intercourse for one to two years [1].

The National Institute for Health and Care Excellence (NICE) published an updated guideline in 2013 on the assessment and treatment of fertility problems (NICE CG156) [1]. The guideline was further updated in September 2017 and includes access criteria for IVF.

Solutions for Public Health (SPH), part of NHS Arden and Greater East Midlands Commissioning Support Unit (AGCSU), was commissioned to review existing fertility policies across the five East Midlands ICBs to inform future commissioning policy for fertility services.

This work included the following:

- A review of national and local policies
- A workshop to confirm scope and methodology
- Rapid evidence enquiries covering clinical effectiveness and safety questions agreed at the scoping workshop
- A discussion of the questions agreed at the workshop that relate to ethical considerations by relating each question to the ethical and decision-making principles that each ICB has adopted for the purpose of policy development
- Analysis of activity data
- Development of a range of policy options that differ in relation to factors for which data and evidence are available
- Model the impact of these policy options in terms of estimated activity, cost and outcomes (live births), to assist ICBs in decisions on future policy

The components of the project are presented in the following order:

1. Background epidemiology / context
2. Policy comparison
3. Evidence findings
4. Ethical considerations
5. Activity, outcomes and cost
6. Model outcomes for a wide range of scenarios
7. Discussion and conclusions

2.1 Epidemiology

Definitions of infertility vary.

The World Health Organisation defines infertility as *"a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse"* [2].

NICE defines infertility as *"the period of time people have been trying to conceive without success, after which formal investigation is justified and possible treatment implemented"* [1]. In addition, the NICE guideline CG156 [1] states that:

> *"1.2.13.5 A woman of reproductive age who has not conceived after 1 year of unprotected vaginal sexual intercourse, in the absence of any known cause of infertility, should be offered further clinical assessment and investigation along with her partner.*
>
> *1.2.13.6 A woman of reproductive age who is using artificial insemination to conceive (with either partner or donor sperm) should be offered further clinical assessment and investigation if she has not conceived after 6 cycles of treatment, in the absence of any known cause of infertility. Where this is using partner sperm, the referral for clinical assessment and investigation should include her partner."*

The Human Fertilisation and Embryology Authority (HFEA) defines infertility as the *inability of a couple to achieve a pregnancy after one year of regular unprotected sexual intercourse, or the inability of a woman to carry a pregnancy to live birth"* [3].

The HFEA estimates that infertility affects one in seven heterosexual couples in the UK [4]. Most couples (about 84 out of every 100) who have regular unprotected sexual intercourse (that is, every two to three days) will get pregnant within a year. About 92 out of 100 couples who are trying to get pregnant will do so within two years [4]. Causes of infertility include unexplained infertility, male factor infertility, tubal disease, ovulatory disorders, endometriosis and multiple factors, often both male and female.

Once a diagnosis has been established, treatment falls into three main types [5]:

- Medical treatment to restore fertility (for example, the use of drugs for ovulation induction)
- Surgical treatment to restore fertility (for example, laparoscopy for ablation of endometriosis)
- Assisted reproduction techniques (ART) – any treatment that deals with means of conception other than vaginal intercourse. It frequently involves the handling of gametes or embryos.

ART can include a range of interventions to assist women to have children. These include intra-uterine insemination (IUI), vitro fertilisation (IVF), intra-cytoplasmic sperm injection (ICSI) and donor insemination (DI).

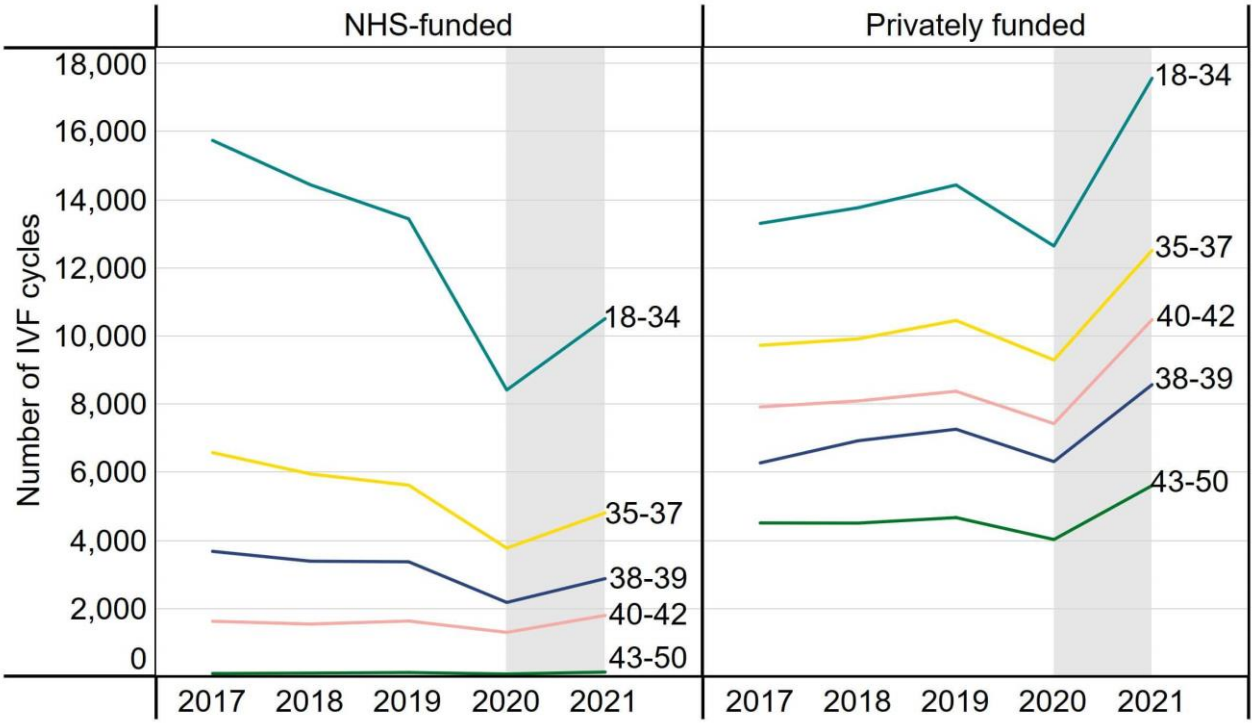
Around 55,000 patients had in vitro fertilisation (IVF) or donor insemination (DI) treatment at HFEA licensed fertility centres in the UK in 2021, rising from around 53,000 patients in 2019. Fertility treatment rates, although reduced during the Covid-19 pandemic returned to, and above, pre-pandemic levels: IVF cycles (fresh and frozen embryo transfers) increased to 76,000 cycles in 2021 from almost 70,000 in 2019 (an increase of 9%). DI cycles increased to 7,000 in 2021 from around 6,000 in 2019 (an increase of 22%) [6]. Live birth rates per IVF cycle have also steadily increased since the mid-1990s, although there remains a stark difference in different age groups with much higher rates among younger women (see section on outcomes by age). Egg and embryo storage rates have increased (2,500 egg storage cycles in 2019 vs 4,200 in 2021; 8,300 embryo storage cycles in 2019 vs 10,700 in 2021). The average age of IVF patients has increased from 35.2 years in 2011 to 36.0 years in 2021. The average age of DI patients has however decreased (35.2 years in 2011 and 34.3 years in 2021) [6].

The HFEA and the fertility sector have successfully collaborated to reduce the IVF multiple birth rate from about 28% in the 1990s, to 5% in 2021 without a reduction in birth rates [6, 7].

Over recent years there has also been an increase in use of fertility treatments across family types, although heterosexual relationships accounted for 90% of all IVF patients in 2021 (NHS and privately funded) [6]. For heterosexual couples, the number having IVF in 2021 was 46,911, having increased by 2% compared to 2019. Including both NHS and privately funded IVF patients, the number with a female partner increased by 33% to 2,201 and the number with no partner increased by 44% to 2,888 between 2019 and 2021 [6].

During the COVID-19 pandemic, the number of IVF cycles in the UK decreased for all age groups, impacting younger patients the most. While the number of NHS-funded IVF cycles increased for all patients from 2020 to 2021, the number of NHS-funded cycles remained below pre-pandemic levels (Figure 4).

Figure 4: Number of IVF cycles by funding type and patient age group, 2017-2021 (preliminary data 2020-2021)



Note: This data includes IVF treatment cycles begun with the intention of having a live birth only. Data is preliminary for 2020 and 2021 (grey band).

Source: [6]

2.2 The intervention

Assisted reproduction techniques are part of the overall management of fertility. The full Clinical Guideline published by NICE [5] addresses and makes recommendations about the:

- prevention of infertility,
- provision of appropriate investigations and diagnosis, as well as a
- range of treatment options and

- assisted reproduction techniques, including in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and artificial insemination (AI), including intrauterine insemination (IUI).[5]

Within this review, we use the term 'IVF' to cover both 'standard' IVF and ICSI. Only IVF using autologous oocytes are within the scope of this review.

IVF usually takes place over a period of two weeks or more. This is referred to as a 'cycle' of treatment. The cycle starts when the woman starts taking drugs to stimulate egg production [8].

NICE [1] describes the main stages of IVF:

1. controlled ovarian stimulation – medication is used to suppress the menstrual cycle and encourage the ovaries to produce more oocytes than usual
2. oocyte maturation – an ultrasound scan is carried out to check the development of the eggs, and medication is used to help them mature
3. egg retrieval – a needle is inserted into the ovaries, via the vagina, to remove the eggs
4. fertilisation of the eggs – in IVF the eggs are mixed with the sperm for several days to allow them to be fertilised. For male factor infertility, the method of fertilisation is usually ICSI where a single sperm is injected directly into the egg
5. embryo transfer – one or two fertilised eggs (embryos) are placed into the uterus. This may be referred to as a fresh embryo transfer (ET)
6. freezing of all surplus embryos - for later transfer(s) if required. This may be referred to as frozen embryo transfer (FET). (In some situations all embryos may be frozen (elective freeze-all strategy) to reduce the chance of ovarian hyperstimulation [9].)

Clinical pregnancy (CP) is tested using a biochemical pregnancy test, which if positive, is confirmed by ultrasound scan at approximately six weeks gestation. The primary outcome of interest for this review is live births.

For this review (unless stated specifically), one IVF/ICSI cycle starts when the woman starts taking drugs to stimulate oocyte production.

IUI is described by NICE [5] as a form of treatment where sperm are inserted into the uterine cavity around the time of ovulation. IUI can be carried out in a natural cycle, without the use of drugs, or the ovaries may be stimulated with oral anti-oestrogens or gonadotrophins.

Surrogacy, pre-implantation genetic diagnosis, surgical sperm retrieval, and other more specialist techniques were out of scope for this review.

For the purpose of this review the following definitions will be used unless otherwise specified:

- **Cycle of IVF:** this term will be used to refer to when the IVF with or without ICSI cycle starts using ovarian stimulation. It is not dependent upon subsequent progress or success of IVF.

[5] NICE guideline CG156 [1] defines IUI as follows: "Intrauterine insemination (IUI) is a type of artificial insemination [AI] in which sperm is placed inside the womb. Another type of artificial insemination is intracervical insemination (ICI), where sperm is placed at the cervix (the neck of the womb)." (https://www.nice.org.uk/guidance/cg156/ifp/chapter/intrauterine-insemination). In practice, AI and IUI are often used interchangeably (communication from local clinician). Hence the use of "AI/IUI" or "AI/DI/IUI" in this report where the exact procedure used is not clear. However, where referring to a specific study, report or guideline, the term used by the author has been used in this report, and where the intervention is specifically IUI, the term "IUI" has been used. ICI may be relevant to self-reported clinically unsupervised AI or to self-funded AI, and in that context or where not specified as IUI, we have used the term "AI" alone.

- **Full Cycle of IVF:** A full cycle of IVF, with or without ICSI, comprises one episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s). Fresh embryos will be transferred first and if implantation fails subsequent transfers of the frozen embryos are made.
- **Embryo transfer:** this refers to the transfer of embryos into the uterus. One of more embryos may be transferred. The embryos may be fresh (i.e. never frozen) (ET) or frozen (i.e. frozen due to being surplus at the first embryo transfer, then thawed for subsequent transfer) (FET).
- **Clinical pregnancy (CP):** confirmed by ultrasound rather than by biochemical test only.
- **Live birth rate (LBR):** probability of a live birth i.e. the number of women who had a live birth following treatment, divided by the total number of women attempted treatment.
- **Multiple births:** births where two or more babies were born alive, including those where one or more babies died within the first month of life.

3 Comparison of national and local NHS policies

3.1 National Guidance

NICE clinical guideline CG156 [1], published in February 2013, replaced the previous 2004 NICE guideline. Although further updates have been made, the last one being in 2017, there have been no changes to NICE recommendations since 2013. The full guideline is comprehensive and covers the full pathway for the management of infertility, including prevention, diagnosis, treatment options and clinical outcomes, including long term safety and research recommendations. It is accompanied by detailed evidence findings and appendices.

The policy comparison table in Appendix 1 highlights the main NICE recommendations that are relevant to ICB commissioning policies for assisted conception. The key recommendations relating to access to IVF/ICSI and DI/IUI are summarised below:

IVF/ICSI: Number of cycles, age and ovarian reserve

1.11.1.3 In women aged under 40 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 3 full cycles of IVF, with or without ICSI. If the woman reaches the age of 40 during treatment, complete the current full cycle but do not offer further full cycles.

1.11.1.4 In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled:

- *they have never previously had IVF treatment*
- *there is no evidence of low ovarian reserve*
- *there has been a discussion of the additional implications of IVF and pregnancy at this age*

1.3.3.1 Use a woman's age as an initial predictor of her overall chance of success through natural conception … or with IVF...

1.3.3.2 Use 1 of the following measures to predict the likely ovarian response to gonadotrophin stimulation in IVF:

- *total antral follicle count of less than or equal to 4 for a low response (follicles of less than or equal to 5 mm measured by transvaginal ultrasound on day 3 of cycle: low response was less than 4 oocytes) …*
- *anti-Müllerian hormone of less than or equal to 5.4 pmol/l for a low response …*
- *follicle-stimulating hormone greater than 8.9 IU/l for a low response…*

1.11.1.2 ... a full cycle of IVF treatment, with or without intracytoplasmic sperm injection (ICSI), should comprise 1 episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s).

NICE CG156 recommends the use single embryo transfer except in specific circumstances (related to age and availability of top quality embryos) where double embryo transfer may be considered. (See NICE CG156 recommendation 1.12.6.5 for details [1].)

1.11.1.8 Healthcare providers should define a cancelled IVF cycle as one where an egg collection procedure is not undertaken. However, cancelled cycles due to low ovarian reserve should be taken into account when considering suitability for further IVF treatment.

IUI

1.9.1.1 Consider unstimulated IUI as a treatment option as an alternative to vaginal sexual intercourse in:

- *people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychosexual problem who are using partner or donor sperm*
- *people with conditions that require specific consideration in relation to methods of conception (e.g. man is HIV positive)*
- *people in same-sex relationships*

1.9.1.2 For people in recommendation 1.9.1.1 who have not conceived after 6 cycles of donor or partner insemination, despite evidence of normal ovulation, tubal patency and semen analysis, offer a further 6 cycles of unstimulated intrauterine insemination before IVF is considered.

1.9.1.3 For people with unexplained infertility, mild endometriosis or mild male factor infertility, who are having regular unprotected sexual intercourse:

- *do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF)*
- *advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered.*

Donor sperm and oocytes

1.14.1.1 The use of donor insemination is considered effective in managing fertility problems associated with the following conditions:

- obstructive azoospermia
- non-obstructive azoospermia
- severe deficits in semen quality in couples who do not wish to undergo intracytoplasmic sperm injection (ICSI).

1.14.1.2 Donor insemination should be considered in conditions such as:

- where there is a high risk of transmitting a genetic disorder to the offspring
- where there is a high risk of transmitting infectious disease to the offspring or woman from the man
- severe rhesus isoimmunisation.

1.15.1.1The use of donor oocytes is considered effective in managing fertility problems associated with the following conditions:

- premature ovarian failure
- gonadal dysgenesis, including Turner syndrome
- bilateral oophorectomy
- ovarian failure following chemotherapy or radiotherapy
- certain cases of IVF treatment failure
- Oocyte donation should also be considered in certain cases where there is a high risk of transmitting a genetic disorder to the offspring.

1.15.3.2 Oocyte recipients and donors should be offered counselling from someone who is independent of the treatment unit regarding the physical and psychological implications of treatment for themselves and their genetic children, including any potential children resulting from donated oocytes.

Body mass index (BMI) and lifestyle factors

1.10.4.1 Women should be informed that female BMI should ideally be in the range 19–30 kg/m^2 before commencing assisted reproduction, and that a female BMI outside this range is likely to reduce the success of assisted reproduction procedures.

1.10.5.1 People should be informed that the consumption of more than 1 unit of alcohol per day reduces the effectiveness of assisted reproduction procedures, including IVF.

1.10.5.2 People should be informed that maternal and paternal smoking can adversely affect the success rates of assisted reproduction procedures, including IVF treatment. Women and men should be informed that smoking is likely to reduce fertility/semen quality.

1.10.5.3 People should be informed that maternal caffeine consumption has adverse effects on the success rates of assisted reproduction procedures, including IVF treatment.

1.2.10.1 A number of prescription, over-the-counter and recreational drugs interfere with male and female fertility, and therefore a specific enquiry about these should be made to people who are concerned about their fertility, and appropriate advice should be offered.

Social / ethical factors

Although the NICE Guideline (CG156) advises that *"people should be informed that IVF treatment is more effective in women who have previously been pregnant and/or had a live birth"* (1.10.3.1), it does not refer to family type or previous children as criteria for ART.

The NICE guideline does not mention transgender individuals, single women, length of relationship, sterilization or reversal of sterilization. See recommendation above for same-sex relationships.

Cryopreservation of gametes

1.2.13.8 Where treatment is planned that may result in infertility (such as treatment for cancer), early fertility specialist referral should be offered.

1.16.1.3 When deciding to offer fertility preservation to people diagnosed with cancer, take into account the following factors:

- *diagnosis*
- *treatment plan*
- *expected outcome of subsequent fertility treatment*
- *prognosis of the cancer treatment*
- *viability of stored or post-thawed material. [new 2013]*

1.16.1.4 For cancer-related fertility preservation, do not apply the eligibility criteria used for conventional infertility treatment.

1.16.1.5 Do not use a lower age limit for cryopreservation for fertility preservation in people diagnosed with cancer.

1.16.1.6 Inform people diagnosed with cancer that the eligibility criteria used in conventional infertility treatment do not apply in the case of fertility cryopreservation provided by the NHS. However, those criteria will apply when it comes to using stored material for assisted conception in an NHS setting.

1.16.1.7 When using cryopreservation to preserve fertility in people diagnosed with cancer, use sperm, embryos or oocytes.

1.16.1.8 Offer sperm cryopreservation to men and adolescent boys who are preparing for medical treatment for cancer that is likely to make them infertile.

1.16.1.10 Offer oocyte or embryo cryopreservation as appropriate to women of reproductive age (including adolescent girls) who are preparing for medical treatment for cancer that is likely to make them infertile if:

- *they are well enough to undergo ovarian stimulation and egg collection and*
- *this will not worsen their condition and*
- *enough time is available before the start of their cancer treatment.*

1.16.1.12 Store cryopreserved material for an initial period of 10 years.

1.16.1.13 Offer continued storage of cryopreserved sperm, beyond 10 years, to men who remain at risk of significant infertility.

3.2 Current East Midlands ICB policies

The following ICB policies were reviewed and compared (* denotes policies received after the scoping workshop):

- Derby and Derbyshire ICB: IVF/ICSI; IUI; Gamete storage
- Leicester, Leicestershire and Rutland ICB: IVF/ICSI; IUI/DI; Gamete/embryo cryopreservation
- Lincolnshire ICB: IVF/ICSI; IUI

- Northamptonshire ICB: IVF/ICSI; IUI*; Gamete storage*
- Nottingham and Nottinghamshire ICB: IVF/ICSI; IUI/DI, etc excluding IVF/ICSI; Gamete and embryo storage policy/prior approval form*
- Bassetlaw CCG (now part of Nottingham and Nottinghamshire ICB): Infertility treatment policy; Cryopreservation*
- Glossop (now part of Derby and Derbyshire ICB): Manchester CCG assisted conception policy*

Appendix 1 provides a detailed comparison between these policies and NICE guideline CG156. The main differences between the policies are:

Criteria for access to IVF/ICSI

- Age: See below under number of cycles
- BMI: All policies except for Bassetlaw require a BMI of 19-30kg/m^2 as a criterion for access to IVF
- Smoking: All policies except for Bassetlaw require both partners to be non-smoking as a criterion for access to IVF; Glossop includes all nicotine products; Derby and Derbyshire considers e-cigarettes as non-smoking
- Alcohol and drugs: Glossop requires couples to give assurance that their alcohol intake is within Department of Health guidelines and that they are not using recreational drugs for access to IVF, with evidence to the contrary resulting in treatment stopping; other policies do not require this
- Ovarian reserve: Glossop offers IVF with donor oocytes to women aged 40-42 years with low ovarian reserve (as defined by NICE); other policies do not offer IVF if low ovarian reserve (Bassetlaw defines this as per NICE; other policies define satisfactory ovarian reserve as FSH ≤8.9 IU/l); all policies offer oocyte donation for premature ovarian failure, ovarian dysgenesis, bilateral oophorectomy, chemotherapy and radiotherapy

IVF/ICSI pathway

- Number of cycles / age: Bassetlaw and Glossop offer three IVF cycles for women under age 40 years; other policies offer one cycle (all offer only one IVF cycle for 40-42 year olds.
- Storage of embryos: Glossop offers storage of viable embryos from IVF treatment after a live birth for 10 years (or in line with HFEA regulations if these change) or until woman's 43rd birthday, whichever is shorter (available for private treatment); other policies offer storage for up to three years but only for six months after a live birth
- Cancelled or abandoned cycles: Glossop offers a second IVF cycle after a cancelled or abandoned cycle only after individual prior approval; other policies include one further cycle within the single IVF cycle offered
- Surgical sperm retrieval: Glossop does not offer surgical sperm retrieval (funding must be sought from NHS England); other policies include this where eligible for IVF but not after previous vasectomy; Bassetlaw does not mention this

Criteria for access to IUI/DI

- Indications for IUI/DI: Most ICBs offer IUI for couples where vaginal intercourse is difficult or not possible due to a physical or psychosexual condition and for same-sex relationships; Glossop also includes single women. Policies for unexplained infertility,

endometriosis and mild male factor infertility vary from 0 to 3 cycles or no mention of these conditions.

- Woman's age: Leicester, Leicestershire and Rutland ICB, Lincolnshire ICB and Bassetlaw offer IUI up to 42 years; Nottingham and Nottinghamshire ICB, Northamptonshire ICB and Derby and Derbyshire ICB offer IUI up to 40 years; Glossop does not mention age criteria
- Man's age: Leicester, Leicestershire and Rutland ICB, Nottingham and Nottinghamshire ICB and Northamptonshire ICB require the man's age to be ≤55 years
- BMI: All ICB policies except Glossop (not mentioned) require the woman's BMI to be between 19 and 30 kg/m^2; one ICB (Nottingham and Nottinghamshire ICB) requires the man's BMI to be less than 30 kg/m^2
- Only Bassetlaw does not require both partners to be non-smoking; Glossop does not mention smoking in relation to IUI

IUI/DI pathway

- Number of cycles offered varies from one (Northamptonshire) to six (Derby and Derbyshire; Bassetlaw, Glossop); Nottingham and Nottinghamshire ICB offers six cycles of DI or three of IUI, Lincolnshire offers three cycles
- Requirement for prior self-funded cycles: Some policies require previous self-funded AI cycles in a clinical setting for some groups (same-sex couples in Lincolnshire, same-sex couples and people with physical or psychosexual condition preventing vaginal intercourse in Derby and Derbyshire); Glossop requires self-reporting of 6 previous AI cycles for same-sex couples and single women, three cycles if age >36 years

Social / ethical factors

- Existing children: Most ICB policies require that there is no living child (including adopted) from any relationship, with some clearer than others that this means either partner; Glossop requires no living child from current relationship and one partner having no child from a previous relationship
- Sterilisation/reversal: Most will not fund IVF or IUI if either partner was ever sterilised even if reversed; Bassetlaw will fund if sterilisation successfully reversed; Glossop will fund IVF if successfully reversed and the other partner suffers from infertility or the couple has unexplained infertility
- Same-sex couples: IVF offered if evidence of infertility. Varying requirements and funding to prove infertility - see under IUI above
- Transgender: Only mentioned by Bassetlaw - considered as inability to conceive if conception by regular sexual intercourse is not possible
- Single women: Mentioned only by Derby and Derbyshire and Glossop (offer IVF if evidence of infertility – see under IUI above), and Lincolnshire (assisted conception not funded)
- Length of relationship: Only Bassetlaw requires a stable relationship of ≥2 years to access IVF
- Cryopreservation: Policies generally similar – cryopreservation of gametes and embryos funded if about to start treatment that risks permanent infertility (not for social or congenital reasons) and procedure or delay will not be harmful, no lower age limit but till 43rd birthday for women and 56th birthday for men, storage for 10 years (some policies require checks that criteria are still met at 1 and/or 5 years) or until reached 43rd birthday (female) or 56th birthday (male), then can self fund, and IVF offered according to criteria at the time of use. Slight variations in policies e.g. Northamptonshire offers storage if age <38 for female and <45 for men for 10 years or till age 42 (female) and 55 (male) or fertility restored; Bassetlaw offers a second cycle of egg retrieval if <10 oocytes in first cycle, and storage of at least 2

and up to 3 semen samples. No policy received from Lincolnshire and not in scope of IVF policy

Table 6 provides a comparison of key policy criteria relating to IVF.

Table 6: Summary of the main East Midlands commissioning policy criteria relating to IVF

IVF access criteria						
	NICE guidance	**Derby and Derbyshire**	**Leicester, Leicestershire and Rutland**	**Lincolnshire**	**Northamptonshire**	**Nottingham and Nottinghamshire (Including Bassetlaw)**
Age (years) and number of cycles	<40: 3 full cycles 40-42: 1 full cycle if no previous IVF and no evidence of low ovarian reserve	<42: 1 cycle **Glossop:** <40: 3 cycles (includes abandoned, cancelled and privately funded) 40-42: 1 cycle (in no previous IVF; donor eggs if needed)	<42: 1 cycle	<42: 1 cycle	<42: 1 cycle	<42: 1 cycle **Bassetlaw:** <40 years: 3 cycles (includes privately funded cycles) 40-42: 1 cycle
BMI	Advice/information only. No set criteria.	Female BMI 19-30. **Glossop:** Female BMI ideally 19-30. If BMI <19 or >30: add to 'watchful-waiting' list unless can show not clinically obese or underweight using another acceptable measure.	Female BMI 19-30.	Female BMI 19-30.	Female BMI 19-30.	Female BMI 19-30. **Bassetlaw:** lifestyle support, interventions and referrals. No BMI criteria for access.
Ovarian reserve	Age and one of the following as an indicator for low IVF ovarian response: AFC ≤4 AMH ≤5.4pmol/l or FSH ≥8.9 IU/l	IVF not offered if low ovarian reserve (if FSH >8.9 IU/l) **Glossop:** Offers IVF with donor oocytes to women aged 40-42 years with low ovarian reserve (as defined by NICE).	IVF not offered if low ovarian reserve (if FSH >8.9 IU/l)	IVF not offered if low ovarian reserve (if FSH >8.9 IU/l)	IVF not offered if low ovarian reserve (if FSH >8.9 IU/l)	IVF not offered if low ovarian reserve (if FSH >8.9 IU/l) **Bassetlaw**: IVF not offered if low ovarian reserve (as per NICE definition)

3.3 Evidence enquiry questions

The policy comparison was discussed in detail at a project scoping workshop for commissioning leads from the East Midlands ICBs in May 2023. Through this, it was agreed that evidence enquiries were needed for the following questions where there were differences either between ICB policies or between the ICB policies and NICE guideline recommendations:

A Age

- How does the clinical effectiveness of 1 full cycle of IVF vary with the age of the female?
- How does the clinical effectiveness of 1 full cycle of IUI vary with the age of the female?
- How does the clinical effectiveness of 1 full cycle of IUI vary with the age of the male?

B Number of IVF cycles (woman under 40 years)

- For women under 40 years of age, what is the effectiveness of a 2nd and 3rd full cycle compared to the 1st?

C Ovarian response / IVF

- What are the relative values of antral follicle count and FSH levels in predicting ovarian response to ovarian stimulation and effectiveness of IVF/ICSI and what are the optimum thresholds below which response/effectiveness of IVF/ICSI is significantly lower?

D BMI

- What is the effectiveness of IVF/ICSI where the woman has a BMI>=30 compared to <30?
- What is the effectiveness of IVF/ICSI where the woman has a BMI <=19 compared to >19?
- What is the effectiveness of IVF/ICSI where the man has a BMI >=30 compared to <30?
- What is the effectiveness of IVF/ICSI where the man has a BMI <=19 compared to >19?
- What is the effectiveness of IUI where the woman has a BMI >30 compared to <30?
- What is the effectiveness of IUI where the woman has a BMI <=19 compared to >19?
- What is the effectiveness of IUI where the man has a BMI over 35 compared to <35?

E Betel nut and chewing tobacco

- What is the clinical effectiveness evidence that betel nut use adversely affects the success of IVF?
- What is the clinical effectiveness evidence that chewing tobacco adversely affects the success of IVF?
- What is the clinical effectiveness evidence that betel nut use adversely affects the success of IUI?
- What is the clinical effectiveness evidence that chewing tobacco adversely affects the success of IUI?

F Indications for IUI

- What is the effectiveness of IUI compared to IVF for women with unexplained infertility, mild endometriosis or mild male factor infertility?

G Sterilisation and reversal

- What is the effectiveness of a cycle of IVF when the woman undergoing IVF has had a successful reversal of a sterilisation procedure versus in a woman who has never had a sterilisation procedure?
- What is the effectiveness of a cycle of IUI when the woman undergoing IUI has had a successful reversal of a sterilisation procedure versus in a woman who has never had a sterilisation procedure?
- What is the effectiveness of a cycle of IVF when the male partner in the couple has had a reversal of a vasectomy versus when the male partner in the couple has never had a vasectomy?
- What is the effectiveness of a cycle of IUI when the male partner in the couple has had a reversal of a vasectomy versus when the male partner in the couple has never had a vasectomy?

H Cryopreservation of gametes and embryos

- How is the quality of sperm stored for future use in IVF affected by the duration of cryopreservation?
- How is the quality of oocytes stored for future use in IVF affected by the duration of cryopreservation?
- How is the quality of embryos stored for future use in IVF affected by the duration of cryopreservation?

3.4 Questions relating to ethical and decision-making principles

Over the course of the project scoping workshop, the second workshop and email communications, it was agreed that a discussion of the ethical considerations or decision-making principles would be included for the following areas:

- Same-sex female couples
- Single females
- Transgender individuals
- Individuals with a physical disability or comorbidity that made vaginal intercourse difficult or impossible
- The presence of an existing child
- Previous sterilization
- Cryopreservation of gametes or embryos for the purpose of preserving fertility

It was agreed that surrogacy and immigration status were issues with important legal considerations and hence would not be covered by this project. It was also agreed that the length of a relationship would not be covered because treatment for single women is being discussed, and because policies required a period of trying to conceive before referral for IVF.

4 Evidence enquiries

4.1 Methodology

PICO[6] frameworks were developed for each of the evidence enquiry questions agreed at the project scoping workshop in May 2023. These are provided in Appendix 2. The frameworks were used by an information specialist at the Bodleian Library, Oxford, to develop a search strategy (Appendix 3), which was used to search Medline, Embase and Cochrane databases for peer reviewed English language studies published between January 2013 and May 2023 inclusive. Titles identified by the searches were screened by the information scientist to exclude papers that were obviously not relevant. Evidence reviewers focussed on different groups of questions, reviewing study abstracts, selecting studies for full paper review and reviewing full papers for inclusion. Where a reviewer was uncertain about a decision to include/exclude a study this was discussed with a second reviewer and a joint decision was made. The rationale for inclusion/exclusion of each study was noted. For these rapid evidence enquiries, reviewers selected the studies that were most informative in the current context, **including** for example the most recent large systematic reviews that were most generalisable to the UK NHS where available or, where relevant systematic reviews were not available or were not recent, selecting the most recent larger studies that most closely match the NHS context.

For each question, evidence reviewers summarised the current NICE guidance, including what evidence that is based on, and the findings of the most relevant studies identified by the recent evidence searches. These are summarised for each question below. Detailed evidence extraction tables for each question are included in Appendix 4.

A Age and number of IVF cycles

Because of the effectiveness of IVF by age and by number of cycles are closely interrelated, it was decided to combine these questions into a single question:

How does the clinical effectiveness of one full cycle of IVF vary with the age of the female and the number of IVF cycles?

NICE Guideline

The 2013 NICE guideline (CG156) [A1] definition of an IVF cycle notes that "a full cycle of IVF treatment, with or without intracytoplasmic sperm injection (ICSI), should comprise 1 episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s)".

It identifies age as a key predictor of IVF success and recommends that patients seeking ART are informed "*that the chance of a live birth following IVF treatment falls with rising female age*".

This is based on evidence from a meta-analysis of 3 studies that showed an association between higher female age and lower pregnancy rates (OR 0.95, 95% confidence interval (CI) 0.94 to 0.96) [A2], rated moderate in quality, and two models using HFEA data [A3, A4], rated as low quality evidence, which showed an inverse gradient between higher maternal age and lower odds of live birth. NICE noted that these data did not suggest any lower age limit for IVF treatment.

[6] PICO frameworks are a structured approach for developing review questions that divide each question into four components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).

With respect to successive IVF cycles, the NICE guideline describes how *"the overall chance of a live birth following IVF treatment falls as the number of unsuccessful cycles increases".* This is based on evidence from 2 papers - in Nelson and Lawlor (2011) [A3], the odds of live birth was lower after one or more unsuccessful previous cycles (for example live birth OR 0.72, 95% CI 0.65 to 0.81, after one previous unsuccessful cycle compared to no previous unsuccessful cycles, adjusted for factors such as age, infertility duration and cause). Although the guideline reports the chances of a live birth decreased with a greater number of unsuccessful cycles and fell rapidly after 4 previous unsuccessful cycles (OR 0.55, 95% CI 0.45 to 0.69, after four unsuccessful cycles compared to after no unsuccessful cycles), this low value was not seen with the OR for ≥5 unsuccessful cycles (OR 0.68, 95% CI 0.55 to 0.83).

The second paper, Roberts et al (2010) [A4] examined live births resulting from further IVF cycles and showed lower odds of live birth during cycles 2-6 compared to the 1st cycle but there was no precipitate decline in live births after a particular IVF cycle. ORs from both studies did not appear to show a consistent decline in odds of live births with an increasing number of cycles or unsuccessful cycles. Despite this, the NICE guideline said that data from these studies suggested an inverse relationship between IVF success and the number of prior unsuccessful attempts, based on low quality of evidence.

Table 7: Relationship between number of previous unsuccessful IVF cycles and odds of live birth [A1]

Table 13.3 Associations of potential predictors of live birth following IVF (Nelson and Lawlor, 2011)

Characteristic	Categories	Univariable odds ratio of live birth (95% CI)	Multivariable odds ratio of live birth (95% CI)	*P* -value
Number of previous unsuccessful IVF	0	1 (Reference)	1 (Reference)	< 0.001
	1	0.74 (0.70–0.79)	0.72 (0.65–0.81)	
	2	0.69 (0.64–0.76)	0.70 (0.62–0.80)	
	3	0.74 (0.66–0.84)	0.77 (0.66–0.91)	
	4	0.51 (0.42–0.62)	0.55 (0.45–0.69)	
	≥ 5	0.57 (0.48–0.69)	0.68 (0.55–0.83)	

Human Fertilisation and Embryology (HFEA) Code of Practice

The HFEA Code of Practice 9th Edition (last revised October 2021) [A5] does not place restrictions on IVF eligibility on the basis of age provided patients are of an age to consent to treatment (except in relation to age-dependent limits placed on the number of embryos that can be transferred at one time) or on the basis of number of previous IVF cycles.

Evidence summary

The questions that were considered relating to maternal age and the number of cycles were:

A1 How does the clinical effectiveness of 1 full cycle of IVF vary with the age of the female?

A2 For women under 40 years of age, what is the effectiveness of a 2nd and 3rd full cycle compared to the 1st?

Further details of the scope of these questions is provided in Appendix 2. We conducted searches for the different elements of this rapid evidence review on Medline, Embase and the Cochrane Library since January 2013, limited to English language. The searches for the different topics were carried out between the 1st and 8th of June 2023. The Medline search strategy is provided in Appendix 3.

For both of these questions, the indication of interest was patients undergoing IVF for treatment of infertility rather than for other indications such as preimplantation genetic testing. For each evidence review question, we selected the most reliable and relevant studies available using standard hierarchy of evidence selection criteria.

Historically, success rates from IVF/ICSI treatments have been reported per embryo transfer [A6,A7] combining data from different IVF cycles. However, repeated IVF cycles are more likely to occur in the context of failure of previous IVF cycles (this is also relevant to repeated embryo transfers within the same IVF cycle) which is often seen as a potential indicator of poorer prognosis in future cycles in clinical practice and by NICE [A1]. Women with a poor prognosis are likely to be overrepresented when calculating live birth rate from a dataset that pools data from across multiple treatment attempts leading to underestimation of the LBR for earlier IVF cycles [A8]. Therefore, for the purposes of the evidence summary, studies that presented the age-dependent effectiveness of IVF cycles stratified by cycle number were favoured during study selection. Outcomes from a full IVF cycle (including fresh embryo transfer and any subsequent frozen embryo transfers following an ovarian stimulation) were considered more relevant to commissioning decisions than outcomes from the first embryo transfer, therefore studies that used the same definition of an IVF cycle as used by NICE were also preferentially selected.

Key studies found

We found no systematic reviews that investigated maternal age-stratified LBR per full IVF cycle rather than per embryo transfer. We found four large-scale observational cohort studies that reported LBR per full IVF cycle and across sequential IVF cycles whose results are summarised in Appendix 4. All studies reported on live births as an outcome and focussed primarily on IVF cycles performed for infertility. None of the included studies presented data on pregnancy rates by maternal age and cycle count, however live births are more relevant as an outcome for commissioners, patients and clinicians as the primary objective of IVF/ART. The most recent relevant papers were based on study cohorts in China [A9,A10] and Australia/New Zealand [A11]. Smith et al (2015) [A12] was also included as the most recent relevant paper that used data from a UK study cohort. All studies defined a full IVF cycle in a way that aligned with NICE.

The two most recent studies were from Chinese study cohorts. Wang et al (2022) [A9] reports outcomes for over 20,000 women who received IVF with either single or double embryo transfer from a single centre between 2007-2016. Reported outcomes were LBR and CLBR based on a conservative model (where all treatment discontinuations were assumed to be due to poor prognosis in females who would have gone on to have a LBR of zero in any subsequent cycles) and an optimal model (where all treatment discontinuations were assumed to be unrelated to poor prognosis in females who would have gone on to have the same LBR in future cycles as those who had received additional cycles) by maternal age and cycle count. Odds ratios from a multivariate regression model were presented for age and cycle count adjusted for cause of infertility and infertility type. With respect to generalisability, the study included only women who had received IVF cycles where a freeze-all strategy had been used. This strategy was used in 85% of cycles performed at the centre in the study period and was preferentially used in females who had a poorer IVF prognosis (such as those with poor ovarian reserve and ovarian response) who would therefore be anticipated to have lower LBRs. However, the paper did not explore the extent to which this would have been counteracted by differences in effectiveness resulting from use of the freeze-all strategy rather than a combined initial fresh/subsequent frozen embryo transfer strategy as described by NICE.

Gu et al (2021) [A10] included data from females aged 35 years and over who underwent IVF at a single centre between 2009-2015 to calculate LBRs and CLBRs stratified on the basis of IVF prognosis. Up to 3 embryos were transferred at a time, in contrast to the maximum of 2 recommended in the NICE guideline [A1]. We have selectively presented data from the subgroups

of patients who had good ovarian reserve (AFC≥5) - the non-POSEIDON group (N=1,473) and the POSEIDON 2 group (N=1,321) - but not from the POSEIDON 4 subgroup given that females from this subgroup would not be eligible for IVF under current NICE criteria on the basis of having an AFC<5 (for further details see Appendix 4). Outcome measures of LBRs and cumulative CLBRs were calculated stratified by age groups and cycle counts, using the same assumptions relating to discontinuation in their optimal and conservative models as in Wang et al (2022) [A9].

Law et al (2019) [A11] looked at data from a registry cohort of over 110,000 females who started IVF for infertility in Australia or New Zealand between 2009-2015. Odds ratios from a multivariate model are presented across age groups and cycle counts, adjusted for number of oocytes retrieved and parity. The handling of discontinuations between IVF cycles was not explicitly described in the published paper.

Smith et al (2015) [A12] used UK HFEA data from over 153,000 women who started IVF between 2003-2010. Given it is a legal requirement that all ART activity is reported to the HFEA national registry, these data represent complete treatment capture. In addition to presenting LBRs and CLBRs from optimal and conservative models, they additionally produced a prognosis-adjusted CLBR estimate which assumes that 30% of females who discontinue IVF treatment do so due to poor prognosis (and would therefore have had a LBR of zero in any future IVF cycles). The authors estimated that 3% of discontinuations in their study cohort had been due to poor prognosis, the true CLBR is therefore likely to lie between the prognosis-adjusted CLBR and the optimal CLBR estimate.

A1 Maternal age: key findings/results

All studies confirmed that greater maternal age is associated with a lower LBR per IVF cycle.

Wang et al (2022) [A9] reported that live birth rates after the 1st cycle declined with maternal age from 53.0% in those aged 31-34 to 4.7% in those aged >40, with a steeper decline seen between 35-37 years and 38-40 years (first cycle LBRs of 39.2% and 21.7% respectively).

In Gu et al (2021) [A10], amongst females in the study cohort with AFC≥5, LBRs decreased between the maternal ages of 35-37 and 40-42, from 53.8% to 27.0% in the first cycle in the good ovarian response (non-POSEIDON) subgroup and from 32.0% to 15.4% in the first cycle in the poor ovarian response (POSEIDON 2) subgroup. Between 35-37 years and 38-39 years, the decline in LBR by age was similar across these subgroups, however between 38-39 and 40-42 years a steeper decline in LBR was seen in the good ovarian response group than in the poor ovarian response group. The difference in LBRs between these subgroups was substantial: compared to the poor ovarian response subgroup, LBRs in the good ovarian response subgroup were more than twenty percentage points higher in females <40 years and more than ten percentage points higher in females aged 40-42 years. In a patient cohort where assessment for IVF eligibility considers ovarian reserve but not oocyte response in previous cycles, CLBRs would be expected to lie in between the estimates for the good and poor ovarian response subgroups. These results suggest that consideration of ovarian response in previous cycles during decision-making for subsequent IVF cycles could lead to higher LBRs from these cycles (based on observational rather than experimental evidence).

In Smith et al (2015) [A12], LBRs from the 1st IVF cycle declined with maternal age from 32.3% to 3.7%, and LBRs for the 3rd cycle from 24.3% to 3.3% in the <40 years maternal age group compared to the >42 years maternal age group.

The age-stratified LBRs from Wang et al (2022) [A9] are comparable to those from the POSEIDON 2 subgroup from Gu et al (2021) [A10] (see Appendix 4). This is consistent with both being based on Chinese study cohorts and the freeze-all strategy inclusion criteria in Wang et al

(2022) biasing participant selection towards those with a poorer IVF prognosis and the POSEIDON 2 subgroup representing a cohort of patients with a history of lower oocyte response.

ORs for Law et al (2019) [A11], although from an Australian-New Zealand study cohort, are not dissimilar to those from Wang et al (2022) despite inclusion of different covariates in the multivariate models (see Appendix 4). However, the OR estimates from Law et al (2019) suggest a less steep gradient of decline in LBR between the ages of 35 and 44 years compared to that seen in the Wang et al cohort. Notably, Law et al excluded IVF cycles where no oocytes were retrieved, given the negative correlation between maternal age and ovarian response [11], this would be expected to lead to greater inflation of LBR (and therefore of CLBR) in older maternal age groups – the other included studies made no mention of excluding cycles with zero oocyte retrieval, this could therefore provide an explanation for the differences in results between Law et al (2019) and Wang et al (2022).

Table 8: Comparison of LBRs after the 1st IVF cycle across maternal age groups

<table>
<tr><td rowspan="2">Maternal age group (years)</td><td colspan="3">LBR after 1st cycle, % (95% CI)</td></tr>
<tr><td>Wang et al (2022) [A9]</td><td>Gu et al (2021) [A10]</td><td>Smith et al (2015) [A12]</td></tr>
<tr><td></td><td></td><td>non-POSEIDON group (good ovarian response)</td><td>POSEIDON 2 group (poor ovarian response)</td><td></td></tr>
<tr><td><31</td><td>63.81 (62.80, 64.81)</td><td>No data available</td><td>No data available</td><td>32.3 (32.0-32.5)</td></tr>
<tr><td>31
32
33
34</td><td>53.02 (51.78, 54.25)</td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="3"></td></tr>
<tr><td>35
36
37</td><td>39.23 (37.36, 41.13)</td></tr>
<tr><td>38
39</td><td>21.67 (19.58, 23.87)</td><td>43.6 (38.3, 49.0)</td><td>21.3 (16.6, 25.9)</td></tr>
<tr><td>40</td><td rowspan="2">4.71 (3.61, 6.02)[1]</td><td>27 (20.1, 33.9)</td><td>15.4 (10.7, 20.0)</td><td>12.3 (11.8-12.8)</td></tr>
<tr><td>41
42</td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td></tr>
<tr><td>≥43</td><td>No data available</td><td>No data available</td><td>3.3 (3.2-4.3)</td></tr>
</table>

[1]LBR for the >40 years age group

Table 9: Comparison of Odds Ratios (OR) for live births after the 1st IVF cycle across maternal age groups

<table>
<tr><td rowspan="2">Maternal age group (years)</td><td colspan="2">Law et al (2019)</td><td>Wang et al (2022)</td></tr>
<tr><td>OR (95% CI)[1]</td><td>ORs recalculated relative to the <30 age group</td><td>OR (95% CI)[2]</td></tr>
<tr><td><30</td><td>1.85 (1.79–1.91)</td><td>1.00</td><td>1</td></tr>
<tr><td>30
31
32
33
34</td><td>1.62 (1.58–1.66)</td><td>0.88</td><td>0.68 (0.63, 0.73)</td></tr>
<tr><td>35
36
37</td><td>1.00</td><td>0.54</td><td>0.38 (0.34, 0.42)</td></tr>
<tr><td>38
39</td><td rowspan="2"></td><td rowspan="2"></td><td>0.17 (0.15, 0.20)</td></tr>
<tr><td>40
41
42
43
44</td><td>0.35 (0.33–0.36)</td><td>0.19</td><td>0.04 (0.03, 0.05)[3]</td></tr>
<tr><td>>=45</td><td>0.05 (0.04–0.07)</td><td>0.03</td><td></td></tr>
</table>

[1]Odds ratios from a multivariate regression model adjusted for number of oocytes retrieved and parity.
[2]Odds ratios from a multivariate regression model adjusted for cause of infertility and infertility type.
[3]OR for the >40 maternal age group

The most recent published outcome data from the HFEA are from the HFEA report “Fertility treatment 2019: trends and figures” [A13]. Birth rates by age are reported per embryo transfer only:

Maternal age	Birth rate per embryo transfer
< 35	32%
35-37	25%
38-39	19%
40-42	11%
43-44	5%
45-50	4%

The HFEA data are consistent with lower LBRs being achieved through IVF at greater maternal ages. Birth rates per embryo transfer will underestimate live birth rates after an IVF cycle, given a full cycle may involve more than one embryo transfer procedures, and provide an underestimate of LBR in earlier cycles and overestimate of LBR in later cycles (see Section A2 on number of cycles).

Safety

Our search identified one relevant systematic literature review, Ribeiro et al (2023) [14], that examined prevalence of adverse outcomes after ART by maternal age. As this did not provide quantitative estimates of the differences in risks of adverse outcomes, findings from a primary paper, Sydsip et al (2019) [A15] (selected based on relevance and size), were also included.

Ribeiro et al (2023) [A14] reported evidence of higher miscarriage rates and macrosomia in neonates but lower multiple pregnancy and multiple birth rates with higher maternal age based on evidence from 1-3 studies. The evidence for a correlation between higher conceiving female age and congenital birth defects, preterm birth and low birth weight was mixed (based on results from 1-2 studies).

Sydsip et al (2019) [A15] presented prevalence for different adverse neonatal outcomes as a percentage of IVF-associated births stratified by maternal age. They found statistically significant differences in the prevalence of adverse outcomes post-IVF by age band for twin pregnancy, preterm and birthweight based on univariate analysis, however this is not necessarily indicative of a trend between higher maternal age and increased or decreased risk of the outcome and visual inspection does not reveal evidence of a clear positive or negative trend for these outcomes with maternal age.

Cost-effectiveness

No studies on cost-effectiveness by maternal age which used UK data from within the last 10 years were identified.

A2 Number of cycles in females under 40 years: key findings/results

In females aged ≤ 40 years, Wang et al (2022) [A9] observed that cumulative LBRs increased by a statistically significant amount after a 2nd cycle compared to the 1st cycle, and in the 3rd cycle compared to the 2nd in the <45 age groups. The absolute increase in CLBR between the 1st and 2nd cycles was 9-11% for conservative CLBR (15-18% for optimal CLBR) below 38 years, and 6% for conservative CLBR (10% for optimal CLBR) for those aged 38-40 years. Between the 2nd and

3rd cycles, the absolute increase in CLBR was similar across age groups (3-4% for conservative CLBR, 8-10% for optimal CLBR) in the ≤ 40 years age group.

Gu et al (2021) [A10] observed that amongst females with AFC≥5, CLBR increased between the 1st and 2nd cycle when optimal CLBR estimates were used but did not reach statistical significance when conservative CLBR estimates were used for 38-42 year olds in the good ovarian response subgroup or 40-42 year olds in the poor ovarian response subgroup. Detection of statistically significant differences is affected by the smaller sample size of this study which leads to estimates of CLBR being less precise. Between the 2nd and 3rd cycles, across both ovarian response subgroups, the optimal model places the absolute increase in CLBR at 6-12%, whilst conservative CLBR places the absolute increase in CLBR at 1-4%.

In Smith et al (2015) [A12], CLBR was statistically significantly higher after the 2nd cycle compared to the 1st across the <40 to >42 age groups, and after the 3rd cycle compared to the 2nd across different CLBR models (optimal, prognostic and conservative) in those aged ≤42. Based on the prognostic and optimal estimates, in females aged ≤ 40 years, CLBR was 16-18% higher in the 2nd cycle compared to the 1st cycle and 9-12% higher in the 3rd cycle compared to the 2nd cycle.

Across these studies, the absolute increase in CLBR between the 2nd and 3rd cycles appears smaller than between the 1st and 2nd cycles (assessment for statistical significance is not possible based on the published data). The absolute increase also shows age dependence, with less of an increase being seen in CLBR between sequential cycles in the 40-42 (or >40 years) age group compared to younger age groups (based on Wang et al (2022), the POSEIDON 2 study group in Gu et al (2021) and Smith et al (2015)). Data from Wang et al also suggest a more modest change in CLBR per additional cycle in those aged 38-40 compared to the 35-37 age group, though this pattern is not seen in the two subgroups from Gu et al (2021).

In Law et al (2019) [A11], the odds of having an aspiration resulting in a live birth decreased by 11% (95% CI 0.87-0.91) between the 1st and 2nd cycles and 20% (95% CI 0.78–0.83) between the 2nd and 3rd cycles, after adjusting for maternal age, parity and number of oocytes retrieved.

Based on the most recent HFEA report “Fertility treatment 2019: trends and figures” [A13], almost 53,000 patients had around 69,000 fresh and frozen IVF cycles and around 5,700 DI cycles in 2019, however no data on success rates by number of cycles was available from the report.

Safety

No systematic reviews or primary papers were identified that examined prevalence of adverse outcomes in females receiving ART by cycle count, accounting for confounding by maternal age.

Cost-effectiveness

No studies on cost-effectiveness by cycle count, accounting for maternal age, which used UK data from within the last 10 years were identified.

Discussion and conclusions for maternal age and number of cycles

Four primary studies provide estimates of LBR by maternal age, stratified by cycle count, in Chinese, Australian/New Zealand and UK study cohorts. There is broad comparability across LBR estimates from Wang et al (2022) and the POSEIDON 2 group from Gu et al (2021) in the 35-39 age range, and Smith et al (2015) in the 40+ years age range. Similarity of estimates in Smith et al to those from Wang et al and Gu et al (from study cohorts expected to have worse-than-average IVF prognosis) could reflect introduction of newer techniques since 2010 which enabled achievement of better outcomes in those with poorer prognosis in the two more recent studies.

All identified studies have limitations in terms of their generalisability to the current clinical context in the UK. Use of optimal versus conservative model assumptions for CLBR led to substantial differences in the resulting estimates, however data on the proportion of the study cohort discontinuing between cycles and the reasons for this were not commonly reported amongst the included studies (except for Smith et al 2015). There is therefore uncertainty in relation to how the proportion of participants discontinuing for prognostic-related reasons in the included studies compares to that in the UK IVF-seeking patient population currently.

In relation to Smith et al (2019), as stated above, UK clinical practice may have undergone changes both in terms of IVF protocols (such as moving away from multiple embryo transfers in line with NICE guidelines published in 2013 [A1]) and technological advancements. In the non-UK studies, differences that could potentially have a major impact on generalisability were, for Law et al [A11], the method used for calculation of CLBRs (which excluded IVF cycles where no oocytes were retrieved) and lack of detail on how discontinuations were handled within CLBR calculations and, for Gu et al [A10], the high prevalence of high parity amongst females included in the study cohort, which may contribute to higher LBRs compared to a context in which IVF access is dependent on not already having a living child (as in current ICB policies).

Whilst the patient inclusion criteria in Wang et al [A9] is likely to have selected for patients with worse IVF prognosis, the limitation of number of embryos transferred at one time to 1-2 and presentation of CLBRs for the overall study population make it more relevant to our evidence question than CLBRs stratified based on ovarian response (as in Gu et al [A10]), and the methods used in the calculation of optimal and conservative CLBR are better aligned with the outcomes of interest when compared to Law et al (2019) [A11]. Wang et al also presents LBRs by small age bands over the whole age range of interest and the magnitude of LBRs and increases in CLBR between sequential cycles are comparable to those identified in the UK study cohort from Smith et al (2015).

By maternal age group, the LBR estimates from Wang et al are slightly higher than the birth rates per embryo transfer from the 2019 HFEA report, in line with what we expect to see based on the different methodologies used to calculate these outcome measures. This further supports generalisability of the LBR and CLBR estimates from Wang et al (2022) to the current UK context.

B Age and effectiveness of IUI

The questions covered in this section are:

B1 How does the clinical effectiveness of one full cycle of IUI vary with the age of the female?

B2 How does the clinical effectiveness of one full cycle of IUI vary with the age of the male?

IUI may be ‘stimulated’, i.e. combined with ovarian stimulation (OS) using for example gonadotrophins (follicle-stimulating hormone or hMG) or Clomiphene Citrate, or ‘unstimulated’, i.e. carried out during ‘natural’ cycles without OS. OS increases the chances of ovulation but may increase the risk of multiple pregnancy and may rarely be associated with Ovarian Hyperstimulation Syndrome (OHSS).

NICE Guideline

The 2013 NICE guideline (CG156) [B1] does not include any recommendations that relate to IUI and the age of the female or the male.

Human Fertilisation and Embryology (HFEA) Code of Practice

The HFEA Code of Practice 9th Edition (last revised October 2021) [B2] does not discuss age of the female or the male in relation to IUI.

Current policy relating to IUI and the age of the female and of the male

Current East Midlands ICS assisted conception policies vary with respect to access to IUI and age. The current policy in Leicester, Leicestershire and Rutland specifies an age range for the female of 18-42 years. The policy for Bassetlaw CCG (now part of Nottingham and Nottinghamshire ICS) also specifies 18-42 years and the Armed Forces policy less than 43 years, assuming that in these two areas the criteria listed apply both to IVF and IUI. Lincolnshire specifies 18-42 years for same-sex couples, and that heterosexual couples are required to meet the criteria in the IVF policy. Nottinghamshire and Northamptonshire specify 23-39 years and Derbyshire less than 39 years.

Regarding the age of the male partner this is mentioned in the policies for Leicester, Leicestershire and Rutland, Nottinghamshire and Northamptonshire which all state that the male partner should be aged 55 years or less.

The workshop discussion suggested that criteria should be the same for IUI as for IVF, but that the man's age also needed to be considered. It was therefore decided that the question for consideration should relate to the age of both the female and male.

Key studies found

The PICO framework developed for the review of evidence in relation to this question is provided in Appendix 2.

We searched for new evidence published since January 2013. We searched for studies reporting outcomes for IUI by the age of the female and of the male partner, and prioritised the larger studies and those which reported outcomes and age groups most relevant to the population of interest. We found five key relevant studies for inclusion. These were all cohort studies. Ombelet et al (2021) [B3] reported prospectively collectively data from 2565 IUI procedures (most with OS) in 989 couples. The remaining four were retrospective studies; Luo et al (2021) [B4] reported outcomes from 3015 IUI treatment cycles (74% with OS) in 1853 couples, Immediata et al (2019) [B5] reported outcomes from 6323 IUI cycles with OS in 2901 couples, Michau et al (2019) [B6] reported outcomes from 4146 IUI cycles with OS in 1312 couples, and Tatsumi et al (2018)[B7] reported outcomes from 1576 IUI cycles (41% with OS). No relevant systematic reviews were identified.

All five studies reported pregnancy rates, and two also reported live birth rates [B5, B7]. Four reported outcomes by both male and female age, and one [B6] reported outcomes by female age only. In four of the studies the oldest age group compared with younger age groups was ≥40 years or >40 years for both males and females. The fifth [B7] reported male outcomes up to age ≥47 years (the upper age limit was not stated) and female outcomes up to age 38-40 years compared with younger age groups. No studies were identified which reported outcomes in men older than ≥47 years, and none of the studies included data on cost/cost-effectiveness or adverse events.

Key findings/results

B1 Outcomes of IUI in females

Although Ombelet et al (2021) [B3] found a significantly lower clinical pregnancy rate in older women than in younger women on univariate analysis, when analysed allowing for potential confounding factors they reported no statistically significant difference in clinical pregnancy rate by female age group. However, it appeared that a more effective approach to insemination was used in more older women than younger women, so it is possible this affected the overall pregnancy rates reported. The female age groups compared were <30, 30-34.99, 35-39.99 and ≥40 years.

Luo et al (2021) [B4] found no evidence of a significant difference in pregnancy rate by cycle by age of female on univariate analysis, but on multivariate analysis which allowed for confounding factors, women aged ≥40 years had significantly lower pregnancy rates than those aged <40 years.

Immediata et al (2019) [B5] found statistically significantly lower pregnancy rates and live birth rates in older than younger women, based on both univariate analysis and multivariate analysis allowing for potential confounding factors. The age groups compared were ≤35, 36-38, 39-40 and >40 years but there was no direct statistical comparison between the different age groups.

Michau et al (2019) [B6] reported that women aged <38 had a significantly higher chance of clinical pregnancy than those older than this. Comparing different age groups, they found that women aged >40 years (with an upper age limit of <43 years) had a significantly lower chance of pregnancy than those aged 35-38 and younger, but their chance of pregnancy was not significantly different from those aged 38-40. Because of the way the results of the age band comparisons were reported it was not clear which age bands included the women aged 35 and 38 years.

Tatsumi et al (2018) [B7] reported that the clinical pregnancy rate, and the odds of a pregnancy cycle on multivariate analysis (allowing for confounders) were significantly lower in women aged 38-40 than in younger age groups. The live birth rate was significantly lower in women aged 38-40 than in younger age groups, but on multivariate analysis allowing for confounders there was no significant difference between women of different ages in the odds of a live birth cycle. The study only included women in the age groups ≤34, 35-37 and 38-40 years.

B2 Outcomes of IUI in males

Ombelet et al (2021) [B3] reported that clinical pregnancy rates were significantly lower in men aged ≥40 years than in those aged <35 years, when analysed allowing for potential confounding factors. They also found that clinical pregnancy rates were significantly lower in men aged 35-39.99 years than in those aged <30 years. The male age groups compared were <30, 30-34.99, 35-39.99 and ≥40 years, but they did not report the upper age limit of men included in the study.

Luo et al (2021) [B4] found no evidence of a significant difference in pregnancy rate by cycle by age of male on either univariate or multivariate analysis. The age groups compared were from <30 to ≥40 years but the upper age limit of men included in the study was not reported.

Immediata et al (2019) [B5] reported statistically significant associations on univariate analysis between male age and clinical pregnancy rate, and male age and live birth rate, but the actual rates by male age group were not reported. The results of multivariate analysis for male age were not reported (the paper only reported results for this analysis which were statistically significant) so the paper provided no evidence of an association with male age once potential confounders were allowed for.

The age groups compared for both males and females were ≤35, 36-38, 39-40 and >40 years but the upper age limit of men included in the study was not reported.

Tatsumi et al (2018) [B7] reported that the clinical pregnancy rate was significantly lower in the older age groups of men than in younger age groups, but on multivariate analysis allowing for confounders there was no significant difference between men of different ages in the odds of a pregnancy cycle. The live birth rate was significantly lower in the older age groups of men than in younger age groups, but on multivariate analysis allowing for confounders there was no significant difference between men of different ages in the odds of a live birth cycle. The authors concluded that advanced paternal age did not adversely affect the clinical pregnancy rate or live birth rate. This study included men aged ≤34, 35-37, 38-40, 41-43, 44-46 and ≥47 years but the upper age limit was not stated.

No studies reported adverse event or cost/cost-effectiveness outcomes.

Table 10: Summary of findings where statistical significance was reported

	Pregnancy rate	Live birth rate	Age groups compared
Female age			
Ombelet 2021 [B3]	On multivariate analysis there was no significant difference in clinical pregnancy rate between older women and younger women.		From <30 to ≥40 years
Luo et al 2021 [B4]	On multivariate analysis, there was a significantly lower pregnancy rate in women aged ≥40 years than those aged <30 or 30-39 years.		From <30 to ≥40 years
Immediata 2020 [B5]	On multivariate analysis clinical pregnancy rate was statistically significantly lower in older women than younger women, but statistical comparisons between specific age groups were not reported.	On multivariate analysis live birth rate was statistically significantly lower in older women than younger women, but statistical comparisons between specific age groups were not reported.	From ≤35 to >40 years.
Michau 2019 [B6]	On multivariate analysis women aged <38 had a significantly higher chance of clinical pregnancy than those older than this. When age groups were compared the chance of pregnancy was not significantly different in women aged >40 years compared with those aged 38-40.		From <30 to >40 years (upper age limit <43 years).
Tatsumi 2018 [B7]	On multivariate analysis the odds of a pregnancy cycle were significantly lower in women aged 38-40 than in younger age groups.	On multivariate analysis there was no significant difference between women of different ages in the odds of a live birth cycle.	From ≤34 to 38-40 years.
Male age			
Ombelet 2021 [B3]	On multivariate analysis the clinical pregnancy rate was significantly lower in men aged ≥40 than in those aged <35 years, and in those aged 35-39.99 than in those aged <30 years.		From <30 to ≥40 years
Luo 2021 [B4]	There was reported to be no significant association between pregnancy rate and male age on multivariate analysis (actual results not reported).		From <30 to ≥40 years
Immediata 2020 [B5]	There was reported to be no significant association between clinical pregnancy rate and male age on multivariate analysis (actual results not reported).	There was reported to be no significant association between live birth rate and male age on multivariate analysis (actual results not reported).	From ≤35 to >40 years.
Tatsumi 2018 [B7]	On multivariate analysis there was no significant difference between men of different ages in the odds of a pregnancy cycle.	On multivariate analysis there was no significant difference between men of different ages in the odds of a live birth cycle.	From ≤34 to ≥47 years.

Discussion and conclusions for age and effectiveness of IUI

The NICE infertility guideline [B1] does not include any recommendations that relate to IUI and the age of the female or the male.

This review identified five key studies relevant to this question, all of which were cohort studies; one was prospective and the remaining four analysed data retrospectively. They reported outcomes (pregnancy rates and/or live birth rates) from between 1,576 and 6,323 IUI cycles, some or all of which involved OS. In four of the studies the oldest age group compared with younger age groups was ≥40 years or >40 years for both males and females. The fifth study [B7] reported male outcomes up to age ≥47 years (the upper age limit was not stated) and female outcomes up to age 38-40 years compared with younger age groups. None of the studies reported outcomes for age groups which aligned exactly with those in the PICO. Further details are provided in Appendix 4.

Studies reported the findings of univariate analyses examining associations between single variables (such as age) and the outcomes of interest. Because these findings can be influenced by confounding factors (for example, the age of the partner, sperm quality or approach to OS), they also reported carrying out multivariate analyses which aim to allow for potential confounders. Some studies only reported details of the findings which were statistically significant.

For outcomes by female age, four studies found that older women had significantly lower pregnancy rates than younger women; one of these also reported significantly lower live birth rates in older women [B4, B5, B6, B7] while another found no significant difference in live birth rates by female age [B3]. The age groups compared varied; one study reported that women aged ≥40 years had a significantly lower pregnancy rate than those aged <30 or 30-39 years [B4] and two reported that women aged 38 or over had significantly lower chances of pregnancy than younger women [B6, B7]. One reported that clinical pregnancy rate was statistically significantly lower in older women than younger women (in age groups from ≤35 to >40 years) but statistical comparisons between age groups were not reported [B5]. The fifth study reported no significant difference in clinical pregnancy rate between older women and younger women (in age groups from <30 to ≥40 years) (although it is possible this finding may have been influenced by a more effective approach to insemination being used in more older women) [B3].

For outcomes by male age, three studies found no significant association between pregnancy rates and male age [B4, B5, B7], and two of these also found no significant association between live birth rates and male age. The upper age ranges reported were >40 or ≥40 years in two of the studies [B4, B5], and ≥47 years in the third [B7], although none reported the upper age limit of subjects included. The fourth study reported that the clinical pregnancy rate was significantly lower in men aged ≥40 than in those aged <35 years, and in those aged 35-39.99 than in those aged <30 years [B3].

No relevant systematic reviews were identified and no relevant studies were identified which reported adverse event or cost/cost-effectiveness outcomes.

In conclusion, while the majority of evidence identified reported that IUI outcomes were significantly worse in older women (over the age of 38 or 40 years) this was not a universal finding, and no studies reported the specific comparison between those aged 40-42 years and those aged 23-39 years. Most of the evidence found no association between male age and IUI outcomes, but one study did report an association. The oldest age group reported was ≥47 years in one study, which found no association between male age and outcomes.

C Ovarian response (IVF) – relative value of AFC vs FSH in predicting outcomes

One question was considered relating to the measurement of ovarian reserve and its relationship to the outcome of IVF:

What are the relative values of antral follicle count (AFC) and follicle-stimulating hormone (FSH)[7] levels in predicting ovarian response to ovarian stimulation and effectiveness of IVF/ICSI and what are the optimum thresholds below which response/effectiveness of IVF/ICSI is significantly lower?

NICE Guideline

The 2013 NICE guideline (CG156) [C1] includes recommendations that relate to the measurement of ovarian reserve testing. The NICE guideline recommends the use of a woman's age as an initial predictor of her overall chance of success through natural conception or with IVF and use of one of the following measures to predict a low ovarian response to gonadotrophin stimulation in IVF:

- total AFC of ≤4 (follicles of ≤5 mm measured by transvaginal ultrasound on day 3 of cycle: low response was <4 oocytes)
- anti-Müllerian hormone of ≤5.4 pmol/l (Beckman–Coulter assay: poor response defined as <4 oocytes or cancellation)
- FSH >8.9 IU/l (low response defined as <4 oocytes or cancellation).

The NICE guideline does not discuss the relative merits of using FSH compared to AFC as an indicator of ovarian reserve or IVF outcome and does not mention any alternative thresholds below which ovarian response or IVF effectiveness is lower.

The NICE guideline recommendations relating to FSH and AFC tests are based on a review of the evidence carried out to investigate how accurate tests of ovarian reserve are in predicting pregnancy and its outcomes for women undergoing treatment for infertility. Searches were updated on 30th November 2011. The review was carried out in two parts. Firstly, receiver operator characteristic area under the curve (ROC-AUC) data were reviewed. Secondly, GRADE[8] findings for evaluation of ovarian reserve using likelihood ratios were reviewed for AFC, anti-Müllerian hormone (AMH) and FSH.

The first part of the review found that for four tests (namely FSH, AFC, AMH and clomiphene citrate challenge test (CCCT)), the accuracy criterion (defined as an ROC-AUC of ≥0.8) was fulfilled for low response following ovarian stimulation but was not fulfilled for the key outcomes of achievement of pregnancy or a live birth or cancellation rates following ovarian stimulation. CCCT was excluded due to the low quality of the evidence and the fact that it is not used in clinical practice in the UK.

In the second part of the review, likelihood ratios were calculated for FSH, AFC and AMH for a range of different thresholds as these provide more detailed information on the characteristic of a test. Likelihood ratios were not calculated for combinations of tests because combinations of tests did not demonstrate any better accuracy than the tests in isolation.

NICE accepted criteria define a test as definitely useful if the positive likelihood ratio is >10 and the negative likelihood ratio is <0.1. For a test to be moderately useful, the corresponding values are 5 to 10 for the positive likelihood ratio and 0.1 to 0.5 for the negative likelihood ratio. The NICE team

[7] Note that FSH in this context refers to basal FSH, measured prior to ovarian stimulation.
[8] GRADE (Grading of recommendations assessment, development and evaluation) is a systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.

only carried out these assessments with respect to ovarian response because the tests had not been shown to fulfil the accuracy criterion for predicting pregnancy or live births.

For AFC, the results from moderate quality evidence were that: AFC of ≤2 was definitely useful in predicting a low ovarian response; AFC of ≤4 was moderately useful in predicting a low response; AFC >4 was moderately useful in excluding a low response and AFC >10 was definitely useful in excluding a low response.

For AMH, moderate quality evidence suggested that: AMH of ≤0.75 ng/ml was definitely useful in predicting a low ovarian response and AMH of >0.75 ng/ml was moderately useful in excluding a low response.

For FSH, different studies provided moderate quality evidence suggesting different cut-off values as being moderately or definitely useful in predicting a low response to ovarian stimulation: moderate quality evidence suggested that: FSH >8.9 IU/l was moderately useful in predicting a low ovarian response; FSH <8.9 IU/l was moderately useful in excluding a low response; FSH >10 IU/l was definitely useful in predicting a low response; FSH <10 IU/l was moderately useful in excluding a low response; FSH of ≥11 IU/l was moderately useful in predicting a low response; FSH ≥13.4 IU/l was moderately useful in predicting a low response; and FSH of >15 IU/l was definitely useful in predicting a low response.

No health economic papers were identified and no specific health economic analysis was undertaken.

Human Fertilisation and Embryology (HFEA) Code of Practice

The HFEA Code of Practice 9th Edition (last revised October 2021) [C2] does not discuss the measurement of ovarian reserve in women undergoing IVF.

Current policy relating to prediction of ovarian response and IVF outcomes in East Midlands ICSs

Current East Midlands ICS assisted conception policies all require FSH to be ≤8.9 IU/l for eligibility for NHS funded IVF/ICSI, except for Bassetlaw CCG (now part of Nottingham and Nottinghamshire ICS), and the Armed Forces policy. The Armed Forces policy exactly reflects the NICE guideline (CG156) and Bassetlaw CCG's policy is very similar to the NICE guideline (FSH ≥9 IU/l using Leeds assay OR antral follicle count ≤4 OR AMH ≤5 pmol/l).

Discussion at the scoping workshop for this project suggested the following:

- FSH was thought to be the least accurate test and is often performed on the wrong day of the cycle which can be misleading.
- AMH is assessed in different laboratories using different assays with different threshold values for high/low AMH and ICSs are unlikely to be able to introduce a single assay across all providers.
- AFC was thought to be the preferred option based on clinical consistency

Issues around access to secondary care for AMH tests and to ultrasound scans were discussed. However, it was agreed that all women should be having an ultrasound scan during assessment for assisted conception and AFC could easily be added to this. While this ultrasound scan was likely to be part of the standard fertility service contract, the group discussed current problems with ensuring that ultrasound scans are actually delivered/accessible for women and the need to improve equity of access to these scans. It was felt that AFC is likely to be easier to deliver consistently across all geographies because it is a point of care test.

Cost implications were also discussed, including that FSH is relatively inexpensive, AMH costs in the region of £60 per test and AFC should involve negligible additional time or resource cost if performed during routine ultrasound scans.

It was therefore decided that the question for consideration in relation to published evidence was around the comparative value of using FSH levels vs AFC in predicting the effectiveness of IVF/ICSI.

The PICO framework developed for the review of evidence in relation to this question is provided in Appendix 2.

Key studies found

We searched for new evidence published since January 2013. We searched for studies comparing the use of FSH and AFC, preferably in the same population[9], for prediction of a low ovarian response and particularly reporting pregnancy rates and live birth rates, as the latter were stated as the outcomes of interest in the PICO framework for the question that was being considered. The largest studies reporting these outcomes were prioritised. From the included studies, any information on optimum thresholds below which response and effectiveness of IVF/ICSI is significantly lower was also extracted where available. Information on poor response to ovarian stimulation was also extracted from the included studies. Studies were excluded if they excluded or only included patients who were already predicted to have a poor ovarian response to stimulation (for example as a result of using one of the ovarian response tests, or having had previously cancelled cycles due to poor ovarian response), did not report live birth or pregnancy rates (apart from one very large study (Wang et al 2021 [C8])), were not published in English, were published prior to 2013 or were relatively small (n<200).

Three systematic reviews were identified for inclusion. However, none reported information regarding optimum thresholds below which ovarian response / effectiveness of IVF/ICSI was significantly lower. Three individual studies that most directly answered the question posed were included: Li et al (2021) [C4] (n=6,580, China); Brodin et al (2015) [C6] (n=892, Sweden); and Dai et al (2014) [C7] (n=200, China). In addition, Wang et al (2021) [C8] (n=89,002, China) was included because it was by far the largest study (n=89,002) reporting ovarian response to controlled ovarian stimulation (although it did not report pregnancy or live birth rates).

Results/Key findings

Relative value of AFC and FSH in predicting pregnancy

Prediction of pregnancy rate was reported by one systematic review and meta-analysis (Broer et al 2013) [C5] and one retrospective cohort study (Dai et al 2014) [C7] as well as in only a brief narrative form by two further systematic reviews (Ribeiro et al 2014 [C3] and Liu et al 2017 [C4]).

Ribeiro et al (2014) [C3] reported that three studies reported that low basal FSH levels are associated with a higher pregnancy rate, and one of those studies reported that this was only the case in women aged >38 years, whereas a different study reported that AFC was not associated with pregnancy rate in patients undergoing IVF. Liu et al (2014) [C4], also in narrative form, reported that FSH results have been shown to be predictive of non-pregnancy only when levels are extremely elevated and that AFC is not a good predictor of pregnancy.

The systematic review and meta-analysis by Broer et al (2013) [C5] reported that among 420 women undergoing IVF, FSH and AFC had only a very small or no predictive effect in predicting

[9] Studies comparing the predictive value of FSH and AFC in the same population (rather than different populations) were preferred in order to minimise bias from indirect comparisons because studies varied in individual patient populations, stimulation protocols, hormone assays, ultrasound techniques and other features that are likely to be confounders in any indirect comparisons.

pregnancy after IVF (area under the curve (AUC) for FSH: 0.53 (95% confidence interval (CI) 0.43 to 0.62), p=0.348; and for AFC: AUC 0.50 (95% CI 0.40 to 0.59), p=0.100).

The retrospective cohort study by Dai et al (2013) (n=201) reported that for women undergoing their first IVF cycle, FSH correlated with clinical pregnancy rate in <35 year olds (p<0.05, correlation coefficient -0.115, AUC 0.509) but not in women aged ≥35 years (p>0.05, correlation coefficient -0.036, AUC 0.521). AFC, on the other hand, correlated with clinical pregnancy rate in women aged ≥35 years (p<0.05, correlation coefficient 0.404, AUC 0.729) but not in <35 year olds (p>0.05, correlation coefficient -0.035, AUC 0.520).

In summary, the evidence identified relating to the use of FSH and AFC to predict pregnancy rates in IVF was mixed for both older and younger women. For older women, one study suggested that FSH may be useful and another suggested that AFC may be useful. None of the included studies discussed the optimal cut-off values for FSH or AFC for the prediction of pregnancy in IVF/ICSI.

Relative value of AFC and FSH in predicting live birth

Prediction of live birth was reported in narrative form only by one systematic review (Ribeiro et al 2014) [C3] and by one cohort study from a private infertility centre in Sweden (Brodin et al 2015) [C6].

The systematic review by Ribeiro et al (2014) [C3] reported in brief narrative form only that two studies reported that low FSH levels are associated with higher live birth rates and one of those studies reported that this was only the case for women aged >38 years, whereas a different study reported that AFC was not associated with live birth rate in patients undergoing IVF.

The retrospective cohort study by Brodin et al (2015) [C6] (n=892 consecutive women; 1,230 IVF/ICSI cycles) defined live birth rate as live births per started stimulation cycle (including cancelled cycles). The study assessed FSH in combination with LH and divided patients into 3 groups based on different combinations of high and low FSH and LH levels. Cut-off values for FSH and LH were defined as 6.7 U/l and 4.9 U/l respectively. Results suggested that this measure was not a good predictor of live birth rate (odds ratio (OR) 0.86, (95% confidence interval (CI) 0.64 to 1.16), p=0.33. For AFC, the study used log AFC. This was found have some predictive value for predicting live birth rates in IVF (OR for live birth 1.64 (95% CI 1.22 to 2.12), p value not reported, c statistic[10] 0.58. However, it was not as good a predictor as age (c statistic for age was 0.61).

In summary, results of the predictive value of FSH and AFC for live birth rates were mixed with some evidence that: AFC could be used as a predictor of live birth rates, although not a strong predictor; that FSH-LH groups defined by different combinations of high vs low FSH or LH are not useful as a predictor of live births; and that FSH levels are associated with live birth rates in women aged >38 years, although it is not clear if this translates to being useful as a predictor of live births. None of the included studies discussed the optimal cut-off values for FSH or AFC for the prediction of live births in IVF/ICSI.

Relative value of AFC and FSH in predicting low ovarian response to ovarian stimulation

Prediction of a low ovarian response to ovarian stimulation was reported in brief narrative form by two systematic reviews (Ribeiro et al 2014 [C3], Liu et al 2017[C4]) and by one systematic review and meta-analysis (Broer et al 2103 [C5). It was also reported by one retrospective cohort study from Sweden (Brodin et al 2015 [C6]) and two retrospective cohort studies from China (Dai et al 2014 and Wang et al 2021).

Ribeiro et al (2014) [C3] reported that five studies reported a negative association between FSH and number of oocytes retrieved, and cited one study as reporting that AFC was positively

[10] The c statistic is a measure of the discriminative capacity of the test to predict live birth. It is interpreted relative to 0.5 which is the equivalent of pure guessing.

correlated with the number of retrieved oocytes. Liu et al (2017) [C4] reported that both basal FSH levels and AFC have been shown to be useful for prediction of poor response to ovarian stimulation. Neither systematic review provided any further details.

Broer et al (2013) [C5], in a systematic review and meta-analysis (n=617 women), defined poor response as ≤4 oocytes at follicle aspiration or a cancelled cycle due to poor response. Their results suggested that AFC may be a better predictor of poor ovarian response than FSH (AFC: AUC 0.76 (95% CI 0.70 to 0.82), p<0.001; vs FSH: AUC 0.68 (95% CI 0.61 to 0.74), p=0.051).

Brodin et al (2015) [C6] reported from a retrospective cohort study of consecutive women from a private clinic in Sweden that AFC was a better predictor of poor ovarian response than FSH-LH groups defined by different combinations of high vs low FSH or LH (Log AFC: n=830, c statistic for poor response 0.85, p<0.0001; vs FSH-LH groups: n=942, c statistic for poor response 0.60, p<0.0001).

Dai et al (2014) [C7] reported from a retrospective cohort study in China that both FSH and AFC correlated with poor ovarian response, defined as ≤4 oocytes retrieved, in women <35 years of age and not in women aged ≥35 years (FSH: in <35 year olds p<0.001, correlation coefficient -0.279, AUC 0.752 vs in women aged ≥35 years p>0.05, correlation coefficient -0.199, AUC 0.619. AFC: in women aged <35 years p<0.05, correlation coefficient 0.179, AUC 0.661 vs in women aged ≥35 years p>0.05 correlation coefficient -0.126, AUC 0.574).

Wang et al (2021) [C8] reported results for prediction of poor ovarian response from a large retrospective cohort study from five centres in China (n=89,002) and reported that AFC (defined as the number of 2 to 10mm follicles in 2 ovaries) was a better single factor predictor than FSH (AFC: OR per extra follicle: 0.707 (95% CI 0.702 to 0.711), p<0.0001, AUC 0.842 (95% CI 0.838 to 0.846)
vs FSH: OR per IU/l: 1.258 (95% CI 1.250 to 1.266), p<0.0001, AUC 0.689 (95% CI 0.683 to 0.695)).

Wang et al (2021) [C8] also described the specificity and sensitivity for different cut-off values of AFC and FSH, noting that it was important to have a high specificity in order to minimise false positive determination of diminished ovarian reserve. Cut-off values that provided a specificity of around 90%, overall and for different age groups, were as follows:

AFC:
Overall cut-off: ≤5 (90.8% specificity, 55.9% sensitivity)

Cut-off including age group stratification:
<35 years: ≤6 (specificity 89.5%, sensitivity 53.8%)
35-38 years: ≤4 (specificity 92.5%, sensitivity 37.7%)
38-40 years: ≤3 (specificity 93.3%, sensitivity 31.9%)
>40 years: ≤3 (specificity 87.5%, sensitivity 46.5%)

FSH:
Overall cut-off: ≤9.8 mIU/ml (90.0% specificity, 38.4% sensitivity)

Cut-off including age group stratification:
<35 years: ≤9.62 (specificity 90.0%, sensitivity 35.4%)
35-38 years: ≤10.18 (specificity 90.0%, sensitivity 35.1%)
38-40 years: ≤10.49 (specificity 90.0%, sensitivity 36.2%)
>40 years: ≤11.51 (specificity 90.0%, sensitivity 32.0%)

In summary, from the studies included in this report, including one large study with over 80,000 women undergoing IVF, evidence suggests that AFC is a better predictor than FSH of ovarian response to ovarian stimulation in IVF. One study reported optimal cut-off values for FSH and AFC for the prediction of ovarian response to stimulation in IVF/ICSI, providing different cut-off values for different age groups that would result in high (around 90%) specificity.

Safety

No studies were identified relating to the safety of using different indicators or different thresholds for indicators below which response/effectiveness of IVF/ICSI is significantly lower.

Cost effectiveness

No studies were identified relating to the cost effectiveness of using different indicators or different thresholds for indicators below which response/effectiveness of IVF/ICSI is significantly lower.

Discussion and conclusions

The evidence review conducted for the 2013 NICE guideline, using evidence published up to 2011, concluded that neither AFC nor FSH were good predictors of pregnancy or live birth following IVF and that age together with AMH or AFC or FSH were useful as predictors of ovarian response to ovarian stimulation in IVF. Cut-off values suggested were ≤4 follicles of ≤5 mm on day 3 of the cycle for AFC and an FSH level of >8.9 IU/l. It was recommended that age should be used as the initial predictor, followed by either AFC or FSH or AMH.

The more recent evidence identified for this review, which selected studies published from 2013 onwards that best addressed the question of the relative value of AFC vs FSH as a predictor of IVF outcomes, particularly of pregnancy and live birth rates, found only a small amount of evidence and mixed results in relation to the value of using AFC or FSH to predict pregnancy rates and live birth rates (although there was some indication that AFC could be a weak predictor of live birth rates). The evidence suggested, however, that both AFC and FSH had value as predictors of low ovarian response to ovarian stimulation, with AFC being a better predictor than FSH.

These results are not surprising given that it has been suggested that both AFC and FSH are indicators of the number of follicles present, with AFC being a more direct measure of this. Hence it is not surprising that both AFC and FSH levels correlated with the number of oocytes retrieved, and that AFC was more closely correlated. However, pregnancy and live birth rates are dependent not only on the number, but also on the quality of the oocytes, and AFC and FSH are less likely to reflect oocyte quality, and hence they are less likely to be correlated with pregnancy and live birth rates. (Liu et al 2017, Broer et al 2013)

None of the included studies discussed the optimal cut-off values for FSH or AFC for the prediction of pregnancy or live births in IVF/ICSI. One study reported optimal cut-off values for FSH and AFC for the prediction of ovarian response to stimulation in IVF/ICSI, providing different cut-off values for different age groups that would result in high (around 90%) specificity.

No studies of safety or cost-effectiveness of the use of FSH or AFC as predictors of outcomes of IVF were identified.

Note that following this evidence review, at the second project workshop in July 2023, clinicians suggested that AMH would be a more useful test than AFC because AFC is operator dependent and many sonographers are not able to reliably measure AFC, and because the results depend on the timing with respect to the menstrual cycle and which follicle size cut-off is used. However, time and resource did not allow a further evidence review on the relative value of AMH vs AFC for predicting IVF outcomes to be carried out. A review of this evidence, together with a discussion of the other issues that were discussed at the scoping workshop, may be helpful in future. Issues discussed at the scoping workshop included the potentially higher cost of AMH measurements (in the region of £60 per test) compared to AFC (assuming negligible additional time and resource if carried out during routine ultrasound assessments), the feasibility of AFC being carried out during the routine ultrasound assessment for assisted conception, whether ultrasound assessments are currently being carried out consistently, and the inconsistency across East Midlands providers in machines and reference values used for AMH measurements.

D Obesity / BMI

Seven questions were considered relating to body mass index (BMI)

D1 What is the effectiveness of IVF/ICSI where the woman has a BMI ≥30 compared to BMI <30?

D2 What is the effectiveness of IVF/ICSI where the woman has a BMI ≤19 compared to BMI >19?

D3 What is the effectiveness of IVF/ICSI where the male partner has a BMI ≥30 compared to BMI <30?

D4 What is the effectiveness of IVF/ICSI where the male partner has a BMI ≤19 compared to BMI >19?

D5 What is the effectiveness of IUI where the woman has a BMI ≥30 compared to BMI <30?

D6 What is the effectiveness of IUI where the woman has a BMI ≤19 compared to BMI >19?

D7 What is the effectiveness of IUI where the male partner has a BMI ≥30 compared to BMI <30?

The international guidelines for Body Mass Index (BMI) are defined by the World Health Organisation (WHO), with the following definitions:

- Normal weight – BMI 18.5 kg/m^2 to 24.99 kg/m^2
- Underweight – BMI ≤18.5 kg/m^2
- Overweight – BMI 25 kg/m^2 to 29.99 kg/m^2
- Obese – BMI ≥ 30 kg/m^2

NICE Guideline

The 2013 NICE guideline (CG156; last updated September 2017) [D1] includes information on fertility concerns that relate to obesity (BMI ≥30) and low body weight (BMI <19) supported by varying levels of evidence.

The strongest evidence (level 1b[11]) suggested that women who have a BMI of 30 or over who are not ovulating should be informed that losing weight is likely to increase their chance of conception and that participating in a group programme involving exercise and dietary advice leads to more pregnancies than weight loss advice alone.

The guideline also states that men who have a BMI of over 30 are likely to have reduced fertility.

For women with a BMI of less than 19 and have irregular menstruation, or have ceased menstruating, increasing their body weight is likely to improve their chance of conception.

The NICE guideline recommends that:

[11] at least one randomised controlled trial

Women should be informed that female BMI should ideally be in the range 19 to 30 before commencing assisted reproduction, and that a female BMI outside this range is likely to reduce the success of assisted reproduction procedures.

The guideline does not recommend that BMI ≥30 should be an exclusion criteria for access to assisted reproduction treatment.

D1 What is the effectiveness of IVF/ICSI where the woman has a BMI ≥30 compared to a BMI <30?

Key studies found

We searched for new evidence published since January 2013. Three systematic reviews (Ribeiro et al 2022 [D2], Supramaniam et al 2018 [D3] and Tang et al 2021 [D4]) were identified that explored BMI and IVF/ICSI outcomes.

All three systematic reviews included meta analyses. None of the included reviews examined randomised controlled trials; all studies included were observational studies, primarily retrospective.

Effectiveness

All included reviews presented outcomes on pregnancy rate and rate of livebirths following IVF/ICSI; the data presented showed lower rates of pregnancy and livebirths for women with a BMI ≥30.

Ribeiro et al [D2] included 53 observational studies in their systematic review and meta-analysis. The data presented showed low certainty evidence of decreasing pregnancy (RR = 1.09, 95% CI 1.03 to 1.21, p-value not presented) and live birth rates (RR = 1.08, 95% CI 1.00 to 1.16, p-value not presented) in women with a BMI ≥30 when compared to women with a BMI <25. The lower rate of clinical pregnancy was statistically significant.

Supramaniam et al [D3] included 49 observational studies in their meta-analysis, reporting a statistically significant lower odds of pregnancy (OR = 0.80, 95% CI 0.74 to 0.87, p<0.001) and livebirth (OR = 0.81, 95% CI 0.79 to 0.82, p<0.001) per IVF/ICSI cycle in women with a BMI ≥30 compared to women with a BMI of 18.5 – 24.9.

Tang et al [D4] presented risk ratios per unit increase in BMI after reviewing 18 observational studies. The data presented showed that for each five-unit increase in a woman's BMI, the pregnancy rate following IVF was statistically significantly decreased by 5% (RR = 0.95, 05% CI 0.94 to 0.97, p<0.001) and the livebirth rate following IVF was statistically significantly decreased by 7% (RR = 0.93, 95% CI 0.92 to 0.95, p<0.001). The dose response was non-linear, particularly with the livebirth rate, which suggests a more rapidly decreasing livebirth rate in women with a BMI ≥30.

Safety

The evidence presented focused on the risk of miscarriage following IVF/ICSI. All three systematic reviews presented results showing statistically significantly higher risk of miscarriage for women with a BMI ≥30.

Ribeiro et al [D2] reported low certainty evidence showing a statistically significant difference in the rate of miscarriage when comparing women with a BMI ≥30 and those with a BMI <25 (RR = 1.21, 95% CI 1.02 to 1.44, p-value not presented).

Supramaniam et al [D3] reported a statistically significant higher odds of miscarriage in women with a BMI ≥30 compared to women with a BMI of 18.5 – 24.9 (OR = 1.52, 95% CI 1.28 to 1.81, p<0.001).

The risk of miscarriage following IVF was shown to increase 9% per five-unit increase in BMI in the meta-analysis conducted by Tang et al [D4]; this result was statistically significant (1.09, 95% CI 1.05 to 1.12, p<0.001). The results were non-linear with the highest risks in women with a BMI ≥35.

Cost effectiveness

Cost effectiveness studies were not identified in relation this question.

Discussion and conclusions

The evidence review conducted for the 2013 NICE guideline concluded that women who have a BMI ≥30 are likely to have reduced fertility. The current review found that for women with a BMI ≥30, IVF/ICSI was less likely to be effective. Likewise, the safety of IVF/ICSI (in terms of miscarriage rates) was lower in women with higher BMIs.

D2 What is the effectiveness of IVF/ICSI where the woman has a BMI ≤19 compared to BMI >19?

Key studies found

We searched for new evidence published since January 2013. Two systematic reviews (Tang et al 2021 [D4] and Xiong et al [D5]) were identified that explored BMI and IVF/ICSI outcomes.

Both systematic reviews included meta analyses. None of the included reviews examined randomised controlled trials; all studies included were observational studies, primarily retrospective.

Effectiveness

Xiong et al [D5] presented outcomes on pregnancy rate and rate of livebirths following IVF/ICSI in women with a BMI ≤18.5 compared to women with a BMI 18.5 – 24.99. The authors report that, when compared to women of a normal BMI, women who are underweight (BMI ≤18.5) at the time of IVF have a statistically significantly lower odds of achieving pregnancy (OR = 0.84, 95% CI 0.75 to 0.95, p-value not presented). There was no significant difference in the odds of livebirth in women with a BMI of ≤18.5 compared to women with a BMI 18.5 – 24.99 (OR = 0.97, 95% CI 0.87 to 1.09, p-value not presented).

Safety

The risk of miscarriage following IVF/ICSI were mixed across the two systematic reviews evaluated.

Tang et al [D4] reported that the lowest risk of miscarriage was for women with a BMI of 22-25. The data suggested that women with a BMI <22 and ≥25 had an increased risk of miscarriage; this was statistically significant (RR = 1.09, 95% CI 1.05 to 1.12, p<0.001).

Xiong et al [D5], on the other hand, reported no statistically significant difference in the odds of miscarriage in women with a BMI of ≤18.5 compared to women with a BMI 18.5 – 24.99 (OR = 1.00, 95% CI 0.93 to 1.07, p-value not presented).

Cost effectiveness

No studies were identified relating to the cost effectiveness of IVF/ICSI in women who have a BMI ≤19 compared to women with a BMI >19.

Further details are provided in Appendix 4.

Discussion and conclusions

The evidence review conducted for the 2013 NICE guideline concluded that for women with a BMI of less than 19 and have irregular menstruation, or have ceased menstruating, increasing their body weight is likely to improve their chance of conception. We found limited evidence showing decreased effectiveness of IVF/ICSI in women with a BMI of ≤18.5 compared to women with a BMI of 18.5 – 24.99. The safety of IVF/ICSI cannot be clearly defined, however, as the systematic reviews have conflicting results. No cost effectiveness data were identified in the literature.

D3 What is the effectiveness of IVF/ICSI where the male partner has a BMI ≥30 compared to BMI <30?

Key studies found

We searched for new evidence published since January 2013. One systematic review (Zhang et al 2022 [D6]) was identified that explored male partner BMI and IVF/ICSI outcomes.

The review included a meta-analysis. A total of 19 observational studies were examined; 6 prospective and 13 retrospective.

Effectiveness

Zhang et al [D6] presented outcomes on pregnancy rate and rate of livebirths following IVF/ICSI in the male partner with a BMI ≥30 compared to male partners with a BMI 18.5 – 24.99. The authors report low to very low certainty evidence that, when compared to men of a normal BMI, men who are obese (BMI ≥30) at the time of IVF have a no statistically significant difference in IVF/ICSI outcomes (pregnancy rate: OR = 1.09, 95% CI 0.87 to 1.36, p-value not presented; livebirth rate: OR = 0.94, 95% CI 0.81 to 1.09, p-value not presented). When combining all male partners with a high BMI (≥25) compared to those with a BMI <25, there was low to very low certainty evidence of statistically significant decreasing pregnancy (OR = 0.69, 95% CI 0.54 to 0.88, p-value not presented) and livebirth (OR = 0.76, 95% CI 0.69 to 0.83, p-value not presented) rates.

Safety

No studies were identified relating to safety of IVF/ICSI in male partners who have a BMI ≥30 compared to male partners with a BMI <30.

Cost effectiveness

No studies were identified relating to the cost effectiveness of IVF/ICSI in male partners who have a BMI ≥30 compared to male partners with a BMI <30.

Further details are provided in Appendix 4.

Discussion and conclusions

The evidence review conducted for the 2013 NICE guideline concluded that men with a BMI ≥30 may have reduced fertility. We found no statistically significant evidence of reduced clinical effectiveness of IVF/ICSI when the male partner has a BMI ≥30 compared to BMI <30. There is limited, low to very low certainty evidence of statistically significant decreasing pregnancy and livebirth rates when male partners were of high weight (BMI ≥25) compared to normal weight. No safety or cost effectiveness data were identified in the literature.

D4 What is the effectiveness of IVF/ICSI where the male partner has a BMI ≤19 compared to BMI >19?

Key studies found

We searched for new evidence published since January 2013. We did not identify any studies relating to the clinical effectiveness of IVF/ICSI where the male partner has a BMI ≤19 compared to >19.

Effectiveness

No studies were identified relating to the clinical effectiveness of IVF/ICSI where the male partner has a BMI ≤19 compared to >19.

Safety

No studies were identified relating to the safety of IVF/ICSI where the male partner has a BMI ≤19 compared to >19.

Cost effectiveness

No studies were identified relating to the cost effectiveness of IVF/ICSI where the male partner has a BMI ≤19 compared to >19.

Discussion and conclusions

We are unable to draw any conclusions about the use of IVF/ICSI where the male partner has a BMI ≤19 as no evidence was identified.

D5 What is the effectiveness of IUI where the woman has a BMI ≥30 compared to BMI <30?

Key studies found

We searched for new evidence published since January 2013. No systematic reviews were found that examined the clinical effectiveness of IUI where the woman has a BMI ≥30 compared to a woman with a BMI <30. One observational study was found, a prospective cohort study (Thijssen et al 2017 [D7]), that examined at IUI outcomes against a number a patient demographic and procedure characteristics.

A retrospective cohort study (Zheng et al 2022 [D8]), of one hospital in China, presented IUI outcomes for a subgroup of interest: women with a BMI 25 – 29.99.

Effectiveness

Thijssen et al [D7] reported outcomes for 556 women undergoing IUI in Belgium. In univariate analysis, women with a BMI ≥30 had a lower pregnancy rate than those in the other BMI groups; this outcome was statistically significant (pregnancy rate ± SE – BMI <20: 0.065 ± 0.016, BMI 20-24.99: 0.080 ± 0.010, BMI 25-29.99: 0.163 ± 0.023, BMI: ≥30: 0.094 ± 0.024; p=0.0319). After adjusting for age, basal follicle stimulating hormone, basal luteinizing hormone, basal antral follicle count, a diagnosis of polycystic ovarian syndrome, a diagnosis of endometriosis, unilateral tubal obstruction, parity, duration of infertility (years) and post wash total motile sperm count, maternal BMI was no longer statistically significant.

Zheng et al [D8] reported outcomes for 6,407 couples undergoing IUI. Women in the overweight subgroup (BMI 25 – 29.99) were more likely to be older and had a statistically significantly longer infertility duration when compared to women that were underweight (BMI ≤18.5). Zheng et al reported a statistically significantly increased cumulative pregnancy and livebirth rates in multivariate analysis in women that were overweight compared to women that had a BMI of 18.5 –

24.9 (pregnancy rate: HR = 1.19, 95% CI 1.04 to 1.36, p-value not reported; livebirth rate: HR = 1.19, 95% CI 1.02 to 1.38, p-value not reported).

Safety

No studies were identified relating to the safety of IUI in women who have a BMI ≥30 compared to women with a BMI <30.

Cost effectiveness

No studies were identified relating to the cost effectiveness of IUI in women who have a BMI ≥30 compared to women with a BMI <30.

Further details are provided in Appendix 4.

Discussion and conclusions

The evidence review conducted for the 2013 NICE guideline concluded that women who have a BMI ≥30 are likely to have reduced fertility. We found limited evidence regarding effectiveness of IUI in women with a BMI ≥30. One cohort study found no statistically significant difference in the pregnancy rate on multivariate analysis. A study looking at overweight (BMI 25 – 29.99) rather than obese (BMI ≥30) women, found that this subgroup had statistically significantly higher pregnancy and livebirth rates than women with a normal BMI.

No recent evidence was found for safety or cost effectiveness for women with a BMI ≥30 having IUI.

D6 What is the effectiveness of IUI where the woman has a BMI ≤19 compared to BMI >19?

Key studies found

We searched for new evidence published since January 2013. No systematic reviews were found that examined the clinical effectiveness of IUI where the woman has a BMI ≤19 compared to a woman with a BMI >19. One retrospective cohort study (Zheng et al 2022 [D8]), of a single hospital site in China, presented IUI outcomes for a women with a BMI ≤18.5 compared to women with a BMI of 18.5 to 24.99.

Effectiveness

Zheng et al [D8] reported outcomes for 6,407 couples undergoing IUI. Women who had a BMI ≤18.5 were more likely to be younger and have a diagnosis of endometriosis when compared to women in the normal weight group (BMI 18.5 – 24.9). Zheng et al reported statistically significantly decreased cumulative pregnancy (HR = 0.85, 95% CI 0.73 to 0.98, p-value not reported) and livebirth (HR = 0.80, 95% CI 0.67 to 0.95, p-value not reported) rates in multivariate analysis in women that had a BMI of ≤18.5 compared to women that had a BMI of 18.5 – 24.9 (reference group).

Safety

No studies were identified relating to the safety of IUI in women who have a BMI ≤18.5 compared to women with a BMI >18.5.

Cost effectiveness

No studies were identified relating to the cost effectiveness of IUI in women who have a BMI ≤18.5 compared to women with a BMI >18.5.

Further details are provided in Appendix 4.

Discussion and conclusions

The evidence review conducted for the 2013 NICE guideline concluded that for women with a BMI of less than 19 and have irregular menstruation, or have ceased menstruating, increasing their body weight is likely to improve their chance of conception. We found limited evidence regarding effectiveness of IUI in women with a BMI ≤18.5. One cohort study that women with a BMI ≤18.5 had statistically significantly lower pregnancy and livebirth rates following IUI than women with a normal BMI.

No recent evidence was found for safety or cost effectiveness for women with a BMI ≤18.5 having IUI.

D7 What is the effectiveness of IUI where the male partner has a BMI ≥30 compared to BMI <30?

Key studies found

We searched for new evidence published since January 2013. No systematic reviews were found that examined the clinical effectiveness of IUI where the male partner has a BMI ≥30 compared to a male partner with a BMI <30. One observational study was found, a prospective cohort study (Thijssen et al 2017 [D7]), that examined at IUI outcomes against a number a patient demographic and procedure characteristics.

Effectiveness

Thijssen et al [D7] reported outcomes for 556 women and their partners undergoing IUI in Belgium. Paternal BMI was not found to be statistically significant in univariate or multivariate analyses (pregnancy rate ± SE – BMI <20: 0.100 ± 0.056, BMI 20-24.99: 0.092 ± 0.012, BMI 25-29.99: 0.091 ± 0.012, BMI ≥30: 0.123 ± 0.027; p-value reported as not significant). Multivariate analyses corrected for age (patient and partner), smoking (patient and partner), IUI procedure characteristics and sperm characteristics.

Safety

No studies were identified relating to safety of IUI in male partners who have a BMI ≥30 compared to male partners with a BMI <30.

Cost effectiveness

No studies were identified relating to the cost effectiveness of IUI in male partners who have a BMI ≥30 compared to male partners with a BMI <30.

Further details are provided in Appendix 4.

Discussion and conclusions

The evidence review conducted for the 2013 NICE guideline concluded that men with a BMI ≥30 may have reduced fertility. We found no statistically significant evidence of reduced clinical effectiveness of IUI when the male partner has a BMI ≥30 compared to BMI <30. No safety or cost effectiveness data for IUI in male partners who have a BMI ≥30 compared to male partners with a BMI <30 were identified in the literature.

E Betel nut and chewing tobacco

Four questions relating to betel nut use and chewing tobacco were reviewed.

E1 What is the clinical effectiveness evidence that betel nut use adversely affects the success of IVF?

E2 What is the clinical effectiveness that chewing tobacco adversely affects the success of IVF?

E3 What is the clinical effectiveness evidence that betel nut use adversely affects the success of IVF?

E4 What is the clinical effectiveness evidence that chewing tobacco use adversely affects the success of IUI?

NICE Guideline

The 2013 NICE guideline (CG156; last revised September 2017) [E1] does not include any specific reference to either chewing tobacco or betel nut use.

There are clear Department of Health guidelines in relation to tobacco smoking in general, and evidence that smoking reduces fertility in both men and women. The NICE guideline recommends that women who smoke should be offered referral to a smoking cessation programme to support their efforts in stopping smoking.

E1 What is the clinical effectiveness evidence that betel nut use adversely affects the success of IVF?

Key studies found

We searched for new evidence published since January 2013. We did not identify any studies relating to betel nut use in IVF.

Effectiveness

No studies were identified relating to the effectiveness of betel nut use in IVF.

Safety

No studies were identified relating to the safety of betel nut use in IVF.

Cost effectiveness

No studies were identified relating to the cost effectiveness of betel nut use and/or betel nut cessation interventions in IVF.

Discussion and conclusions

We are unable to draw any conclusions about the use of betel nuts during IVF treatment as no evidence was identified.

E2 What is the clinical effectiveness that chewing tobacco adversely affects the success of IVF?

Key studies found

We searched for new evidence published since January 2013. We did not identify any systematic reviews relating to the use of chewing tobacco in IVF. We did not identify any studies that

specifically focused on pregnancy rates, live birth rates or adverse events in women or men using chewing tobacco and having IVF treatment.

The most relevant study identified reported embryo quality at day three and day five from 105 women and their partners in India, of which 16 of the male partners used chewing tobacco (Kumari et al) [E2]. A second study (Parn et al) [E3] included 62 men recruited for a physical activity intervention before beginning IVF due to male infertility.

Effectiveness

Kumary et al (2023) [E2] included 105 women and their partners in their retrospective cohort study; 16 of the male partners used chewing tobacco. The authors reported statistically significantly lower quality embryos at day three and day five of development compared to those that did not use chewing tobacco. The authors did not report on pregnancy rate.

Parn et al (2015) [E3] included 62 men in their physical activity intervention. At baseline, 28% of the men reported using “snuff” or chewing tobacco. Snuff use was statistically significantly negatively correlated with sperm concentration, sperm numbers, motile concentration, total motile sperm and total sperm motility. The effect on sperm volume was not statistically significant. The authors did not report any data on the female partners or pregnancy rate.

Further details of these studies are provided in Appendix 4.

Safety

No studies were identified relating to the safety of chewing tobacco use in IVF.

Cost effectiveness

No studies were identified relating to the cost effectiveness of chewing tobacco use and/or chewing tobacco cessation interventions in IVF.

Discussion and conclusions

The NICE guideline did not cite any published evidence relating to chewing tobacco use during IVF. We found limited recent evidence reporting outcomes by chewing tobacco use in IVF treatment; no studies were found for chewing tobacco use in the female partner. The two studies identified reported lower quality sperm and embryos in men that used chewing tobacco. No data on pregnancy rates or live births was reported.

E3 What is the clinical effectiveness evidence that betel nut use adversely affects the success of IUI?

Key studies found

We searched for new evidence published since January 2013. We did not identify any studies relating to betel nut use in IUI.

Effectiveness

No studies were identified relating to the effectiveness of betel nut use in IUI.

Safety

No studies were identified relating to the safety of betel nut use in IUI.

Cost effectiveness

No studies were identified relating to the cost effectiveness of betel nut use and/or betel nut cessation interventions in IUI.

Discussion and conclusions

We are unable to draw any conclusions about the use of betel nuts during IUI treatment as no evidence was identified.

E4 What is the clinical effectiveness evidence that chewing tobacco use adversely affects the success of IUI?

Key studies found

We searched for new evidence published since January 2013. We did not identify any studies relating to chewing tobacco use in IUI.

Effectiveness

No studies were identified relating to the effectiveness of chewing tobacco use in IUI.

Safety

No studies were identified relating to the safety of chewing tobacco use in IUI.

Cost effectiveness

No studies were identified relating to the cost effectiveness of chewing tobacco use and/or chewing tobacco cessation interventions in IUI.

Discussion and conclusions

We are unable to draw any conclusions about the use of chewing tobacco during IUI treatment as no evidence was identified.

F Indications for IUI

One question was considered relating to the effectiveness of IUI compared with IVF.

What is the effectiveness of IUI compared to IVF for women with unexplained infertility, mild endometriosis or mild male factor infertility?

We conducted searches for the different elements of this rapid evidence review on Medline, Embase and the Cochrane Library since January 2013, limited to English language. The searches for the different topics were carried out between the 1st and 7th of June 2023. The Medline search strategy is provided in Appendix 3.

For each evidence review question, we selected the most reliable and relevant studies available using standard hierarchy of evidence selection criteria.

Mild male factor infertility is defined by NICE as when 2 or more semen analyses have 1 or more variables below the 5th centile (as defined by the World Health Organization, 2010).

Unexplained infertility is defined as when there is no identified male or female cause.

The NICE guidelines on infertility and on endometriosis do not include a definition of mild endometriosis.

IUI may be ‘stimulated’, i.e. combined with ovarian stimulation (OS) using for example gonadotrophins (follicle-stimulating hormone or hMG) or Clomiphene Citrate, or ‘unstimulated’, i.e. carried out during ‘natural’ cycles without OS. OS is also used in IVF. In both IUI and IVF it

increases the chances of ovulation but may increase the risk of multiple pregnancy and may rarely be associated with Ovarian Hyperstimulation Syndrome (OHSS).

NICE guideline

The NICE infertility guideline [F1] makes the following recommendations:

1.8.1.4 Offer IVF treatment…to women with unexplained infertility who have not conceived after 2 years (this can include up to 1 year before their fertility investigations) of regular unprotected sexual intercourse

1.9.1.3 For people with unexplained infertility, mild endometriosis or mild male factor infertility, who are having regular unprotected sexual intercourse, do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF)

The evidence review for the NICE guideline included consideration of the following question:

- What is the effectiveness of intrauterine insemination (IUI) in people with unexplained infertility, mild endometriosis or 'mild' male factor infertility?

This only included comparisons of IUI with expectant management and of unstimulated vs stimulated IUI. There was no review of evidence comparing IUI with IVF.

Regarding IVF, the NICE guideline recommends that no more than 2 embryos should be transferred in any cycle. For women aged under 37 years, the first full IVF cycle should use single embryo transfer (SET), and double embryo transfer (DET) may be considered in the second and third cycles. For women aged 37 to 39 years, DET may be considered in all cycles if there are no top quality embryos, and for women aged 40 to 42 years, DET should be considered in all cycles (recommendation 1.12.6.5).
Cryopreservation should be offered to store any remaining good-quality embryos after embryo transfer (recommendation 1.12.6.10). A full cycle of IVF treatment, with or without ICSI, should comprise 1 episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s).

Human Fertilisation and Embryology (HFEA) Code of Practice

The HFEA Code of Practice 9th Edition (last revised October 2021) [F2] does not discuss the effectiveness if IUI compared with IVF.

Current policy relating to when IUI might be offered for unexplained infertility, mild endometriosis or mild male factor infertility in East Midlands ICSs

The policies for Bassetlaw CCG (now part of Nottingham and Nottinghamshire ICS), Derbyshire and the Armed Forces are in line with NICE guidance, stating that IUI or donor insemination are not funded but exceptional circumstances may include social, cultural or religious objections to IVF. The policies for Nottinghamshire and Lincolnshire do not mention IUI for these indications.

The current policy in Leicester, Leicestershire and Rutland states that up to three stimulated IUI cycles may be offered if there is minimal/mild endometriosis and laparoscopic surgical treatment has been tried. Northampton offers one cycle for fully investigated infertility or unexplained subfertility considered amenable to IUI, if the couple have not conceived after two years of regular sexual intercourse, there is no previous IUI or IVF in this relationship, no history of tubal surgery or evidence of tubal damage, and neither partner has a history of sterilisation.

In view of the variation in policies it was agreed to compare outcomes for IVF and IUI for couples with these indications.

Key studies found

The PICO framework developed for the review of evidence in relation to this question is provided in Appendix 2.

We searched for new evidence published since January 2013. We searched for studies comparing outcomes for IVF and IUI, and prioritised the larger studies and those most relevant to the population of interest. We excluded studies which were included in the SRs, unless they also reported additional relevant outcomes which were not included in the SRs. We found seven key relevant studies for inclusion; four systematic reviews, two RCTs and one database study.

Four systematic reviews (SRs) compared birth rate and pregnancy rate outcomes for IUI and IVF. Three of the SRs [F3, F4, F5] included a majority of couples with unexplained infertility; all three also included some couples with mild endometriosis and one SR [F3] also included some couples with mild male factor infertility. The fourth SR [F6] included couples with mild male factor infertility only. Differences in search dates and inclusion criteria meant that each SR included different combinations of RCTs although most of the RCTs were included in more than one SR. Some included RCTs compared equal numbers of cycles of IVF and IUI, while others compared more than one cycle of IUI with one cycle of IVF. Information was included on some but all of the RCTs as to whether they used SET or a maximum of DET.

Two RCTs compared pregnancy and/or birth outcomes and cost/ cost-effectiveness outcomes for stimulated IUI and IVF in couples with unexplained or mild male factor infertility in Holland [F7, F8]. Van Rumste et al (2014) reported short-term findings from a multicentre RCT, while Tjon-Kon-Fat et al (2015) reported longer-term findings from a larger multicentre RCT.

One study reported a retrospective analysis of five years' data from the HFEA database, including couples with all types of infertility [F9].

Key findings/results

Unexplained infertility

Effectiveness and safety

Pandian et al (2015) [F3] included two RCTs comparing IVF with unstimulated IUI and found no conclusive evidence of a difference in pregnancy rates between IVF and unstimulated IUI, but that IVF may result in more live births than unstimulated IUI. They included five RCTs comparing IVF with stimulated IUI and found no conclusive evidence of a difference in live birth rates between IVF and stimulated IUI. They also reported that there was no evidence of a difference in multiple birth rates between IVF and stimulated IUI. This SR followed the Cochrane methodology and the certainty of the evidence for these outcomes was graded between moderate and very low.

Wang et al (2019) [F4] included three RCTs comparing IVF with stimulated IUI, and found no conclusive evidence of a difference in clinical pregnancy rates or live birth rates between IVF and stimulated IUI. They also reported that there was no evidence of a difference in multiple birth rates between the two groups. The SR followed the Cochrane methodology and the certainty of the evidence for these outcomes was graded low.

Nandi et al (2022) [F5] included a total of eight studies comparing IVF with stimulated IUI. They found that IVF may result in more clinical pregnancies and more live births than stimulated IUI (although the 95% confidence intervals for both findings only just reached statistical significance). They also reported no significant difference in multiple pregnancy rates between the two groups. The SR appeared to be well-conducted and the certainty of the evidence for these outcomes was graded low.

Tjon-Kon-Fat et al (2015) [F8] randomised 602 couples with unexplained or mild male factor subfertility to three cycles of IVF with SET plus cryocycles, six cycles of IVF in modified natural

cycles (MNC), or six cycles of stimulated IUI. They found no conclusive evidence of a difference in live birth rates, rates of birth of a healthy child or ongoing pregnancies between stimulated IUI and either method of IVF.

Cost/ cost-effectiveness

Van Rumste et al (2014) [F7] randomised 116 couples with unexplained or mild male factor infertility to either one cycle of IVF-SET followed by one cryocycle or three cycles of stimulated IUI. They found similar numbers of ongoing pregnancies in both groups at 12 weeks but no measures of statistical significance were reported. Costs were compared using Dutch healthcare costs for 2010. They found that the mean cost of treatment per couple, and the mean cost per ongoing pregnancy were both statistically significantly lower for stimulated IUI compared with IVF. However the short follow-up and limited cost analysis limit the usefulness of this study.

Tjon-Kon-Fat et al (2015) [F8] also conducted a cost analysis, including healthcare costs up to 12 months after randomisation, using Dutch healthcare costs for 2013. They reported that the mean cost per couple was significantly lower for stimulated IUI than for either method of IVF. Stimulated IUI was reported to be more cost-effective than IVF with SET with an estimated ICER of €43,375. Compared with IVF in MNC, stimulated IUI was the dominant strategy being both more effective and less costly. The authors also reported a cost-effectiveness estimate using UK hospital costs inputted into the same model. This produced estimated costs of IVF-SET of €10,100 and stimulated IUI of €6174, with an ICER for IVF with SET vs stimulated IUI of €80,429.

Mild endometriosis

No studies were identified which compared outcomes for IUI and IVF in patients with mild endometriosis only.

Mild male factor infertility

Effectiveness and safety

Cissen et al (2016) [F6] included two RCTs reporting outcomes for couples with mild male factor subfertility; both compared IVF with stimulated IUI and one also compared IVF with unstimulated IUI. Both studies included a larger number of couples with subfertility, a minority of whom had male factor subfertility: the results reported in the SR are for the couples with mild male factor subfertility only. They reported no conclusive evidence of a difference in pregnancy rates between IVF and IUI with ovarian stimulation, and no conclusive evidence of a difference in live birth rates between IVF and IUI with or without ovarian stimulation. Multiple pregnancy rates were not reported. The SR followed the Cochrane methodology and the certainty of the evidence for these outcomes was graded low or very low.

All causes of infertility

Cost/cost-effectiveness

Bahadur et al (2020) [F9] carried out a retrospective analysis of data from the UK HFEA database. This included 319,105 IVF/ICSI and 30,669 IUI cycles performed between 2012 and 2016. Many details were not available including cause of subfertility, age of patient, and details of procedures, and the database reported number of cycles rather than number of patients. Specific causes of infertility and specific procedures therefore could not be linked to outcomes. Live birth rates for a single cycle of IVF were reported to be more than double the rates for a single cycle of IUI. Multiple pregnancy rates were reported to be significantly higher for IVF than for IUI.

Costs were estimated using a previously developed model, and a cost-effectiveness analysis was modelled on the 2016 national mean IVF and IUI success rates, with allowance for clinics with variable success rates. Mean 2016 IVF tariffs and common tariffs for IUI treatment cycles were used. The authors reported that the overall maternal and neonatal cost of one baby over the period

2012-2016 was higher for IVF than IUI (statistical significance not reported). They also reported that IVF activity in 2016 was approximately 17 times that of IUI activity, while the maternal and neonatal costs resulting from IVF were approximately 39 times those resulting from IUI. This was largely due to the higher rates of multiple pregnancies resulting from IVF. The study reported that IUI was more cost-effective than IVF in terms of cost for one live birth using varying estimates for success rates of IVF and IUI and varying estimates for IVF and IUI tariffs.

Although this study used a very large dataset, the limited details available about the patients and procedures included limit its usefulness for a direct comparison of IVF vs IUI.

Table 11: Summary of findings where statistical significance was reported

	Pregnancy rate	Live birth rate	Cost outcomes	Cost-effectiveness
Unexplained infertility				
Pandian 2015 (SR) [F3]	IVF vs UnIUI: NSD	IVF vs UnIUI: IVF better IVF vs SIUI: NSD		
Wang 2019 (SR) [F4]	IVF vs SIUI: NSD	IVF vs SIUI: NSD		
Nandi 2022 (SR) [F5]	IVF vs SIUI: IVF better	IVF vs SIUI: IVF better		
Van Rumste 2014 (RCT) [F7]			Mean cost per couple IVF vs SIUI: SIUI lower Mean cost per ongoing pregnancy IVF vs SIUI: SIUI lower	
Tjon-Kon-Fat 2015 (RCT) [F8]	IVF vs SIUI: NSD	IVF vs SIUI: NSD	Mean cost per couple IVF vs SIUI: SIUI lower	IVF-SET vs SIUI: SIUI more cost-effective
Mild male factor infertility				
Cissen 2016 (SR) [F6]	IVF vs SIUI: NSD	IVF vs UnIUI: NSD IVF vs SIUI: NSD		
All causes of infertility				
Bahadur 2020 (database analysis) [F9]				IVF vs IUI: IUI more cost-effective

Abbreviations

IVF-SET: IVF with single embryo transfer; NSD: no significant difference; RCT: randomised controlled trial; SIUI: stimulated IUI; SR: systematic review; UnIUI: unstimulated IUI

Discussion and conclusions

The NICE infertility guideline recommends IVF for women with unexplained infertility, and states that IUI should not be routinely offered to people with unexplained infertility, mild endometriosis or mild male factor infertility. The evidence review for the guideline did not include consideration of comparisons of IUI with IVF.

This review identified seven key studies relevant to this question; four systematic reviews, two RCTs and one database study. The systematic reviews included different combinations of RCTs due to differences in search dates and inclusion criteria, although most of the RCTs were included in more than one systematic review. The RCTs compared varying numbers of cycles of IVF and IUI; some compared equal numbers of cycles, while others compared more than one cycle of IUI with one cycle of IVF. Some studies included comparisons of both stimulated and unstimulated IUI. The IVF regimes also varied, for example some studies included only SET while others included a maximum of DET. It is therefore important to note that when the results of different studies are being compared, they are not always comparing like with like. Further details are provided in Appendix 4 (summary of studies).

Two systematic reviews [F3, F4] and one RCT [F8] which compared pregnancy and birth outcomes of stimulated IUI and IVF in unexplained infertility found there was no statistically significant difference in outcomes between the two; a third systematic review [F5] found that outcomes with IVF were better (although these findings only just reached the level of statistical significance). One systematic review [F3] found that live birth rates were significantly better in IVF than in unstimulated IUI, but pregnancy rates were not significantly different between the two. All three systematic reviews and the RCT found no evidence of a difference in multiple pregnancy rates or OHSS rates between stimulated IUI and IVF.

One systematic review which considered outcomes in mild male factor infertility [F6] found there was no statistically significant difference in pregnancy rates or live birth rates between stimulated IUI and IVF, and no significant difference in live birth rates between unstimulated IUI and IVF.

No studies were identified which compared outcomes for IUI and IVF in patients with mild endometriosis only.

Two RCTs considered cost outcomes of stimulated IUI compared with IVF in unexplained infertility. The larger multicentre RCT reported that mean costs per couple for stimulated IUI were significantly lower than for IVF using SET, and that stimulated IUI was more cost-effective [F8]. A smaller multicentre RCT reported that mean costs per couple and mean costs per ongoing pregnancy were lower for stimulated IUI than IVF, but did not report cost-effectiveness [F7].

An analysis of data from the HFEA database for 2012-2016 [F9] found that live birth rates and multiple pregnancy rates were both statistically significantly higher with IVF than with IUI. They also assessed costs and cost-effectiveness of IUI and IVF, and found that IUI was more cost-effective when a range of different estimates for success rates and costs of both procedures were used. Although this was a very large database including data on 319,105 IVF cycles and 30,669 IUI cycles, the lack of details such as cause of subfertility, number of patients rather than number of cycles, and details of the procedures carried out limit its usefulness for a direct comparison of IVF and IUI.

G Sterilisation and reversal (IVF)

Four questions were considered relating to sterilisation and reversal.

G1 What is the effectiveness of a cycle of IVF when the woman undergoing IVF has had a successful reversal of a sterilisation procedure versus in a woman who has never had a sterilisation procedure?

G2 What is the effectiveness of a cycle of IUI when the woman undergoing IUI has had a successful reversal of a sterilisation procedure versus in a woman who has never had a sterilisation procedure?

G3 What is the effectiveness of a cycle of IVF when the male partner in the couple has had a reversal of a vasectomy versus when the male partner in the couple has never had a vasectomy?

G4 What is the effectiveness of a cycle of IUI when the male partner in the couple has had a reversal of a vasectomy versus when the male partner in the couple has never had a vasectomy?

For each of the questions, the indication of interest was patients with infertility. Although the questions specify that the populations of interest are men and women who have had a successful reversal of a sterilisation procedure, it is possible for assisted reproduction techniques to be used in men and women who have had a sterilisation procedure without reversal. Evidence relating to patients who have sought to have a child after a sterilisation procedure, with or without reversal, was therefore considered to be within the scope of these questions.

The studies identified did not make a clear distinction between whether the assisted reproductive technology was IVF or IUI. Therefore outcomes relating to the effectiveness of IVF and IUI after sterilisation are discussed together for women and men respectively.

NICE Guideline

The 2013 NICE guideline (CG156) [G1] does not include any recommendations relating to sterilisation and reversal.

Human Fertilisation and Embryology (HFEA) Code of Practice

The HFEA Code of Practice 9th Edition (last revised October 2021) [G2] does not include any statements relating to sterilisation and reversal.

G1/2 What is the effectiveness of a cycle of IVF/IUI when the woman undergoing IVF/IUI has had a successful reversal of a sterilisation procedure versus in a woman who has never had a sterilisation procedure?

Key studies found

We searched for new evidence published since January 2013. One systematic review and two retrospective cohort studies were identified with relevance to this question:

- A systematic review by van Seeters et al (2017) [G3] included 37 non-randomised comparative or non-comparative studies about women who had been sterilised and then had reversal surgery and also included three retrospective cohort studies comparing women who had been sterilised with reversal and women who had been sterilised and then had IVF (without reversal).

- Chua et al (2020) [G4] reported outcomes for women who had been sterilised and then either had surgical reversal and attempted natural pregnancy or had IVF without surgical reversal

- Libby et al (2021) [G5] reported outcomes for women who had been sterilised and then received IVF/ICSI without sterilisation reversal. Outcomes were contrasted to those of women who received IVF/ICSI for infertility.

No studies considered outcomes for IVF after reversal of a sterilisation procedure. No studies reported outcomes for IUI.

Effectiveness

Van Seeters et al (2017) [G3] reported delivery rates for women who had been sterilised and then had reversal surgery and attempted natural conception. There was no statistically significant difference between the different surgical techniques with pooled delivery rates ranging from 42% to 68%. van Seeters et al (2017) also provided descriptive outcomes from studies comparing women who had been sterilised with reversal and women who had been sterilised and then had IVF (without reversal). Overall, the data favoured sterilisation reversal over IVF without reversal. However, there was some possibility of better outcomes with IVF, rather than reversal, for older women in one study. However, these outcomes are based on limited information.

Chua et al (2020) [G4] included 43 women aged <40 years who had been sterilised and then either had surgical reversal and attempted natural pregnancy (n=12) or had IVF without surgical reversal (n=31). Live birth rates were statistically significantly higher after surgical reversal (58%) than after IVF (26%). The 31 women receiving IVF underwent a total of 39 cycles.

Libby et al (2021) [G5] included 8,478 women (10,74 cycles) receiving IVF/ICSI after prior sterilisation, without reversal and without any other indication for IVF/ICSI. Outcomes for 371,488 women (555,124 cycles) who received IVF/ICSI for infertility were also included. Live birth rates were similar in the two groups (35.6% and 36.9% respectively).

Further details of these studies are provided in Appendix 4.

Safety

The systematic review by van Seeters et al (2017) [G3] reported ectopic pregnancy rate for women who had been sterilised and then had reversal surgery by different surgery type. Pooled rates ranged from 5.6% to 22%. One of the studies included in the review reported an ectopic pregnancy rate of 33% after reversal surgery and 2% after IVF, but did not report a statistical comparison.

Chua et al (2020) [G4] reported higher miscarriage and clinically important ovarian hyperstimulation syndrome with sterilisation and IVF and a higher ectopic pregnancy rate with sterilisation and reversal. However, overall numbers were low and the groups were not statistically compared.

Libby et al (2021) [G5] concluded that fertile couples with a history or sterilisation did not have significantly different perinatal outcomes compared to infertile couples.

Cost effectiveness

Messinger et al (2015) [G6] modelled the cost per pregnancy for women who had been sterilised and then had reversal surgery and attempted natural conception and women who had been sterilised and then had IVF without reversal. The authors reported that sterilisation reversal was more cost effective than IVF for women aged <35 years old and aged 35 to 40 years. However,

IVF was the most cost-effective option for women aged >40 years old. The IVF scenario included a single fresh cycle with the possibility of a single frozen thaw cycle if required.

Further details of this study are provided in Appendix 4.

Discussion and conclusions

The 2013 NICE guideline does not include any recommendations relating to sterilisation and reversal. We found four studies with relevance to this question, three on effectiveness and one on cost effectiveness. There was limited information that is directly relevant to the research question and no studies addressed a scenario comparing IVF/IUI outcomes for women who had had sterilisation and reversal compared to women who had never had a sterilisation procedure. The systematic review reported pooled delivery rates ranging from 42% to 68% for women who had had sterilisation reversal with different types of surgery and then attempted natural conception. The review and an additional study contrasted outcomes for women who had been sterilised and then either had surgical reversal and attempted natural conception or had IVF without reversal. Results generally favoured reversal over IVF without reversal, although with the possibility that IVF might have better results for older women. A third study contrasted outcomes for women who had had sterilisation and IVF/ICSI without reversal and women undergoing IVF for infertility. Outcomes were similar between the two groups. None of the studies were restricted to outcomes reported after a first round of IVF/ICSI and no studies reported any outcomes following IUI.

The study on cost effectiveness concluded that sterilisation reversal was the most cost effective option for younger women with IVF without reversal the most cost-effective option for women aged >40 years old.

G3/4 What is the effectiveness of a cycle of IVF/IUI when the male partner in the couple has had a reversal of a vasectomy versus when the male partner in the couple has never had a vasectomy?

Key studies found

We searched for new evidence published since January 2013. Three retrospective cohort studies were identified with relevance to this question:

- Lopes et al (2020) [G7] reported outcomes for men who had received a vasectomy and then underwent a first cycle of IVF/ICSI, either without reversal or following failed reversal. In this study, results were contrasted with men who received a first cycle of IVF/ICSI due to congenital obstruction.
- Uvin et al (2018) [G8] included men who had had a vasectomy and then either had a reversal and attempted natural pregnancy with or without later switching to IUI/IVF/ICSI, or received surgical sperm retrieval and IVF/ICSI without vasectomy reversal.
- Kapadia et al (2018) [G9] reported outcomes for men who had had a vasectomy and reversal and contrasted these to national IVF outcomes.

Effectiveness

Lopes et al (2020) [G7] reported outcomes for 621 men receiving a first cycle of IVF/ICSI. There were no statistically significant differences in fertilisation, pregnancy or live birth rates between men who had previously had a vasectomy (n=576) and men with congenital obstruction (n=45). The differences remained non-significant after adjustment for male and female age at IVF/ICSI. Some men who had received a vasectomy had undergone a failed reversal procedure (proportion not stated). Other men had refused a reversal procedure. No patients were reported as receiving IUI. Live birth rates were 18% and 30% respectively for men after vasectomy and with congenital obstruction.

Uvin et al (2018) [G8] reported outcomes for 163 men who had received a past vasectomy. Some men (n=64) had immediate surgical sperm retrieval and IVF/ICSI, achieving a crude cumulative delivery rate of 44% after a mean of 2.4 cycles. Some men (n=54) had a reversal and then later also had IUI (n=4) or IVF/ICSI (n=50). These men had a crude cumulative delivery rate of 57% after a mean of 2.5 cycles. The authors reported no statistically significant differences in cumulative delivery rate between patients who had immediate surgical sperm retrieval and IVF/ICSI and patients who had reversal and then switched to IUI/IVF/ICSI. The remaining men (n=45) had a reversal and attempted natural pregnancy only. These men had a crude cumulative delivery rate of 40%.

Kapadia et al (2018) [G9] reported outcomes for 136 men who had a vasectomy reversal and contrasted these with national IVF outcomes in the US with results broken down by age groups. Of the 47 pregnancies achieved, 42 were natural pregnancies and five were following IUI. The live birth rate was 30.1% overall but decreased with the age of the female. Outcomes were not reported separately for natural and IUI births. It is not clear how many couples received IUI in total.

Further details of these studies are provided in Appendix 4.

Safety

Uvin et al (2018) [G8] reported miscarriage rates for 64 men who had immediate surgical sperm retrieval and IVF/ICSI (23%), 54 men who had a reversal and then later also had IUI/IVF/ICSI (19%) and 45 men who had reversal only (7%). No other safety outcomes were reported.

Cost effectiveness

Cheng et al (2021) [G10] modelled fertility options for men who had undergone vasectomy and had a female partner of advanced maternal age (<35), including vasectomy reversal, sperm retrieval with IVF/ICSI and combinations of vasectomy reversal with sperm retrieval and IVF/ICSI. The authors concluded that for couples with a history of vasectomy and where the female is over >35 years old, the most cost effective option is vasectomy reversal (cost per QALY approximately $7,000). If couples opt for surgical retrieval for IVF/ICSI it is more cost effective to undergo a concomitant vasectomy reversal (cost per QALY approximately $33,000) than do surgical retrieval alone (cost per QALY between $40,821 and $54,599 for different age groups). The periods of time for which natural conception was attempted ranged from six months to one year in the different options. The number of permitted IVF/ICSI cycles was two in the combined reversal and retrieval options and four in the surgical retrieval alone option.

Further details of this study are provided in Appendix 4.

Discussion and conclusions

The 2013 NICE guideline does not include any recommendations relating to sterilisation and reversal. We found four studies with relevance to this question, three on effectiveness and one on cost effectiveness.

One study reported no statistically significant differences in fertilisation, pregnancy or live birth rates between men who had previously had a vasectomy and men with congenital obstruction, all of whom were undergoing a first cycle of IVF/ICSI. The vasectomy group included men who had undergone a failed reversal and men who had refused reversal but the numbers in these categories were not reported. Another study reported no statistically significant differences in cumulative delivery rate between men who had had a vasectomy who went straight to surgical sperm retrieval and IVF/ICSI and men who had a vasectomy reversal and later switched to IUI/IVF/ICSI. The mean number of cycles in both of these groups was approximately 2.5 which limits the applicability of the results. A third study was included that reported outcomes for men following vasectomy and reversal. The majority of pregnancies achieved in this study occurred

naturally with only a small number reported as occurring after IUI. It was not possible to draw any conclusions about the effectiveness of a cycle of IUI when the male partner in the couple has had a reversal of a vasectomy.

The study on cost effectiveness concluded that vasectomy reversal was the most cost effective option, both alone and in combination with concomitant sperm retrieval and IVF/ICSI. The applicability of the results is limited by the shorter time periods for which natural conception was attempted after vasectomy reversal (one year, rather than the two years specified in NICE guidance) and the allowance of either two or four cycles of IVF/ICSI in different options.

H Cryopreservation of gametes and embryos (IVF)

Three questions were considered relating to the length of storage of gametes and embryos.

H1 How is the quality of sperm stored for future use in IVF affected by the duration of cryopreservation?

H2 How is the quality of oocytes stored for future use in IVF affected by the duration of cryopreservation?

H3 How is the quality of embryos stored for future use in IVF affected by the duration of cryopreservation?

Further details of the scope of these questions is provided in Appendix 2. For each of the questions, the indication of interest was patients storing gametes or embryos because they are about to undergo treatment that is likely to cause infertility.

NICE Guideline

The 2013 NICE guideline (CG156) [H1] includes recommendations that relate to the storage of gametes and embryos. For people with cancer who wish to preserve fertility it is recommended that cryopreserved material be stored for an initial period of 10 years.

The NICE guideline also recommends that continued storage of cryopreserved sperm beyond 10 years should be offered to men who remain at risk of significant infertility, stating that "*Cryopreserved semen from cancer patients before chemotherapy, although generally of poor quality, are sufficient for success with IVF or ICSI, irrespective of the duration of storage*"

This statement was described as 'Evidence Level 3', which is defined as "well-designed non-experimental studies, such as comparative studies, correlation studies or case series".

The NICE guideline does not include any statements about the storage of oocytes or embryos beyond 10 years. The NICE guideline does not cite any published evidence relating to the storage duration of oocytes or embryos.

The NICE guideline does not include any recommendations about the storage duration of gametes and embryos for people who do not have cancer.

Human Fertilisation and Embryology (HFEA) Code of Practice

The HFEA Code of Practice 9th Edition (last revised October 2021) [H2] states that the statutory storage period for gametes and embryos *"is such period not exceeding ten years as the licence may specify"*.

Previous versions of the HFEA Code of Practice have included statements regarding criteria for the longer term storage of gametes and embryos (up to 55 years). However, the HFEA website states

that new laws governing the storage of gametes and embryos came into effect on 1st July 2022. Areas of the current Code of Practice that are no longer accurate under the new law, including the statements relating to longer storage periods, have been struck through. The HFEA website states that they are planning a full update of the Code of Practice in 2023 to reflect the new law governing the storage of gametes and embryos[12].

A HFEA document reviewing the details of the new laws states that[13]:

"Patients can store gametes or embryos for their own treatment for up to 55 years from the date of first storage. Keeping gametes or embryos in storage for treatment for longer than 55 years is prohibited. There is no longer a requirement for patients to satisfy the premature infertility criteria to be able to store gametes or embryos for more than 10 years as was required by the 2009 Regulations. There is also no longer a requirement to obtain a written opinion from a registered medical practitioner as to premature infertility often in the form of a HFEA Medical Practitioner's Statement (MPS). All patients may store their gametes or embryos for their own treatment for the maximum of 55 years, but they can only do this if they 'renew' their consent to storage, and this must take place within 10 years of first storage and at each successive 10-year period."

H1 How is the quality of sperm stored for future use in IVF affected by the duration of cryopreservation?

Key studies found

We searched for new evidence published since January 2013. We did not identify any systematic reviews relating to the storage duration of sperm for future use in IVF. We did not identify any studies that specifically focused on comparing outcomes for different durations of sperm cryopreservation for the indication of interest, namely patients storing sperm because they are about to undergo treatment that is likely to cause infertility.

The most relevant study identified reported outcomes for the use of cryopreserved sperm from 78 cancer patients (Muller et al 2016) [H3]. However, this included limited information on the effect of storage duration.

Effectiveness

Muller et al (2016) [H3] included 78 cancer patients who returned to use their cryopreserved sperm after a mean storage time of 4.8 years (range 0.5 to 13.3). Sixty (78%) patients fathered at least one child using their cryopreserved sperm. The authors reported no significant difference between time since cryopreservation and fertilisation or live birth rate, but did not report the figures associated with this analysis. Further details are provided in Appendix 4.

Safety

No studies were identified relating to the safety of different durations of sperm storage.

Cost effectiveness

No studies were identified relating to the cost effectiveness of different durations of sperm storage for patients storing sperm because they are about to undergo treatment that is likely to cause infertility.

[12] Read the Code of Practice | HFEA
[13] HFEA Clinic Practical Guide on legal changes to storage limits and guidance - v3 - 8th March 2023

Discussion and conclusions

The evidence review conducted for the 2013 NICE guideline concluded that cryopreserved sperm from cancer patients are sufficient for successful IVF or ICSI irrespective of the storage duration. We found limited recent evidence considering whether cryopreservation duration affects the quality of sperm stored for future use by patients about to undergo treatment that is likely to cause infertility. The study that was identified is in line with the conclusion drawn by NICE. No recent evidence was identified relating to the impact of longer term storage (>10 years) on the quality of sperm that have been cryopreserved by patients about to undergo treatment that is likely to cause infertility.

H2 How is the quality of oocytes stored for future use in IVF affected by the duration of cryopreservation?

Key studies found

We searched for new evidence published since January 2013. We did not identify any systematic reviews relating to the storage duration of oocytes for future use in IVF. We did not identify any studies that specifically focused on comparing outcomes for different durations of oocyte cryopreservation for the indication of interest, namely patients storing oocytes because they are about to undergo treatment that is likely to cause infertility.

The most relevant study identified reported outcomes for the use of cryopreserved oocytes from 44 cancer patients (Porcu et al 2022) [H4]. A second study (Mayeur et al 2021) [H5] included 21 cancer patients who returned to use their cryopreserved oocytes. However, these studies did not directly address the effect of storage duration.

Effectiveness

Porcu et al (2022) [H4] included 44 cancer patients who returned to use their cryopreserved oocytes after a mean storage time of 5.0 years (range 2 to 15). There were 13 live births (15 newborns). The authors contrasted their findings for cancer patients with those of non-oncological patients who had cryopreserved and then returned to use oocytes. No statistically significant differences were seen in outcomes for cancer and non-oncological patients. The authors did not comment on the effect of storge duration. However, they did provide the storage duration of the cryopreserved oocytes for the 13 live births which ranged from two to seven years.

Mayeur et al (2021) [H5] included 21 cancer patients who returned to use their cryopreserved oocytes. Outcomes were reported separately according to the process used to collect embryos for cryopreservation (controlled ovarian stimulation (COS) or in vitro maturation (IVM)). Median storage times were three and five years respectively for the COS and IVM groups. There were three live births. The authors did not comment on the effect of storge duration. However, they did provide the storage duration of the cryopreserved embryos for the five live births which ranged from 47 to 73 months.

Further details of these studies are provided in Appendix 4.

Safety

Porcu et al (2022) [H4] reported a miscarriage rate of 22% for cancer patients who had returned to use their cryopreserved oocytes (n=44). There was no significant difference in miscarriage rate compared to non-oncological patients who had cryopreserved and then returned to use their oocytes. The authors reported that the children born showed normal growth and development. A minor malformation (labiopalatoschisis) was detected in one child.

Cost effectiveness

No studies were identified relating to the cost effectiveness of different durations of oocyte storage for patients storing oocytes because they are about to undergo treatment that is likely to cause infertility.

Discussion and conclusions

The evidence review conducted for the 2013 NICE guideline recommended that cryopreserved material for people with cancer who wish to preserve fertility should be stored for an initial period of 10 years. The NICE guideline did not cite any published evidence relating to the storage duration of oocytes. We found limited recent evidence reporting outcomes by storage duration for patients who stored oocytes before undergoing treatment that is likely to cause infertility. The two studies that were identified reported the use of cryopreserved oocytes that were stored for up to 15 years and reported live births associated with oocytes stored for up to six and seven years respectively. No live births were reported from oocytes stored for more than seven years, but it is not known how many oocytes were used after longer storage durations and no comparison by storage time was reported in either study. No recent evidence was identified relating to the impact of longer term storage (>10 years) on the quality of oocytes that have been cryopreserved by patients about to undergo treatment that is likely to cause infertility.

H3 How is the quality of embryos stored for future use in IVF affected by the duration of cryopreservation?

Key studies found

We searched for new evidence published since January 2013. We found one systematic review (Ma et al 2021) [H6] that included a dose-response meta-analysis examining the relationship between duration of embryo storage time and pregnancy outcomes. A retrospective cohort study (Shi et al 2022) [H7] evaluated the effect of different lengths of cryopreservation duration on the clinical and neonatal outcomes of slow-frozen embryos. No information was provided on the reason for embryo cryopreservation in either of these studies.

We did not identify any studies that specifically focused on comparing outcomes for different storage durations of embryo cryopreservation for the indication of interest, namely patients storing embryos because they are about to undergo treatment that is likely to cause infertility.

Two retrospective cohort studies reported outcomes for the use of cryopreserved embryos from 19 and five cancer patients respectively (Mayeur et al 2021, Barcroft et al 2013) [H5, H8]. However, these studies included limited information on the effect of storage duration.

Effectiveness

Ma et al (2021) [H6] included seven studies in the meta-analysis, all of which were retrospective cohort studies. A long storage time was described as being less than eight years based on the highest storage timeframe in the included studies. No information was provided on the reason for embryo cryopreservation. It is not known if any of the patients cryopreserved embryos prior to treatment that is likely to cause infertility. The authors concluded that the duration of embryo storage does not influence pregnancy outcomes.

Shi et al (2022) [H7] reported outcomes for 4,630 cryopreserved and thawed embryos with outcomes compared for five storage duration groups: 6-12 months, 13-36 months, 37-60 months, 61-84 months and >84 months. No information was provided on the reason for embryo cryopreservation. It is not known if any of the patients cryopreserved embryos prior to treatment that is likely to cause infertility. There were no statistically significant differences between storage duration groups for survival rates, implantation rates, clinical pregnancy, live birth, term birth or birth weight outcomes. In analyses adjusted for factors such as maternal age, body mass index

and transfer processes, there was no correlation between storage duration and outcomes. Shi et al also reported descriptive outcomes for a subgroup of embryos that were stored for >10 years. The outcomes were lower for this group, for example live birth rate was 28% for this subgroup and between 31% and 35% in the main groups analysed. The authors did not conduct comparative analysis for this subgroup and concluded that the sample size was too small to draw solid conclusions.

Mayeur et al (2021) [H5] included 19 cancer patients who returned to use their cryopreserved embryos. Outcomes were reported separately according to the process used to collect embryos for cryopreservation (controlled ovarian stimulation (COS) or in vitro maturation (IVM)). Median storage times were three and five years respectively for the COS and IVM groups. There were five live births. The authors did not comment on the affect of storge duration. However, they did provide the storage duration of the cryopreserved embryos for the five lives births which ranged from 12 to 77 months.

Barcroft et al (2013) [H8] included five cancer patients who returned to use their cryopreserved embryos after a mean storage time of 4.2 years (range 2.4 to 7.9). There were two live births (3 newborns). The authors did not comment on the affect of storage duration or provide further details of the storage duration for the cryopreserved embryos associated with live births.

Further details of these studies are provided in Appendix 4.

Safety

Safety outcomes reported by Ma et al (2021) [H6] were miscarriage rate and congenital malformation rate. The authors concluded that the duration of embryo storage does not influence safety outcomes. Shi et al (2022) [H7] reported no statistically significant differences between storage duration groups for malformation rates.

The miscarriage rate per thaw cycle was 11.1% in Barcroft et al (2013) [H8].

Cost effectiveness

No studies were identified relating to the cost effectiveness of different durations of embryo storage for patients storing embryos because they are about to undergo treatment that is likely to cause infertility.

Discussion and conclusions

The evidence review conducted for the 2013 NICE guideline recommended that cryopreserved material for people with cancer who wish to preserve fertility should be stored for an initial period of 10 years. The NICE guideline did not cite any published evidence relating to the storage duration of embryos.

We found two studies which compared outcomes for different storage durations of cryopreserved embryos. Both these studies reported no statistically significant differences in embryo storage duration and the clinical or safety outcomes reported. One of the studies included a group of embryos that had been stored for more than seven years, with descriptive outcomes for a subgroup of embryos that had been stored for more than 10 years. Neither of these studies provided information on the reason for embryo cryopreservation and it is not known if they included any patients who stored embryos before undergoing treatment that is likely to cause infertility.

We found limited recent evidence reporting outcomes by storage duration for patients who stored embryos before undergoing treatment that is likely to cause infertility. The two studies that were identified reported the use of cryopreserved embryos that were stored for up to 7.9 years and reported live births associated with embryos stored for up to 6.4 years. No comparison by storage time was reported in either study. No recent evidence was identified relating to the impact of longer

term storage (>10 years) on the quality of embryos that have been cryopreserved by patients about to undergo treatment that is likely to cause infertility.

5 Ethical considerations and equity issues

Over the course of this ICB review, it was agreed that for the following cohorts, a commentary of the ethical considerations or decision-making principles would be carried out:[14]

- Same-sex female couples
- Single females
- Individuals with a physical disability or comorbidities that make vaginal intercourse difficult or impossible
- Transgender individuals
- The presence of an existing child
- Previous sterilization
- Cryopreservation of gametes or embryos for the purpose of preserving fertility

5.1 Methodology

An ethical framework states the process by which decisions will be made and the values that underlie the process. Such a framework is important in allowing a structured discussion of all the important issues. It is particularly useful when making difficult decisions as it helps to ensure consistent decision making and enables articulation of reasons for decisions. It supports accountability for the reasonableness of decisions and of decision making processes in the event of scrutiny [10].

Also relevant is that under the Equality Act 2010 [11], it is against the law to discriminate against someone because of:

- age
- disability
- gender reassignment
- marriage and civil partnership
- pregnancy and maternity
- race
- religion or belief
- sex
- sexual orientation

These are called protected characteristics.

In order to support decision making, the five East Midlands ICBs (and their predecessor organisations) have historically developed and used an ethical framework or a set of principles to underpin their decision-making. These are publicly available online[15]. , Although there is some variation in the exact wording, there are key principles that are common to all ICBs' frameworks:

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[14] Note that for single men and same-sex male couples to conceive, surrogacy would be needed and it was agreed that surrogacy was not within the scope of this project. Hence these two population groups were not included.

[15] The decision-making frameworks available for review at the time of this report were:

- Northamptonshire ICB Prior Approval Scheme Policy and Individual Funding Requests Policy
- Nottingham and Nottinghamshire ICB Ethical Decision-Making Framework

1. Evidence of clinical effectiveness and safety
2. Cost-effectiveness
3. Allocation of resources according to need and/or capacity to benefit from the treatment
4. Avoiding discrimination except where this is relevant to capacity to benefit from the treatment
5. Absolute costs, affordability in relation to the overall ICB resources for healthcare, and hence anticipated impact on the rest of the patient population

Further details on these ethical principles are provided in Appendix 4.

For each of the cohorts of interest identified by the ICBs, we have used the five ethical principles to structure narrative considerations for ICBs to consider when making policy decisions for their populations. For some, the initial question has been broken down into a small number of sub-questions to assist this process. It is important to note that there will always be individuals in particular circumstances (exceptions) for whom these discussions will not apply or will apply to a lesser extent.

AA. Where vaginal intercourse as a means of conception is not possible or very difficult

Questions agreed at project scoping workshop

- What are the ethical and cost considerations around funding six cycles of IUI for same-sex female couples (versus patients self-funding initial cycles)?
- What are the ethical and cost considerations around funding six cycles of IUI for single females (versus patients self-funding initial cycles)?
- What are the ethical and cost considerations around funding six cycles of IUI for individuals with a physical disability or comorbidities that make vaginal intercourse difficult or impossible (versus patients self-funding initial cycles)?
- What are the ethical and cost considerations around funding six cycles of IUI for transgender (biologically female) individuals (versus patients self-funding initial cycles)?

These questions are discussed by considering four sub-questions, each in relation to the five main ICB ethical principles for decision making.

1. Funding IUI as a means of conception where vaginal sexual intercourse for the purpose of conception is not possible or very difficult
2. Access to IVF as for heterosexual couples (i.e. access to IVF if the individual/couple is known to suffer from infertility) for those where vaginal intercourse is not possible or very difficult
3. IUI as an indicator of infertility in a population with unknown fertility status
4. The number of cycles of IUI (0, 1, 3 or 6 cycles) funded by the NHS in order to prove infertility and access IVF treatment (NICE recommends 6 cycles of IUI as a requirement to prove infertility and access IVF treatment)

- Leicester City, Leicestershire County and Rutland ICB East Midlands Commissioning Policy for Individual Funding Requests (IFR) (2011) and East Midlands Commissioning Policy for Individual Funding Requests (IFR), updated version (2023, approval pending)
- Lincolnshire Integrated Care Board Individual Funding Requests (IFR) Commissioning Policy
- Derby and Derbyshire ICB Ethical Framework for Decision Making

NICE guidance

There are several relevant recommendations in the NICE guideline CG156 [1] including:

> *1.2.13.6 A woman of reproductive age who is using artificial insemination to conceive (with either partner or donor sperm) should be offered further clinical assessment and investigation if she has not conceived after 6 cycles of treatment, in the absence of any known cause of infertility. Where this is using partner sperm, the referral for clinical assessment and investigation should include her partner."*
>
> *1.9.1.1 Consider unstimulated intrauterine insemination as a treatment option in the following groups as an alternative to vaginal sexual intercourse:*
>
> *• people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychosexual problem who are using partner or donor sperm*
>
> *• people with conditions that require specific consideration in relation to methods of conception (for example, after sperm washing where the man is HIV positive)*
>
> *• people in same-sex relationships*
>
> *1.9.1.2 For people in recommendation 1.9.1.1 who have not conceived after 6 cycles of donor or partner insemination, despite evidence of normal ovulation, tubal patency and semen analysis,* ***offer*** *a further 6 cycles of unstimulated intrauterine insemination before IVF is considered.*

In summary, NICE recommends that patients are considered for IVF if they have not conceived after 12 cycles of AI, 6 cycles of which should be IUI.

Current ICB policies

Current ICB policies offer IVF to same-sex female couples if there is evidence of infertility, in line with NICE guidance. However, funding for IUI cycles varies.

The number of NHS-funded IUI cycles offered varies from one (Northamptonshire) to six (Derby and Derbyshire; Bassetlaw, Glossop); Nottingham and Nottinghamshire offers six cycles of DI or three of IUI, and Lincolnshire offers three IUI cycles.

The requirement for self-funded AI cycles prior to access to NHS-funded IUI cycles varies: Some policies require six self-funded AI cycles in a clinical setting (Lincolnshire, Derby and Derbyshire); Glossop requires self-reporting of six previous AI cycles (three cycles if the women is aged >36 years). Other policies do not mention this requirement.

Sub-question 1: Funding IUI as a means of conception where vaginal sexual intercourse for the purpose of conception is not possible or very difficult

Ethical principle	Same-sex female couples	Single female	Where vaginal intercourse is not possible or very difficult e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or female partner)
Evidence of clinical effectiveness and safety	NICE guidance CG156 [1] supports the use of IUI as an effective and safe means of conception.		Clinical effectiveness and safety of IUI depends on whether the individual's disabilities make IUI more difficult to achieve or less safe or make a successful pregnancy more difficult to achieve or less safe, for example if the condition or its treatment has an effect on the reproductive system.	Clinical effectiveness of IUI depends on whether the transmasculine or non-binary individual has already undergone pharmacological treatment to commence transition. If they have, the effectiveness of IUI is likely to be reduced [12,13]. How much it is reduced will depend on the duration of treatment and whether the treatment has been stopped and for how long.
Cost-effectiveness	The full NICE guideline CG156 [5] assessed the evidence for the cost effectiveness of 6 cycles of IUI compared to expectant management in women with a fertility problem and reported that it was cost-effective at the willingness to pay threshold currently used by NICE for the NHS (£30,000 per QALY). As a female[16] who cannot have vaginal sexual intercourse cannot become pregnant without DI or IUI, the cost-effectiveness of DI or IUI should be greater than this.		Depending on the underlying condition, the effectiveness of IUI may be lower than for other individuals who have IUI (see above). If IUI requires additional facilities or processes because of the underlying condition, the IUI may cost more. Hence, cost-effectiveness may be lower than for other individuals who have IUI if the individual has some,	Depending on the treatment already undergone for transition (if any), IUI may be less effective than for other individuals who have IUI (see above). The cost of IUI is not likely to be different, but lower effectiveness would make IUI less cost-effective in some individuals who have

[16] Female is used in this context to refer to a biological female individual who wishes to conceive

Ethical principle	Same-sex female couples	Single female	Where vaginal intercourse is not possible or very difficult e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or female partner)
			but not other, co-existing conditions.	already commenced treatments for transitioning.
Allocation of resources according to need and/or capacity to benefit from the treatment	Provision of IUI for same-sex female couples and for single women would mean provision according to need and capacity to benefit as these individuals need assisted conception in order to conceive and NICE recommends IUI if 6 cycles of AI have not been successful. This supposes that the NHS might fund IUI in relation to a need for the purpose of conception (and to identify infertility). If IUI is only funded for the purpose of treating infertility, however, many same-sex female couples and single women will not be clinically infertile and will not need IUI for treating infertility.		Provision of IUI for individuals where vaginal intercourse for the purpose of conception is not possible or very difficult would mean provision according to need because assisted conception is needed in order to conceive and NICE recommends IUI if 6 cycles of AI have not been successful. However, if the clinical effectiveness of IUI in the individual is lower than for other individuals who seek IUI (for example because of hormone or other treatments that reduce the success rate of IUI), they will have a lower capacity to benefit compared to other individuals who are offered NHS-funded IUI. This supposes that the NHS might fund IUI in relation to a need for the purpose of conception (and to identify infertility). If IUI is only funded for the purpose of treating infertility, however, many of these individuals will not be clinically infertile and will not need IUI for treating infertility.	
Avoiding discrimination except where this is relevant to capacity to benefit from the treatment	Individuals who are not able to have vaginal intercourse to conceive are not able to conceive without assisted conception. Provision of IUI for these individuals would avoid discrimination in provision of assisted conception because heterosexual couples who are unable to conceive are provided with assisted conception. NICE recommends IUI after the patient has had 6 unsuccessful cycles of AI. The capacity of same-sex female couples and single women to benefit from IUI is not likely to be different from that of others who receive NHS-funded IUI.		Individuals who are not able to have vaginal intercourse to conceive are not able to conceive without assisted conception. Provision of IUI for these individuals would avoid discrimination in provision of assisted conception because heterosexual couples who are unable to conceive are provided with assisted conception. NICE recommends IUI after the patient has had 6 unsuccessful cycles of AI. However, for some individuals with a condition that prevents vaginal intercourse and for transgender individuals who have commenced medical or surgical treatments for transition, the effectiveness of IUI may be lower than for other individuals. This means that their capacity to benefit maybe lower. ICB	

Ethical principle	Same-sex female couples	Single female	Where vaginal intercourse is not possible or very difficult e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or female partner)
	Sexual orientation is a protected characteristic under the Equality Act 2010.		ethical frameworks allow for differential access to treatments based on different capacity to benefit. Sexual orientation and gender reassignment are protected characteristics under the Equality Act 2010.	
Absolute costs, affordability in relation to the overall ICB resources for healthcare, and hence anticipated impact on the rest of the patient population	The number of NHS-funded IUI cycles for same-sex female couples in the East Midlands increased from zero in 2009 and 2010 to 14 in 2018; the corresponding number that were privately funded increased from 36 in 2009 to 164 in 2018 (>4.5-fold increase in nine years) [14]. One local provider carried out 296 IUI cycles from 2006 to 2020 (NHS and private) for same-sex couples.[17] The number of same-sex female couples in England and Wales increased from 89,000 in 2011 to 113,000 in 2021 (1.27-fold increase) (ONS Census data) [15]. ONS 2021 Census data suggest that roughly 4.9 million of the 59.6 million population live in the East Midlands, suggesting that there are	The number of NHS-funded IUI cycles for single women in the East Midlands was <5 in each year from 2009 to 2018; the corresponding number that were privately funded varied from 23 to 61 each year from 2009 to 2018, with no clear pattern. [14]. One local provider carried out 296 IUI cycles from 2006 to 2020 (NHS and private) for same-sex couples.[21] The number of single women aged 25 to 44 years in the East Midlands is roughly 35,670, based on ONS	Couples not able to have vaginal intercourse would include couples where one partner has a physical disability or psychosexual condition. It has not been possible to estimate the number of couples in this group, and hence we are unable to estimate the likely demand for IUI or cost of NHS-funded IUI for this group if criteria for accessing IUI and the number of cycles offered by ICBs (which currently vary) changed.	One provider in the East Midlands had 18 requests for freezing sperm in 2022 and provided no IUI cycles for transgender individuals.[22] This provides an indication of the level of demand for IUI currently from transgender individuals. However, the current long waiting lists for gender identity services may mean that numbers will rise in future.[23]

[17] Personal communication from local clinician.
[21] Personal communication from local clinician.
[22] Personal communication from local clinician.
[23] Personal communication from AGCSU clinical services

Ethical principle	Same-sex female couples	Single female	Where vaginal intercourse is not possible or very difficult e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or female partner)
	around 9,300 same-sex female couples in the East Midlands [16]. These numbers suggest rapidly increasing demand for DI/IUI among same-sex female couples. However, it is not possible from this to estimate the number that might access NHS-funded IUI if the number of NHS funded cycles were increased and/or criteria restricting access were reduced. (Some ICBs currently require a number of self-funded cycles in a healthcare setting prior to offering NHS-funded IUI.) Given the (increasing) number of same-sex female couples, and assuming that perhaps half might wish to conceive, this number could potentially be high. The cost of a cycle of IUI to the ICB is £825 plus £607 for donor sperm[18] (although the latter may be higher than this at present).[19] Assuming:	2021 Census data for single women in the UK and the registered populations of the 5 East Midlands ICBs. It is not possible to estimate how many of these women may request NHS funded IUI cycles each year as we do not know how many do/do not wish to have a child, have children already, prefer to start a family later or when they have a partner, etc.		

[18] Personal communication from ICB contract lead regarding current NHS tariff
[19] Personal communication from local clinician regarding current shortages of donor sperm, higher costs (£1,200 to £1,400) and longer waiting times.

Ethical principle	Same-sex female couples	Single female	Where vaginal intercourse is not possible or very difficult e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or female partner)
	• half of the 9,300 same-sex female couples in the East Midlands wished to have a child • 1 in 25 of these demanded IUI each year • each of these couples had on average 3.4 cycles of IUI before either a live birth or wishing to discontinue treatment,[20] this would equate to potentially an additional 632 IUI cycles each year at a cost to the five East Midlands ICBs in the region of £900,000. However, the number of assumptions made make this figure unreliable. The number is also likely to rise considerably over future years, assuming current trends continue. This cost does not include the cost of IVF for those who have 6 unsuccessful IUI cycles.			

Summary

[20] Based on Full NICE guideline assessment of evidence for economic modelling

Same-sex female couples

Provision of IUI for same-sex female couples who have had six unsuccessful cycles of AI, in order to assist conception, is clinically effective, safe and cost-effective and would provide access according to need (need for assisted conception though not necessarily need in terms of being clinically infertile) and capacity to benefit and avoid discrimination. However, it is very difficult to estimate the total cost to the ICB and, given recent trends [14], this is likely to increase considerably over time. Sexual orientation is a protected characteristic under the Equality Act 2010. (Note that this supposes that the NHS might fund IUI in relation to a need for the purpose of conception (and to identify infertility). If IUI is only funded for the purpose of treating infertility, however, many of these individuals will not be clinically infertile and will not need IUI for treating infertility.)

Single women

Provision of IUI for single women who have had six unsuccessful cycles of AI, in order to assist conception, is clinically effective, safe and cost-effective and would provide access according to need (need for assisted conception though not necessarily need in terms of being clinically infertile) and capacity to benefit and avoid discrimination. However, it is very difficult to estimate the total cost that this provision would incur for the ICB. (Note that this supposes that the NHS might fund IUI in relation to a need for the purpose of conception (and to identify infertility). If IUI is only funded for the purpose of treating infertility, however, many of these individuals will not be clinically infertile and will not need IUI for treating infertility.)

Where vaginal intercourse is not possible or is very difficult (e.g. for physical or psychosexual reasons)

Provision of IUI for couples where vaginal intercourse is not possible or is very difficult who have had six unsuccessful cycles of AI, in order to assist conception, is clinically effective, safe and cost-effective and would provide access according to need (need for assisted conception though not necessarily need in terms of being clinically infertile) and capacity to benefit and avoid discrimination. If, however, clinical effectiveness or safety of IUI for a particular individual is likely to be significantly reduced (e.g. due to medications taken), not providing IUI in that situation would not be contrary to ICB ethical frameworks because the frameworks allow capacity to benefit to be taken into account when considering possible discrimination. It is very difficult to estimate numbers in this group and hence to estimate the cost that provision of IUI for this group would incur for the ICB if criteria for provision of IUI were changed. (Note that this narrative supposes that the NHS might fund IUI in relation to a need for the purpose of conception (and to identify infertility). If IUI is only funded for the purpose of treating infertility, however, many of these individuals will not be clinically infertile and will not need IUI for treating infertility.)

Transgender (biologically female) individuals (not able to have vaginal intercourse for the purpose of conception e.g. single or female partner)

Provision of IUI for transgender (biologically female) individuals who have had six unsuccessful cycles of AI, in order to assist conception, is clinically effective, safe and cost-effective and would provide access according to need (need for assisted conception though not necessarily need in terms of being clinically infertile) and capacity to benefit and avoid discrimination. If, however, clinical effectiveness or safety of IUI for a particular individual is likely to be significantly reduced (e.g. due to hormone medications taken), not providing IUI in that situation would not be contrary to ICB ethical frameworks because the frameworks allow capacity to benefit to be taken into account when considering possible discrimination. It is very difficult to estimate numbers in this group and hence to estimate the cost that provision of IUI for this group would incur for the ICB if criteria for provision of IUI were changed. Gender reassignment is a protected characteristic under the Equality Act 2010. (Note that this narrative supposes that the NHS might fund IUI in relation to a need for the purpose of conception (and to identify infertility). If IUI is only funded for the purpose of treating infertility, however, many of these individuals will not be clinically infertile and will not need IUI for treating infertility.)

Sub-question 2: Access to IVF as for heterosexual couples (i.e. access to IVF if the individual/couple is known to suffer from infertility) for those where vaginal intercourse is not possible or very difficult

Ethical principle	Same-sex female couples	Single female	Couple not able to have vaginal intercourse (or very difficult) e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or in same-sex female relationship)
Evidence of clinical effectiveness and safety	There is no reason to believe that IVF will be more or less effective for same-sex female couples or single women than for heterosexual couples if both have similar levels of infertility. There is no reason to believe that safety of IVF will be different.		Clinical effectiveness of IVF may be affected by the underlying condition if, for example, the condition or its treatment has an effect on the reproductive system.	Clinical effectiveness of IVF is likely to be affected by whether the transmasculine or non-binary individual has already undergone medical or surgical treatment to commence transition. If they have, the effectiveness of IVF is likely to be reduced [12, 13]. How much it is reduced will depend on the extent of treatment and whether the treatment has Been stopped and for how long.
Cost-effectiveness	There is no reason to believe that IVF will be more or less cost-effective for same-sex female couples or single women compared to heterosexual couples if both have similar levels of infertility. NICE assessed IVF as a cost-effective intervention for the NHS [5].		Depending on the underlying condition, the effectiveness of IVF may be lower (see above) than for other individuals who have IVF. If IVF requires additional facilities or processes because of the underlying condition (for example more sedation or a general anaesthetic), treatment may cost more. Hence, cost-effectiveness may be lower than for other	Depending on the treatment already undergone for transition (if any), IVF may be less effective than for other individuals who have IVF (see above). Assuming the cost of IVF is the same (or higher) than for other individuals, with lower effectiveness, the cost-effectiveness of IVF in individuals who have already commenced treatments for transitioning

Ethical principle	Same-sex female couples	Single female	Couple not able to have vaginal intercourse (or very difficult) e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or in same-sex female relationship)
			individuals who have IVF if the individual has some, but not other, co-existing conditions.	will be lower than for the majority of those who have NHS-funded IVF.
Allocation of resources according to need and/or capacity to benefit from the treatment	Same-sex female couples and single women with infertility have the same need for and capacity to benefit from IVF as heterosexual couples who equally suffer from infertility and are offered NHS-funded IVF (assuming similar levels of infertility).		Provision of IVF for individuals where vaginal intercourse for the purpose of conception is not possible or very difficult, where the individual has a similar level of infertility to heterosexual couples who are offered NHS-funded IVF, would mean provision according to need because both need assisted conception in order to conceive. However, for some individuals with a condition that prevents vaginal intercourse and for transgender individuals who have commenced medical or surgical treatments for transition, the effectiveness of IVF may be lower than for other individuals, for example because of medications taken. This means that their capacity to benefit maybe lower.	
Avoiding discrimination except where this is relevant to capacity to benefit from the treatment	Same-sex female couples and single women with infertility have similar capacity to benefit from IVF as heterosexual couples with infertility who are offered NHS-funded IVF. Hence, providing these individuals with NHS-funded IVF avoids discrimination. Sexual orientation is a protected characteristic under the Equality Act 2010.		Where the capacity to benefit from IVF is similar to that of heterosexual couples with infertility who are offered NHS-funded IVF, provision of NHS-funded IVF avoids discrimination. However, some individuals who are not able to have vaginal intercourse in order to conceive and some transgender individuals have a lower capacity to benefit from IVF than heterosexual couples who also have infertility, for example because of hormonal or other medications. ICB ethical frameworks allow for differential access to treatments based on different capacity to benefit.	

Ethical principle	Same-sex female couples	Single female	Couple not able to have vaginal intercourse (or very difficult) e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or in same-sex female relationship)
			Sexual orientation and gender reassignment are protected characteristics under the Equality Act 2010.	
Absolute costs, affordability in relation to the overall ICB resources for healthcare, and hence anticipated impact on the rest of the patient population	If access to IVF for same-sex female couples was improved through increased NHS funding of IUI for female-female couples, more women would meet the requirements for IVF and NHS costs would increase. The number of NHS-funded IVF cycles for same-sex female couples in the East Midlands increased from 0 in 2009, 2010 and 2011 to 16 in 2018 (from 0% to 1.3% of total NHS-funded IVF cycles); the corresponding number that were privately funded increased from 15 in 2009 to 105 in 2018 (from 0.7% to 4.5% of total privately funded IVF cycles) (a 7-fold increase) [14]. These numbers suggest rapidly increasing demand for IVF among same-sex female couples. However, it is not possible from this to estimate the number that might access NHS-funded IVF if access to IUI cycles to prove infertility was	The number of NHS-funded IVF cycles for single women in the East Midlands was <5 in each year from 2009 to 2018 except 2016 (12 cycles); the corresponding number that were privately funded increased from 28 in 2009 to 56 in 2018 [14]. It is not clear how many privately funded cycles were multiple cycles for the same patient. The number of single women aged 25 to 44 years in the East Midlands is roughly 35,670, based on ONS 2021 Census data for single women in the UK and the registered populations of the 5 East Midlands ICBs. It is not possible to estimate how many single women may request NHS funded IVF cycles each year as we do not know how many do/do	Couples not able to have vaginal intercourse would include couples where one partner has a physical disability or psychosexual condition. It has not been possible to estimate the number of couples in this group, and hence we are unable to estimate the likely demand for IVF or cost of NHS-funded IVF in this group if criteria for accessing IUI and the number of IUI cycles offered by ICBs (which currently vary) changed.	One provider in the East Midlands had 18 requests for freezing sperm in 2022 and provided no IUI cycles for transgender individuals.[25] This provides an indication of the level of demand for IUI and IVF currently from transgender individuals. However, the current long waiting lists for gender identity services may mean that numbers will rise in future.[26]

[25] Personal communication from local clinician.
[26] Personal communication from AGCSU clinical services

Ethical principle	Same-sex female couples	Single female	Couple not able to have vaginal intercourse (or very difficult) e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or in same-sex female relationship)
	more consistently and completely funded by the NHS and/or if couples were allowed to self-report cycles of AI (prior to NHS-funded IUI), rather than having to self-fund these in a healthcare setting as is currently required by some ICBs. The cost of an IVF cycle to the ICB is £3,000 where the woman is ≤37 years; £3,400 for women aged 38 and over plus further costs for a proportion for frozen embryo transfer and luteal support.[24]	not wish to have a child, have children already, prefer to start a family later or when they have a partner, etc.		

Summary

Same-sex female couples

Provision of IVF for same-sex female couples with infertility to assist conception is clinically effective, safe and cost-effective and would provide access according to need and capacity to benefit and avoid discrimination. Sexual orientation is a protected characteristic under the Equalities Act 2010. It is very difficult to estimate the total cost to the ICB and, given recent trends [14], this is likely to increase considerably over time.

[24] Personal communication

Single women

Provision of IVF for single women with infertility to assist conception is clinically effective, safe and cost-effective and would provide access according to need and capacity to benefit and avoid discrimination. Being single is not is a protected characteristic under the Equalities Act 2010. It is very difficult to estimate the total cost to the ICB and, given recent trends [14], this is likely to increase over time.

Where vaginal intercourse is not possible or is very difficult (e.g. for physical or psychosexual reasons)

Depending on the underlying condition, the clinical effectiveness, safety and cost-effectiveness of IVF may be lower than for heterosexual couples with infertility, for example due to medications taken. Where IUI cycles have been unsuccessful, and hence the individual or couple suffers from infertility, there would be a need for IVF in order to conceive, and provision of IVF would be according to need and would avoid discrimination. However, if, because of their underlying condition, the clinical effectiveness or safety of IVF for a particular individual is likely to be significantly lower than for other individuals, not providing IVF in that situation would not be contrary to ICB ethical frameworks, because the frameworks allow capacity to benefit to be taken into account when considering possible discrimination. It is very difficult to estimate numbers in this group and hence to estimate the cost that provision of IVF for this group would incur for the ICB if criteria for provision of IUI were changed.

Transgender (biologically female) individuals (not able to have vaginal intercourse e.g. single or female partner)

The clinical effectiveness, safety and cost-effectiveness of IVF for a transgender individual who is biologically female depends on whether and how much treatment (medical or surgical) they have undergone as part of their transition. This treatment may make IVF less effective, and hence less cost-effective, than for others. Provision of IVF would provide access according to need and capacity to benefit if the individual was not able to conceive through IUI and they have a capacity to benefit from IVF (i.e. if IVF is likely to be an effective treatment for them). In this case provision of IVF would avoid discrimination. However, if clinical effectiveness for the individual is likely to be significantly lower than for other individuals, not providing IVF in that situation would not be contrary to ICB ethical frameworks because the frameworks allow capacity to benefit to be taken into account when considering possible discrimination. It is very difficult to estimate numbers in this group and hence to estimate the cost that provision of IUI and IVF for this group would incur for the ICB if criteria for provision of IUI and IVF were changed. Currently numbers appear to be relatively small, although long waiting lists for gender identity services may be an indication that numbers will rise in the future. Gender reassignment is a protected characteristic under the Equality Act 2010.

Sub-question 3: IUI as an indicator of infertility in a population with unknown fertility status

Ethical principle	Same-sex female couples	Single females	Where vaginal intercourse is not possible or very difficult e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or female partner)
Evidence of clinical effectiveness and safety	NICE guidance CG156 [1] supports the use of IUI as an effective and safe means of conception and hence of identifying infertility. This suggests that failure to conceive after a number of cycles of IUI would be a suitable indicator of infertility.		Clinical effectiveness and safety of IUI as a means of identifying infertility may be lower if the underlying condition makes IUI less safe for the individual. However, as IUI is considered a safe procedure by NICE [5], this it not likely to be the case.	Clinical effectiveness and safety of IUI as a means of identifying infertility is not likely to be different for transmasculine individuals, and NICE guidelines suggest that IUI is a safe procedure [5].
Cost-effectiveness	The full NICE guideline CG156 [5] assessed the evidence for the cost effectiveness of 6 cycles of IUI compared to expectant management in women with a fertility problem and reported that it was cost-effective at the willingness to pay threshold currently used by NICE for the NHS (£30,000 per QALY). As same-sex female couples and single females cannot become pregnant without DI/IUI, the cost-effectiveness of DI/IUI should be greater than this for same-sex female couples or single females who do not already have proven infertility. Given this, and the lack of other ways for same-sex female couples and single females to prove that they suffer from infertility, IUI is likely to be a cost-effective indicator of infertility.		The effectiveness of IUI for identifying infertility is not likely to be different compared to its use in a heterosexual couple. If IUI requires additional facilities or processes because of the underlying condition, the IUI may cost more. Hence, cost-effectiveness may be lower than for other individuals who have IUI if the individual has a co-existing condition that increases the cost of IUI.	The effectiveness of IUI for identifying infertility is not likely to be different compared to a heterosexual couple. If the cost of IUI is greater in a transmasculine individual, for example because of expertise required in relation to adjusting hormone treatments that might be being used for the process of transition, the cost of IUI may be greater than for a heterosexual couple, and hence the cost-effectiveness may be lower.
Allocation of resources according to need and/or capacity to	Provision of IUI for female-female couples and single females would mean provision according to need because they need assisted conception in order to conceive and/or to prove that they suffer from infertility (evidence of infertility is a criterion for		Provision of IUI to identify infertility where vaginal intercourse is not possible or very difficult would mean provision according to need because assisted conception is needed to identify infertility in these individuals (evidence of infertility is a criterion	

Ethical principle	Same-sex female couples	Single females	Where vaginal intercourse is not possible or very difficult e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or female partner)
benefit from the treatment	access to IVF and NICE recommends IUI if 6 cycles of AI have not been successful). (For the majority of heterosexual couples lack of conception after 2 years of regular sexual intercourse is taken as evidence of infertility for access to IVF).		for access to IVF and NICE recommends IUI if 6 cycles of AI have not been successful). (For the majority of heterosexual couples lack of conception after 2 years of regular sexual intercourse is taken as evidence of infertility for access to IVF).	
Avoiding discrimination except where this is relevant to capacity to benefit from the treatment	Provision of IUI for same-sex female couples or single females, in order to prove that they suffer from infertility would avoid discrimination, because they would not be able to prove their infertility (a criterion for access to IVF), through sexual intercourse (and NICE recommends IUI if 6 cycles of AI have not been successful). (Heterosexual couples are able to prove that they suffer from infertility, and hence access IVF, by having regular vaginal intercourse.) The capacity of same-sex female couples and single women to benefit from IUI is not likely to be different from that of others who receive NHS-funded IUI. Sexual orientation is a protected characteristic under the Equality Act 2010.		Provision of IUI to identify infertility for individuals who are not able to have vaginal intercourse would avoid discrimination, because they would not be able to prove their infertility (a criterion for access to IVF), through sexual intercourse (and NICE recommends IUI if 6 cycles of AI have not been successful). (Heterosexual couples are able to prove that they suffer from infertility, and hence access IVF, by having regular vaginal intercourse.) If, for a particular individual, safety is likely to be significantly lower than for other individuals, not providing IUI in that situation would not be contrary to ICB ethical frameworks because the frameworks allow capacity to benefit to be taken into account when considering possible discrimination. Sexual orientation and gender reassignment are protected characteristics under the Equality Act 2010.	
Absolute costs, affordability in relation to the overall ICB resources for healthcare, and hence anticipated impact on the rest	The number of NHS-funded IUI cycles for same-sex female couples in the East Midlands increased from zero in 2009 and 2010 to 14 in 2018; the corresponding number that were privately funded increased from 36 in 2009 to 164 in 2018 (>4.5-fold increase in nine	The number of NHS-funded IUI cycles for single women in the East Midlands was <5 in each year from 2009 to 2018; the corresponding number that were privately funded varied	Couples not able to have vaginal intercourse would include couples where one partner has a physical disability or psychosexual condition. It has not been possible to estimate the number of couples in this group, and hence we are	One provider in the East Midlands had 18 requests for freezing sperm in 2022 and provided no IUI cycles for transgender individuals.[31] This provides an indication of the level of demand for

[31] Personal communication.

Ethical principle	Same-sex female couples	Single females	Where vaginal intercourse is not possible or very difficult e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or female partner)
of the patient population	years) [14]. It is not clear how many privately funded cycles were multiple cycles for the same patient. One local provider carried out 296 IUI cycles from 2006 to 2020 (NHS and private) for same-sex couples.[27] The number of same-sex female couples in England and Wales increased from 89,000 in 2011 to 113,000 in 2021 (1.27-fold increase) (ONS Census data) [15]. ONS 2021 Census data suggest that roughly 4.9 million of the 59.6 million population live in the East Midlands, suggesting that there are around 9,300 same-sex female couples in the East Midlands [16]. These numbers suggest rapidly increasing demand for DI/IUI among same-sex female couples. However, it is not possible from this to estimate the number that might access NHS-funded IUI if the number of NHS funded cycles were increased and/or criteria restricting access were reduced. (Some ICBs	from 23 to 61 each year from 2009 to 2018, with no clear pattern. [14]. One local provider carried out 296 IUI cycles from 2006 to 2020 (NHS and private) for same-sex couples.[30] The number of single women aged 25 to 44 years in the East Midlands is roughly 35,670, based on ONS 2021 Census data for single women in the UK and the registered populations of the 5 East Midlands ICBs. It is not possible to estimate how many of these women may request NHS funded IUI cycles each year as we do not know how many do/do not wish to have a child, have children already, prefer to start a	unable to estimate the likely demand for IUI or cost of NHS-funded IUI for individuals in this group if criteria for accessing IUI and the number of cycles offered by ICBs (which currently vary) changed.	IUI currently from transgender individuals. However, the current long waiting lists for gender identity services may mean that numbers will rise in future. [32]

[27] Personal communication from local clinician.
[30] Personal communication from local clinician.
[32] Personal communication from AGCSU clinical services

Ethical principle	Same-sex female couples	Single females	Where vaginal intercourse is not possible or very difficult e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or female partner)
	currently require a number of self-funded cycles in a healthcare setting prior to offering NHS-funded IUI.) Given the (increasing) number of same-sex female couples, and assuming that perhaps half might wish to conceive, this number could potentially be high. The cost of a cycle of IUI to the ICB is £825 plus £607 for donor sperm.[28] Assuming: • half of the 9,300 same-sex female couples in the East Midlands wished to have a child • 1 in 25 of these demanded IUI each year • each of these couples had on average 3.4 cycles of IUI before either a live birth or wishing to discontinue treatment,[29]	family later or when they have a partner, etc.		

[28] Personal communication from local clinician
[29] Based on Full NICE guideline assessment of evidence for economic modelling [5]

Ethical principle	Same-sex female couples	Single females	Where vaginal intercourse is not possible or very difficult e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or female partner)
	this would equate to potentially an additional 632 IUI cycles each year at a cost to the five East Midlands ICBs in the region of £900,000. However, the number of assumptions made make this figure unreliable. The number is also likely to rise considerably over future years, assuming current trends continue. This cost does not include the cost of IVF for those who have 6 unsuccessful IUI cycles.			

Summary

Same-sex female couples

Provision of IUI for same-sex female couples in order to identify infertility, and hence allow access to IVF, is clinically effective, safe and cost-effective and would provide access according to need (for those who have had six unsuccessful cycles of AI as per NICE recommendations) and capacity to benefit and avoid discrimination. This is because IUI is effective, safe and cost-effective as a means of conception and would identify those who are not successful after a number of IUI cycles as likely to suffer from infertility. (Heterosexual couples do not need IUI for this purpose because regular vaginal intercourse without conception will indicate that they suffer from infertility.) It is very difficult to estimate the total cost to the ICB of providing IUI to same-sex female couples who are not already known to suffer from infertility. Given recent trends [14], the costs of this are likely to increase considerably over time. Sexual orientation is a protected characteristic under the Equality Act 2010. (Note that this supposes that the NHS might fund IUI in relation to a need for the purpose of conception (and to identify infertility). If IUI is only funded for the purpose of treating infertility, however, many of these individuals will not be clinically infertile and will not need IUI for treating infertility.)

Single females

Provision of IUI for single females in order to identify infertility, and hence allow access to IVF, is clinically effective, safe and cost-effective and would provide access according to need (for those who have had six unsuccessful cycles of AI as per NICE recommendations) and capacity to benefit and avoid discrimination. This is because IUI is effective, safe and cost-effective as a means of conception and would identify those who are not successful after a number of IUI cycles as likely to suffer from infertility. (Heterosexual couples do not need IUI for this purpose because regular vaginal intercourse without conception will indicate that they suffer from infertility.) It is very difficult to estimate the total cost that provision of IUI to single females who are not already known to suffer from infertility would incur for the ICB. (Note that this supposes that the NHS might fund IUI in relation to a need for the purpose of conception (and to identify infertility). If IUI is only funded for the purpose of treating infertility, however, many of these individuals will not be clinically infertile and will not need IUI for treating infertility.)

Where vaginal intercourse for the purpose of conception is not possible or very difficult (e.g. for physical or psychosexual reasons)

The clinical effectiveness and safety of IUI as a means of identifying infertility is not likely to be different from other groups that may use IUI for this purpose unless the underlying condition makes IUI less safe. However, IUI is considered by NICE to be a safe procedure so this is unlikely. The cost-effectiveness of IUI is only likely to be lower than for other individuals if the underlying condition necessitates the provision of additional resources for the procedure. Provision of IUI would provide access according to need (need for assisted conception for those who have had six unsuccessful cycles of AI (as per NICE recommendations) and identification of infertility to allow access to IVF) and if IUI is likely to be similarly effective and safe for the individual compared to other people who seek IUI, there would be similar capacity to benefit and its provision would avoid discrimination. However, if safety for a particular individual is likely to be significantly lower than for other individuals, not providing IUI in that situation would not be contrary to ICB ethical frameworks because the frameworks allow capacity to benefit to be taken into

account when considering possible discrimination. It is very difficult to estimate numbers in this group and hence to estimate the cost that provision of IUI for this group would incur for the ICB if criteria for provision of IUI were changed. (Note that this supposes that the NHS might fund IUI in relation to a need for the purpose of conception (and to identify infertility). If IUI is only funded for the purpose of treating infertility, however, many of these individuals will not be clinically infertile and will not need IUI for treating infertility.)

Transgender (biologically female) individuals (not able to have vaginal intercourse e.g. single or female partner)

The clinical effectiveness and safety of IUI as a means of identifying infertility is not likely to be different from other groups that may use IUI for this purpose and IUI is considered by NICE to be a clinically effective and safe procedure. The cost-effectiveness of IUI may be lower than for other individuals if, for example, a transmasculine individual requires additional expertise or resource, for example in for adjusting hormone treatments that might be being used for the process of transition. Provision of IUI would provide access according to need (need for assisted conception for those who have had six unsuccessful cycles of AI (as per NICE recommendations) and identification of infertility to allow access to IVF) and if IUI is likely to be similarly effective and safe for the individual for this purpose compared to other people who seek IUI, there would be similar capacity to benefit and its provision would avoid discrimination. It is very difficult to estimate numbers in this group and hence to estimate the cost that provision of IUI for this group would incur for the ICB if criteria for provision of IUI were changed. Currently numbers appear to be relatively small, although long waiting lists for gender identity services may be an indication that numbers will rise in the future. Gender reassignment is a protected characteristic under the Equality Act 2010. (Note that this supposes that the NHS might fund IUI in relation to a need for the purpose of conception (and to identify infertility). If IUI is only funded for the purpose of treating infertility, however, many of these individuals will not be clinically infertile and will not need IUI for treating infertility.)

Sub-question 4: The number of cycles of IUI (0, 1, 3 or 6 cycles) funded by the NHS in order to prove infertility and access IVF treatment

Ethical principle	Same-sex female couples	Single females	Where vaginal intercourse is not possible or very difficult e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or female partner)
Evidence of clinical effectiveness and safety	NICE guidance CG156 supports the use of IUI as an effective and safe means of conception and hence of identifying infertility. No indication was given that the safety and effectiveness of IUI changes with successive cycles (1, 3 or 6 cycles) [5] as appears to be the case with IVF (see evidence section of this report; a 2nd or 3rd IVF cycle is less effective than the 1st cycle if the 1st cycle was unsuccessful).			
Cost-effectiveness	The full NICE guideline CG156 [5] assessed the evidence for the cost effectiveness of 6 cycles of IUI compared to expectant management in women with a fertility problem and reported that it was cost-effective at the willingness to pay threshold currently used by NICE for the NHS (£30,000 per QALY). Assuming 6 cycles of IUI is cost effective in proving infertility for individuals who cannot become pregnant without DI/IUI and are otherwise not known to be infertile (see sub-question 3 above), offering a maximum of one or 3 cycles of DI/IUI will be less costly but will also be less effective in assisting conception and in proving infertility. We did not identify evidence to suggest offering only 1 or 3 cycles of NHS-funded DI/IUI would be relatively more cost-effective than offering 6 cycles of IUI, although this is conceivable if later cycles of IUI are less effective and cost the same as earlier cycles (as is the case, for example, for a 2nd IVF cycle for those with an unsuccessful 1st IVF cycle (see evidence section of this report)).			
Allocation of resources according to need and/or capacity to benefit from the treatment	Provision of a maximum of 6 cycles of IUI instead of a maximum of 1 or 3 cycles of IUI would constitute provision according to need because those who conceived after a smaller number of cycles would not be offered more, and for those who do not conceive, 6 cycles are required before the individual can access IVF. Given the effectiveness of IUI, the individuals would have capacity to benefit from the IUI.			
Avoiding discrimination except where this is relevant to capacity to benefit from the treatment	Provision of a maximum of 6 cycles of IUI instead of a maximum of 1 or 3 cycles of IUI may be considered as avoiding discrimination in access to assisted conception compared to heterosexual couples if individuals who cannot attempt to conceive through vaginal intercourse would otherwise be expected to pay for the remaining cycles of IUI so as to have 6 IUI cycles before they are able to access IVF. This is because heterosexual couples are not expected to pay for assisted conception before being able to access IVF.			

Ethical principle	Same-sex female couples	Single females	Where vaginal intercourse is not possible or very difficult e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or female partner)
	The capacity to benefit from IUI may be slightly lower for later cycles of IUI than for earlier cycles if later cycles are less likely to result in conception (as is the case, for example, for a 2nd IVF cycle for those with an unsuccessful 1st IVF cycle (see evidence section of this report)). However, evidence for this was not identified within our review. Sexual orientation and gender reassignment are protected characteristics under the Equality Act 2010.			
Absolute costs, affordability in relation to the overall ICB resources for healthcare, and hence anticipated impact on the rest of the patient population	As can be seen from the tables above, it is not possible to estimate with any degree of confidence the total cost to ICBs if 6 cycles of IUI were offered to same-sex female couples. It may be in the region of £900,000 for the five East Midlands ICBs and likely to rise considerably each year. However, this figure included many assumptions and excludes later costs of IVF. This figure assumes that couples would have an average of 3.4 cycles of IUI. If a maximum of 3 cycles of IUI were offered, the average uptake is not known but may be closer to 2 cycles, and hence around £530,000 for the five East Midlands ICBs per year, and likely to rise each year.	The number of NHS-funded IUI cycles for single females in the East Midlands was <5 in each year from 2009 to 2018; the corresponding number that were privately funded varied from 23 to 61 each year from 2009 to 2018, with no clear pattern [14]. One local provider carried out 296 IUI cycles from 2006 to 2020 (NHS and private) for same-sex couples.[33] The number of single women aged 25 to 44 years in the East Midlands is roughly 35,670, based on ONS 2021 Census data for	Couples not able to have vaginal intercourse would include couples where one partner has a physical disability or psychosexual condition. It has not been possible to estimate the number of couples in this group, and hence we are unable to estimate the likely demand for IUI or cost of NHS-funded IUI (1, 3 or 6 cycles) from individuals in this group if criteria for accessing IUI and the number of cycles offered by ICBs (which currently vary) changed.	One provider in the East Midlands had 18 requests for freezing sperm in 2022 and provided no IUI cycles for transgender individuals.[34] This provides an indication of the level of demand for IUI currently from transgender individuals. However, the current long waiting lists for gender identity services may mean that numbers will rise in future. [35]

[33] Personal communication from local clinician.
[34] Personal communication from local assisted conception contract manager.
[35] Personal communication from AGCSU clinical services

Ethical principle	Same-sex female couples	Single females	Where vaginal intercourse is not possible or very difficult e.g. for physical or psychosexual reasons	Transgender (biologically female) (not able to have vaginal intercourse for the purpose of conception e.g. single or female partner)
	If only 1 cycle of IUI was offered, the cost may be around £265,000 per year for the five East Midlands ICBs, and likely to increase considerably each year given current trends [14] (see figures in sub-question 3 above).	single women in the UK and the registered populations of the 5 East Midlands ICBs. It is not possible to estimate how many of these women may request NHS-funded IUI cycles each year as we do not know how many do/do not wish to have a child, have children already, prefer to start a family later or when they have a partner, etc.		

Summary

Same-sex female couples

Provision of one, three or six cycles of IUI for assisted conception and proving infertility (so as to allow access to IVF) are likely to be equally clinically effective, safe and cost-effective (no evidence was identified to suggest that the effectiveness of IUI decreases with successive unsuccessful cycles). Provision of a maximum of one or three cycles of IUI may theoretically be more cost effective than six cycles of IUI (if later cycles, after unsuccessful earlier cycles, are less likely to be successful), but the evidence regarding this was not evaluated. NICE guidelines recommend that IVF is provided if six cycles of IUI (and six of AI) do not result in conception. Provision of a maximum of six cycles of NHS-funded IUI may therefore be more in line with need and less discriminatory than provision of a maximum of one or three cycles of IUI, because to access IVF, the individual would be required to self-fund a further five or three cycles of IUI respectively whereas a heterosexual couple is not required to pay for assisted conception prior to accessing IVF. The total cost of providing a maximum of six cycles may be in the region of 3.4 times the total cost of providing a maximum of one cycle of IUI, with the cost of providing a maximum of three cycles somewhere

in between. However, it is not possible to estimate the total cost with any degree of confidence, and, given recent trends [14], the cost is likely to increase considerably each year. Sexual orientation is a protected characteristic under the Equality Act 2010. (Note that this supposes that the NHS might fund IUI in relation to a need for the purpose of conception (and to identify infertility). If IUI is only funded for the purpose of treating infertility, however, many of these individuals will not be clinically infertile and will not need IUI for treating infertility.)

Single females

Provision of one, three or six cycles of IUI for assisted conception and proving infertility (so as to allow access to IVF) are likely to be equally clinically effective, safe and cost-effective (no evidence was identified to suggest that the effectiveness of IUI decreases with successive unsuccessful cycles). Provision of a maximum of one or three cycles of IUI may theoretically be more cost effective than six cycles of IUI (if later cycles, after unsuccessful earlier cycles, are less likely to be successful), but the evidence regarding this was not evaluated. NICE guidelines recommend that IVF is provided if six cycles of IUI (and six of AI) do not result in conception. Provision of a maximum of six cycles of NHS-funded IUI may therefore be more in line with need and less discriminatory than provision of a maximum of one or three cycles of IUI, because to access IVF, the individual would be required to self-fund a further five or three cycles of IUI respectively whereas a heterosexual couple is not required to pay for assisted conception prior to accessing IVF. The total cost of providing a maximum of six cycles may be in the region of 3.4 times the total cost of providing a maximum of one cycle of IUI, with the cost of providing a maximum of three cycles somewhere in between. However, it is not possible to estimate the total cost with any degree of confidence. (Note that this supposes that the NHS might fund IUI in relation to a need for the purpose of conception (and to identify infertility). If IUI is only funded for the purpose of treating infertility, however, many of these individuals will not be clinically infertile and will not need IUI for treating infertility.)

Where vaginal intercourse for the purpose of conception is not possible or very difficult (e.g. for physical or psychosexual reasons)

Provision of one, three or six cycles of IUI for assisted conception and proving infertility (so as to allow access to IVF) are likely to be equally clinically effective, safe and cost-effective (no evidence was identified to suggest that the effectiveness of IUI decreases with successive unsuccessful cycles). Provision of a maximum of one or three cycles of IUI may theoretically be more cost effective than six cycles of IUI (if later cycles, after unsuccessful earlier cycles, are less likely to be successful), but the evidence regarding this was not evaluated. NICE guidelines recommend that IVF is provided if six cycles of IUI (and six of AI) do not result in conception. Provision of a maximum of six cycles of NHS-funded IUI may therefore be more in line with need and less discriminatory than provision of a maximum of one or three cycles of IUI, because to access IVF, the individual would be required to self-fund a further five or three cycles of IUI respectively whereas a heterosexual couple is not required to pay for assisted conception prior to accessing IVF. The total cost of providing a maximum of six cycles may be in the region of 3.4 times the total cost of providing a maximum of one cycle of IUI, with the cost of providing a maximum of three cycles somewhere in between. However, it is not possible to estimate the total cost with any degree of confidence. (Note that this supposes that the NHS might fund IUI in relation to a need for the purpose of conception (and to identify infertility). If IUI is only funded for the purpose of treating infertility, however, many of these individuals will not be clinically infertile and will not need IUI for treating infertility.)

Transgender (biologically female) individuals (not able to have vaginal intercourse e.g. single or female partner)

Provision of one, three or six cycles of IUI for assisted conception and proving infertility (so as to allow access to IVF) are likely to be equally clinically effective, safe and cost-effective (no evidence was identified to suggest that the effectiveness of IUI decreases with successive unsuccessful cycles). Provision of a maximum of one and three cycles of IUI may theoretically be more cost effective than six cycles of IUI (if later cycles, after unsuccessful earlier cycles, are less likely to be successful), but the evidence regarding this was not evaluated. NICE guidelines recommend that IVF is provided if six cycles of IUI (and six of AI) do not result in conception. Provision of a maximum of six cycles of NHS-funded IUI may therefore be more in line with need and less discriminatory than provision of a maximum of one or three cycles of IUI, because to access IVF, the individual would be required to self-fund a further five or three cycles of IUI whereas a heterosexual couple is not required to pay for assisted conception prior to accessing IVF. The total cost of providing a maximum of six cycles may be in the region of 3.4 times the total cost of providing a maximum of one cycle of IUI, with the cost of providing a maximum of three cycles somewhere in between. It is not possible to estimate the total cost that this would incur for the ICB with any degree of confidence. However, currently numbers appear to be relatively small, although long waiting lists for gender identity services may be an indication that numbers will rise in the future. Gender reassignment is a protected characteristic under the Equality Act 2010. (Note that this supposes that the NHS might fund IUI in relation to a need for the purpose of conception (and to identify infertility). If IUI is only funded for the purpose of treating infertility, however, many of these individuals will not be clinically infertile and will not need IUI for treating infertility.)

BB Presence of an existing child

Question agreed at project scoping workshop

What are the ethical considerations related to provision of IVF and IUI where one or both partners already have a living child?

This question is discussed below for three key subgroups of couples with living children who were identified as presenting differing ethical considerations when viewed through the lens of the ICBs' five main ethical principles for decision making.

Should ICBs fund an equivalent provision of IVF and IUI/DI as they do for couples/single females who have no living children (from any relationship):

- for couples with a living child from the current relationship
- for couples where one partner has a child from a previous relationship
- for couples where both partners have a child from a previous relationship

Alignment with national policies

For legal purposes, an adopted child is treated as if they had been born as the child of the couple who adopted them [17]

NICE guidelines (CG156) [1]: The guidelines state that IVF is more effective in women who have been pregnant or had a baby before, however the guidelines do not make any specific recommendations.

NICE Quality standard (QS73) [18]: The standard states, in its "equality and diversity considerations" section, that the existence of living children should not be a factor that precludes the provision of fertility treatment.

HFEA Code of Practice [19]: No specific recommendations are made by the HFEA Code of Practice, however it notes that "the centre should refuse treatment if it…concludes that…any existing child of the family is likely to be at risk of significant harm or neglect."

Current ICB policies

Glossop funds IVF for couples without living children from their current relationship where one partner does not have any children from a previous relationship. The other ICBs do not fund IVF for couples with a living child from the current or a previous relationship. The wording in these policies suggests exclusion of couples where only one partner has a living child, however this is only specified explicitly in Bassetlaw (for IVF) and Lincolnshire ICB (for IUI).

All policies treat adopted children on par with conceived children. Derby and Derbyshire ICB also specifies that children previously given up for adoption are not counted towards "having living children".

A 2020 report comparing provision across CCGs found that 96% of CCGs did not provide IVF for couples with children (conceived or adopted) from their current relationship, however eligibility for couples where one partner had a child from a previous relationship varied across CCGs, with some applying additional eligibility criteria relating to whether the child is living with the current couple or based on the age of the child [20].

For IUI, policies from Lincolnshire, Leicester, Leicestershire & Rutland, Derby and Derbyshire, Nottingham and Nottinghamshire, and Northamptonshire ICBs specify that couples are not eligible if they have any living children from the current or a previous relationship (including adopted but not fostered).

Question: What are the ethical considerations related to provision of IVF and IUI where one or both partners already have a living child?

Principle	Ethical considerations for:		
	Couples with a living child from the current relationship	**Couples where one partner has a child from a previous relationship**	**Couples where both partners have a child from a previous relationship**
Clinical effectiveness and safety	The NICE guidelines [1] note that IVF is [generally] more effective in females who have been pregnant or had a baby before.[36] This suggests the effectiveness of IVF is likely to be higher in a couple with a living child than for a couple without an existing child. Although no evidence on the effectiveness of IUI where a couple already has a child was included in the NICE guidelines, the higher effectiveness observed for IVF may also be the case for IUI.	For couples where the female partner has a living child from a previous relationship, the NICE guidelines [1] note that IVF is [generally] more effective in females who have been pregnant or had a baby before, so the effectiveness of IVF is likely to be higher than for a couple without an existing child. Although no evidence on the effectiveness of IUI in couples where the female partner already has a child was included in the NICE guidelines, the higher effectiveness observed for IVF may also be the case for IUI. For couples where the male partner has a living child from a previous relationship, no evidence cited in the NICE guideline [1] examined the relationship between previous live birth in relation to the male partner and IVF or IUI outcomes. However, there is no obvious reason to expect the effectiveness of IVF or IUI to be lower than that for a couple without an existing child.	The NICE guidelines [1] note that IVF is [generally] more effective in females who have been pregnant or had a baby before.[37] This suggests the effectiveness of IVF is likely to be higher in a couple where both partners already have a child than for a couple where neither partner has an existing child. Although no evidence on the effectiveness of IUI where both partners already have a child was included in the NICE guidelines, the higher effectiveness observed for IVF may also be the case for IUI.

[36] Evidence cited by the NICE guideline [1] examined IVF outcomes for females following a previous pregnancy or previous live birth without differentiating between whether this was from the current or a previous relationship.
[37] Evidence cited by the NICE guideline [1] examined IVF outcomes for females following a previous pregnancy or previous live birth without differentiating between whether this was from the current or a previous relationship.

Principle	Ethical considerations for:		
	Couples with a living child from the current relationship	**Couples where one partner has a child from a previous relationship**	**Couples where both partners have a child from a previous relationship**
	There is no obvious reason to expect the safety of IVF, or IUI, as a procedure to be different to that for couples without living children.		
Cost-effectiveness	Couples with an existing child from the current relationship would generally be expected to experience higher effectiveness with IVF, and possibly also with IUI, and similar costs compared to couples without a living child. Therefore IVF, and possibly also IUI, are anticipated to be more cost-effective for couples with a living child than for couples without any existing children.	Depending on whether the male or female partner has an existing child, couples where one partner has an existing child from a previous relationship would generally be expected to experience at least equal or greater effectiveness with IVF, and likely also with IUI, and similar costs compared to couples without any existing children. Therefore IVF and IUI are anticipated to be equally or more cost-effective for couples where one partner already has a child compared to couples without any existing children.	Couples where both partners have a living child from a previous relationship would generally be expected to experience higher effectiveness with IVF, and possibly also with IUI, and similar costs compared to couples without any existing children. Therefore IVF, and possibly also IUI, are anticipated to be more cost-effective for couples where both partners already have a living child than for couples without any existing children.
Allocation of resources according to need and/or capacity to benefit	If the need met by IVF and IUI is seen as "enabling patients to start, or complete, their family": couples with an existing child from the current relationship could be seen as having a lower need for IUI or IVF compared to couples without existing children, as couples with an existing child have at least "started" a family in the current relationship.	If the need met by IVF and IUI is seen as "enabling patients to start, or complete, their family": in the context of starting a family in the current relationship, couples where one partner has a child from a previous relationship could be seen as having a similar need for IUI or IVF as couples without any existing children.	If the need met by IVF and IUI is seen as "enabling patients to start, or complete, their family": in the context of starting a family in the current relationship, couples where both partners have an existing child from a previous relationship could be seen as having a similar need for

Principle	Ethical considerations for:		
	Couples with a living child from the current relationship	**Couples where one partner has a child from a previous relationship**	**Couples where both partners have a child from a previous relationship**
		However, in the context of starting a family in any relationship, the need for IUI or IVF could be seen as lower for the partner who already has a child from a previous relationship, and equivalent for the partner without any children from a previous relationship, when compared to a couple where neither partner has living children.	IUI or IVF as a couple without any existing children. However, in the context of starting a family in any relationship, these couples could be seen as having lower need compared to couples without living children from current or previous relationships given both partners have had a chance to start a family in the past.
	If the need met by IVF and IUI is seen as "enabling patients to have a child of their own": couples with an existing child could be seen as having a lower need for IUI or IVF than couples without any existing children.	If the need met by IVF and IUI is seen as "enabling patients to have a child of their own": for couples where one partner has a child from a previous relationship, the partner without a living child could be seen as having similar needs to the partners of a couple where neither have existing children, whereas the partner with an existing child could be seen as having lower needs compared to the partners of a couple without any existing children.	If the need met by IVF and IUI is seen as "enabling patients to have a child of their own": couples where both partners have a child from a previous relationship could be seen as having a lower need for IUI or IVF than couples where neither partner has existing children.
Avoiding discrimination (except where relevant to capacity to benefit)	Having or not having existing children are not protected characteristics under the Equality Act 2010. Not funding IVF or IUI for couples where one or both partners already have a living child is not likely to be seen as discrimination in terms of the Equality Act 2010.		
Absolute costs, affordability in relation to the overall ICB resources	If NHS access for IVF or IUI was expanded to include couples where one or both partners already have an existing child, more couples would become eligible for IVF and IUI and NHS costs are likely to increase.		

Principle	Ethical considerations for:		
	Couples with a living child from the current relationship	**Couples where one partner has a child from a previous relationship**	**Couples where both partners have a child from a previous relationship**
	For this report, data were only available for the number of IVF cycles performed in the UK in couples/single females with a history of a live birth from IVF or IUI. Based on several assumptions, it is estimated that 889 IVF cycles were performed privately in couples/single females with a history of live birth from IUI or IVF in the East Midlands in each of 2017 and 2018[38]. However, it is not possible without further research to estimate the overall increase in demand for IUI and IVF that would result from a change in policy, as this is likely to include increased demand not only from couples with a living child conceived through IUI or IVF but also from those with living children who were conceived naturally or adopted. No data were identified for this group.		

[38] This estimate was calculated by dividing the approximate number of IVF cycles performed in couples/patients with a previous ART-mediated live birth by the total number of private IVF cycles performed in the UK and applying this proportion to the number of private IVF cycles performed in the East Midlands in the same year.
The estimate is based on HFEA data [https://www.hfea.gov.uk/media/3469/ar-2017-2018.xlsx] and makes several assumptions about missingness (data were missing on history of live birth by ART for 35-37% of IVF cycles), how these cycles were funded (all IVF cycles in couples/patients with a previous ART-mediated live birth were assumed to be privately-funded based on information from BPAS [bpas-fertility-ivf-postcode-lottery-report.pdf]) and generalisability of UK data to the East Midlands.

Summary:

In couples where one or both partners already have a living child, previous live birth in the female partner is generally associated with higher IVF effectiveness and likely also higher cost-effectiveness, given no obvious reason to expect a difference in costs or safety (this may also be the case for IUI).

There is no obvious reason to expect 'previous contribution to a live birth' in the male partner of a couple to be associated with lower effectiveness, safety or cost-effectiveness of IVF or IUI compared to in a couple without existing children from any relationship.

How the needs of couples with living children compare to the needs of those without any living children depends on what the needs being met through IVF and IUI are perceived to be. Relative to couples without living children, couples where partners have children from previous relationships could be seen as having similar needs with respect to wanting to start and/or complete a family in their current relationship - and for any partners without existing children, with respect to their need to start a family in the context of any relationship or to have a child of their own. These latter two needs could however be seen as being lower for couples where both partners have had a child previously.

In comparison, couples with a living child from their current relationship could be seen as having lower needs compared to couples without any existing children across these three different perspectives (the need to start and/or complete a family in the context of their current relationship, in the context of any relationship, or to have a child of their own).

Not providing IVF or IUI funding for couples with living children is not likely to be seen as discriminatory under the terms of the Equality Act. Avoiding use of eligibility criteria based on where existing children are ordinarily resident reduces the risk of these children being displaced from their current living arrangements to fulfil eligibility criteria for referral.

Funding IVF and IUI cycles in couples with living children is anticipated to increase demand for NHS-funded cycles from couples who would otherwise seek treatment privately under current policies as well as from couples who are unable to access IVF or IUI privately due to financial constraints currently. It is not possible to estimate the total cost to the ICBs of expanding provision of IVF and IUI for couples with living children (or a subset of this patient group) based on the data available at the time of this report.

CC Previous sterilisation

Question agreed at project scoping workshop

What are the ethical considerations related to provision of IVF and IUI for couples where one partner has previously undergone a sterilisation procedure for the purpose of family planning?

Sub-questions

- What are the ethical considerations relating to provision of IVF and IUI for couples where a partner has previously had a sterilisation procedure and is still infertile (whether reversed or not) and the other partner is fertile?
- What are the ethical considerations relating to provision of IVF and IUI for couples where a partner has previously had a sterilisation procedure and is now fertile (sterilisation successfully reversed) and the other partner is infertile?

- What are the ethical considerations relating to provision of IVF and IUI for couples where a partner has previously had a sterilisation procedure and both partners are now infertile?

Alignment with national policies/ standards

NICE guidelines

The NICE guideline on fertility treatment (CG156) [1] does not provide specific guidance relating to individuals who have previously been sterilised.

HFEA code of practice

The HFEA code of practice [19] does not provide specific guidance relating to individuals who have previously been sterilised.

Current ICB policies:

For IVF, Bassetlaw funds treatment for couples with successful reversal of sterilisation (but does not fund IVF in sterilised patients without reversal or with unsuccessful reversal). Glossop funds IVF for treatment of infertility in a not-sterilised partner of a couple (and in couples diagnosed with unexplained infertility) where the sterilised partner has had a clinically successful reversal of sterilisation. Where a partner has subfertility following reversal of sterilisation, however, Glossop does not routinely fund IVF. The other ICBs do not fund IVF in patients with previous sterilisation regardless of whether it has been successfully reversed.

For IUI, Derby and Derbyshire, Nottingham and Nottinghamshire, and Northamptonshire specify that couples where either partner has previously been sterilised are ineligible for IUI.

Question: What are the ethical considerations related to provision of IVF and IUI for couples where one partner has previously undergone a sterilisation procedure for the purpose of family planning?

Ethical principle	Provision of IVF and IUI for couples where one partner has previously undergone a sterilisation procedure for the purpose of family planning		
	For a couple where the partner who was sterilised is still infertile and the other partner is fertile	**For a couple where one partner has been sterilised but is now fertile (sterilisation successfully reversed) and the other partner is infertile**	**For a couple where one partner has been sterilised and both partners are now infertile**
Evidence of clinical effectiveness and safety	The evidence enquiry (see evidence section of report) did not find evidence that the clinical effectiveness of IVF or IUI is significantly lower where an individual has been previously sterilised compared to someone who has not been sterilised (although the evidence suggested that reversal of sterilisation may increase effectiveness). The evidence enquiry suggested that ectopic pregnancy rates, miscarriage rates and ovarian hyperstimulation rates may be higher after IVF in women who have previously been sterilised and had a reversal. It is not clear whether the success of the reversal of sterilisation has an impact on the success of IVF.[39] The effect on safety of IVF or IUI for men who have previously been sterilised was not clear from the evidence identified.		
Cost-effectiveness	As no evidence of reduced effectiveness of IVF or IUI was identified (see evidence section) and the cost of IVF or IUI is not likely to be different for a person who has been previously sterilised compared to someone who has never been sterilised, the cost-effectiveness is also not likely to be different. However, the indication from the evidence that there are more risks from IVF and IUI (e.g. from ectopic pregnancy or miscarriage) for a woman who has been previously sterilised suggests that the cost-effectiveness of IVF or IUI for this group is lower than for a couple where neither partner has ever been sterilised. In addition, if the IVF or IUI requires additional procedures (e.g. surgical sperm retrieval) due to the previous sterilisation, this could be seen as an extra cost of the IVF or IUI for that couple and hence reduce its cost-effectiveness compared to the majority of other couples. However, some with congenital azoospermia also require surgical sperm retrieval as part of IVF.		
Allocation of resources according to need and/or capacity to benefit from the treatment	Where one partner has previously been sterilised but otherwise the couple meets the other criteria for IVF or IUI and expresses a need for a child, their need for IVF or IUI in order to conceive may not be different from that where neither partner has previously been sterilised. However, people may be more likely to be accepted for sterilisation if they already have a child/children [21]. In this case their need for another child could be considered less than that of people who do not already have a child, and they may not meet other local criteria for IVF or IUI (e.g. not having an existing child) (see section on existing children above e.g. this might depend on whether one or both partners have no existing children).		

[39] Pregnancy is possible without reversal of sterilisation e.g. using surgical sperm retrieval for men or IVF for women.

Ethical principle	Provision of IVF and IUI for couples where one partner has previously undergone a sterilisation procedure for the purpose of family planning		
	For a couple where the partner who was sterilised is still infertile and the other partner is fertile	For a couple where one partner has been sterilised but is now fertile (sterilisation successfully reversed) and the other partner is infertile	For a couple where one partner has been sterilised and both partners are now infertile
	In addition, the likely increased risk of adverse events (e.g. from ectopic pregnancy or miscarriage for a woman who has previously been sterilised) (see above and evidence section of this report) may be considered to reduce their capacity to benefit.		
Avoiding discrimination except where this is relevant to capacity to benefit from the treatment	If a person who has previously been sterilised has a lower need for IVF or IUI (e.g. they already have a child) and/or a lower capacity to benefit from the procedure compared to a person who has not previously been sterilised (e.g. due to the increased risk associated with IVF or IUI in a woman who has been sterilised) (see above), then not providing them with IVF or IUI is unlikely to be seen as discrimination.		
Absolute costs, affordability in relation to the overall ICB resources for healthcare, and hence anticipated impact on the rest of the patient population	Based on NHS data for England in 2021/22 [22] and ONS 2021 Census data for populations aged 18 to 54 [23],[40] there were in the region of 819 female and 725 male sterilisation procedures carried out in the NHS in the East Midlands in 2021/22. The proportion of patients experiencing regret after a sterilisation procedure has been estimated to be 0.9 to 26% after female tubal occlusion and 2% (within 10 years) after a vasectomy [24]. Using NHS data for the 4 years to 2021/22 [22], there were around 11 reversals of female sterilisation and 3 of male sterilisation per year in the East Midlands NHS. Evidence suggests that reversals of female sterilisations have been roughly stable whereas the number for males has been decreasing [25]. However, these data only pertain to NHS-provided treatments and reversal of sterilisation is rarely funded by the NHS. It is not clear how many procedures are carried out privately or how many of those patients then go on to requesting assisted conception.		

Summary

[40] This assumes that rates in the East Midlands are the same as England rates.

For individuals who have previously been sterilised, no evidence was found that suggested a significantly lower effectiveness of IVF and IUI compared to people who have not been sterilised, although there was a suggestion that reversal of sterilisation may increase effectiveness. There was, however, a suggestion that for a woman who has previously been sterilised, there are increased risks of IVF and IUI, for example relating to ectopic pregnancy. This, together with any additional procedures that may be required for IVF or IUI for someone who has been previously sterilised (such as reversal of sterilisation or surgical sperm retrieval), may reduce the cost-effectiveness of IVF and IUI for a person who has been previously sterilised compared to someone who has not. Safety issues may also reduce the capacity to benefit from IVF or IUI.

Whether provision of IVF or IUI for this group is considered to reflect need depends on factors such as whether the couple meet other criteria for needing IVF (e.g. sterilisation is usually provided for people who already have children). If the individual has a lower need and/or capacity to benefit compared to an individual who has not been sterilised, not providing IVF or IUI for them is unlikely to be seen as discriminatory. Most ICBs already have policy statements which limit NHS funding of reversal of sterilisation.

It is not possible to estimate the number of people who may wish to access IVF or IUI following reversal of sterilisation and the potential cost to each ICB that would arise from funding IVF and IUI in people who have previously been sterilised. The analysis did not suggest any differences, in terms of ethical considerations, between couples where the previously sterilised partner is now fertile or infertile and whether the other partner is fertile or infertile.

DD Cryopreservation of gametes and embryos for the purpose of preserving fertility

Question agreed at project scoping workshop

What are the ethical considerations in relation to NHS-funded gamete and embryo storage and the duration of storage offered to patients with different indications/situations for the purpose of preserving fertility? [agreed after the workshop]

This is discussed below through a number of sub-questions relating to different reasons why people may seek to preserve their fertility through cryopreservation of gametes or embryos:

- What are the ethical considerations in relation to NHS-funded gamete and embryo storage prior to NHS treatments that are likely to result in infertility (e.g. treatments for cancer or gender reassignment), and in relation to the duration of storage?
- What are the ethical considerations in relation to NHS-funded gamete and embryo storage for conditions that may result in earlier than average loss of fertility (e.g. endometriosis), and in relation to the duration of storage?
- What are the ethical considerations in relation to NHS-funded gamete and embryo storage for people who choose to store gametes or embryos so that they can postpone having a child for social reasons (e.g. career, caring, relationships, etc), and in relation to the duration of storage?

Alignment with national policies/ standards

NICE guideline CG156 [1]

The 2013 NICE guideline (CG156) [1] includes recommendations that relate to the storage of gametes and embryos. For people with cancer who wish to preserve fertility it is recommended that cryopreserved material be stored for an initial period of 10 years and that continued storage of cryopreserved sperm beyond 10 years should be offered to men who remain at risk of significant infertility, stating that "Cryopreserved semen from cancer patients before chemotherapy, although generally of poor quality, are sufficient for success with IVF or ICSI, irrespective of the duration of storage"

This statement was described as 'Evidence Level 3', which is defined as "well-designed non-experimental studies, such as comparative studies, correlation studies or case series".

The NICE guideline does not include any statements about the storage of oocytes or embryos beyond 10 years and it does not cite any published evidence relating their storage duration.

The NICE guideline does not include any recommendations about the storage duration of gametes and embryos for people who do not have cancer.

Human Fertilisation and Embryology (HFEA) Code of Practice

The HFEA Code of Practice 9th Edition (last revised October 2021) [19] states that the statutory storage period for gametes and embryos *"is such period not exceeding ten years as the licence may specify"*.

Previous versions of the HFEA Code of Practice have included statements regarding criteria for the longer term storage of gametes and embryos (up to 55 years). However, the HFEA website states that new laws governing the storage of gametes and embryos came into effect on 1st July

2022. Areas of the current Code of Practice that are no longer accurate under the new law, including the statements relating to longer storage periods, have been struck through. The HFEA website states that they are planning a full update of the Code of Practice in 2023 to reflect the new law governing the storage of gametes and embryos[41].

An HFEA document reviewing the details of the new laws states that[42]:

“Patients can store gametes or embryos for their own treatment for up to 55 years from the date of first storage. Keeping gametes or embryos in storage for treatment for longer than 55 years is prohibited. There is no longer a requirement for patients to satisfy the premature infertility criteria to be able to store gametes or embryos for more than 10 years as was required by the 2009 Regulations. There is also no longer a requirement to obtain a written opinion from a registered medical practitioner as to premature infertility often in the form of a HFEA Medical Practitioner’s Statement (MPS). All patients may store their gametes or embryos for their own treatment for the maximum of 55 years, but they can only do this if they ‘renew’ their consent to storage, and this must take place within 10 years of first storage and at each successive 10-year period.”

Current ICB policies

An East Midlands-wide policy for cryopreservation of gametes was being developed but is currently on hold awaiting the outcome of this project.

Policies were received for Leicester, Leicestershire and Rutland ICB, Derby and Derbyshire ICB, Northamptonshire ICB, Bassetlaw CCG and Glossop (previously part of Tameside and Glossop CCG), either separately or as a section of the local assisted conception policy. The policy for Nottingham and Nottinghamshire ICB is stated within a local prior approval form. Lincolnshire ICB assisted conception policy states that cryopreservation is not in scope of the IVF policy. A separate cryopreservation policy was not received.

The policies received all include funding for cryopreservation of gametes prior to treatment that risks permanent infertility. The conditions listed under this, and specified exclusions, vary. Only Leicester, Leicestershire and Rutland and Derby and Derbyshire ICB policies mention not storing gametes and embryos for social reasons, with the latter also specifically excluding people with an existing child or who have been sterilised. However, the inclusion criteria in other ICB policies would imply that all ICBs do not fund storage for social reasons. There are also variations in age criteria for storage and duration of storage. The limit for commencement of storage varies from 38 to 42 years (43rd birthday) for females and from not being stated to the 56th birthday for males. The limit of duration of storage was generally to this maximum age or for 10 years, whichever is sooner, with the Bassetlaw CCG and Glossop (previously part of Tameside and Glossop CCG) policies specifying that the duration will remain in line with HFEA regulations if those changed. Where stated, policies specify that later use of gametes for conception will depend on the local policy at the time of use. Table 12 provides further details of the variation in local policies.

[41] Read the Code of Practice | HFEA
[42] HFEA Clinic Practical Guide on legal changes to storage limits and guidance - v3 - 8th March 2023

Table 12: Comparison of policies for gamete/embryo cryopreservation for the purpose of preserving fertility (i.e. not as part of an IVF/ICSI cycle) in the East Midlands (policy not received for Lincolnshire)

	Leicester, Leicestershire and Rutland ICB	Derby and Derbyshire ICB	Nottingham and Nottinghamshire ICB	Northamptonshire ICB	Bassetlaw (CCG)	Glossop (Tameside and Glossop CCG)
Indications for storage of gametes and embryos prior to treatment that risks loss of fertility (provided it is safe to do so prior to cancer treatment)	yes (for cancer chemotherapy, chemotherapy for autoimmune conditions, radiotherapy, male urological surgery, female gynaecological surgery if pregnancy would still be viable) (excludes infertility resulting from a congenital disorder) (includes gametes and embryos; not ovarian or testicular tissue)	yes (for cancer chemotherapy, radiotherapy, male urological surgery, female gynaecological surgery if pregnancy would still be viable, transgender receiving treatment for gender dysphoria) (includes gamete and embryo/blastocyst storage)	yes (single treatment cycle only; excludes embryos using donor sperm and additional costs for transport if needed) (includes gametes and embryos)	yes (via prior approval policy) (NHS treatment likely to result in reduced fertility; excludes superovulation and associated techniques – considered experimental) (embryos not mentioned in policy, only gametes)	yes (medical or surgical treatment likely to permanently affect fertility) (not ovarian or testicular tissue) (includes gametes and embryo storage)	yes (including cancer, lifesaving treatment, treatment for a congenital condition resulting in infertility, gender reassignment) (includes gametes and embryos)
Storage of gametes for non-medical non-surgical e.g. social reasons or sterilization or existing living child	no	no (including not if previously sterilised) Not if existing living child				
Age criteria for commencing storage	Ovarian stimulation before 43rd birthday; no minimum age	Ovarian stimulation before 43rd birthday; sperm retrieval before 56th	Up to 43rd birthday for female, single cycle only; 56th	From sexual maturity; women to	One cycle of egg retrieval; 1 further cycle if <10 oocytes; at least 2	If age over 42 years, IFR required for oocyte storage (will

	Leicester, Leicestershire and Rutland ICB	Derby and Derbyshire ICB	Nottingham and Nottinghamshire ICB	Northamptonshire ICB	Bassetlaw (CCG)	Glossop (Tameside and Glossop CCG)
		birthday; no minimum age but excludes pre-pubertal patients	birthday for male; no minimum age	age 38; men to age 45	semen samples, maximum 3. Age criteria not specified.	be dealt with as urgent).
Duration of storage	Storage of sperm and oocytes for 5 years; 5 further years if criteria still met; for oocytes till 42nd birthday if sooner. Can then opt to self-fund.	Storage of sperm and oocytes for 5 years; 5 further years if criteria still met; for oocytes till 42nd birthday if sooner. Can then opt to self-fund. Semen analysis annually and storage ends if semen analysis is normal	Sperm for 10 years or till age 56, eggs /embryos for 10 years or till age 43, whichever is sooner.	Sperm till age 55, oocytes till age 42, 10 years from retrieval, or death, whichever is sooner. Can then opt to self-fund. Annual health update needed re health and wishes re storage.	10 years. Further storage needs IFR and to be in line with HFEA.	Storage in line with HFEA regulations (at the time of the policy: no lower age, no upper age for men, up to 43 years for women, for up to 10 years). IFR required for extension of storage up to statutory limit (55 years at time of policy).
Future use of gametes	Depends on policy at the future time of use	Depends on policy at the future time of use			Depends on policy at the future time of use	Depends on policy at the future time of use

Question: What are the ethical considerations in relation to NHS-funded gamete and embryo storage and the duration of storage offered to patients in the following groups for the purpose of preserving fertility:

- People about to undergo NHS treatments that are likely to result in infertility (e.g. treatments for cancer or gender reassignment)?
- People with conditions that may result in earlier than average loss of fertility (e.g. endometriosis)?
- People who choose to store gametes so that they can postpone having a child for social reasons (e.g. career, caring, relationships, etc.)?

Ethical principle	What are the ethical considerations in relation to NHS-funded gamete storage and the duration of storage offered to patients in the following groups for the purpose of preserving fertility?		
	People about to undergo treatments that are likely to result in infertility	**People with conditions that may result in earlier than average loss of fertility, e.g. endometriosis**	**People with social reasons for postponing having a child**
Evidence of clinical effectiveness and safety	People who undergo treatments that result in iatrogenic infertility will not be able to conceive without using stored (or donor) gametes or embryos, and the use of these through IVF/ICSI provides an effective and relatively safe means of conception for them. However, effectiveness and safety of both retrieval of gametes and embryos and their use in IVF/ICSI, will depend on the patient's co-morbidities and health status and for some individuals the treatment, or the delay caused to their cancer treatment, may reduce effectiveness and/or increase risk. The evidence enquiry conducted for this project did not identify any evidence to suggest that longer duration of storage reduces effectiveness, particularly given that otherwise the individual may have little or no chance of conception.	Endometriosis is a condition which results in reduced fertility to a degree that varies between individuals. Given the natural reduction in fertility with age, the fertility of someone with endometriosis at increased age is likely to be lower than that of people who do not have endometriosis, for whom fertility is already very reduced by the age of 40 to 42. IVF/ICSI using stored gametes or embryos is an effective treatment for people with endometriosis. [26] However, the safety of storing gametes or embryos to allow conception at a later age compared to at a younger age is lower. There are higher risks for the mother and the child of a later pregnancy. There are also risks associated with retrieval of gametes for storage, such as ovarian hyperstimulation which though usually mild, can occasionally be serious. [27] The evidence enquiry conducted for this project did not identify any evidence to	The effectiveness of having a child at a later age using gametes or embryos stored when younger in achieving a live birth is greater than attempting to conceive naturally at a later age. However, the safety of conceiving at a later age compared to at a younger age is lower. There are higher risks for the mother and the child of a later pregnancy. There are also risks associated with retrieval of gametes for storage, such as ovarian hyperstimulation which though usually mild, can occasionally be serious. [27] The evidence enquiry conducted for this project did not identify any evidence to suggest that longer duration of storage would reduce effectiveness, particularly given that by the later age, the individual may have a relatively low chance of conception.

Ethical principle	What are the ethical considerations in relation to NHS-funded gamete storage and the duration of storage offered to patients in the following groups for the purpose of preserving fertility?		
		suggest that longer duration of storage would reduce effectiveness, particularly given that otherwise the individual, at a later age, may have little chance of conception.	
Cost-effectiveness	The procedure is likely to be considered cost-effective given that otherwise the individual may not have a chance to have a child. It is recommended by NICE for people about to undergo cancer treatment that is likely to affect their fertility [1]. However, the cost-effectiveness will depend on the likelihood that the gametes or embryos will be used for future conception. One recent study suggests that the utilisation rate is under 10% [28]. This will impact on cost-effectiveness.	A brief evidence search did not identify any evidence relating to the cost-effectiveness of storage of gametes or embryos or of IVF/ICSI in people with endometriosis. Unless, e.g. for medical reasons, there is no option of trying to conceive at a younger age, the cost-effectiveness of gamete or embryo storage in order to conceive at a later age (e.g. through IVF/ICSI) is lower than the cost-effectiveness of an individual with endometriosis attempting to conceive naturally or through IVF/ICSI at a younger age. This is because of the cost of gamete or embryo storage, the risks associated with gamete and embryo retrieval, and the risks associated with pregnancy at a later age.	The cost-effectiveness of gamete or embryo storage in order to conceive at a later age for social reasons is lower than the cost-effectiveness of an individual attempting to conceive naturally or through IVF/ICSI (if there is evidence of infertility) at a younger age. This is because of the cost of gamete or embryo storage, the risks associated with gamete and embryo retrieval, and the risks associated with pregnancy at a later age. (However, this does not take into account the cost to the patient, for example in terms of career progression, etc.) Evidence suggests that if gametes and embryos are to be stored, their effectiveness is greater in IVF/ICSI if they are stored at a younger age [28]. This may imply the need for longer durations of storage. Evidence suggests that the majority of people who store gametes or embryos for social reasons do not return to use them, regardless of the age of storage (59.8% “no use” rate over a 10 to 15 year follow-up period) [28]. This will also impact on cost-effectiveness.
Allocation of resources according to need and/or capacity to benefit from the treatment	Where a person requires treatment that will result in iatrogenic infertility and, for medical reasons, does not have the option to conceive prior to the treatment,	If a person with, for example, endometriosis, is not able to attempt conception because of medical needs, such as need for prior treatment for their endometriosis, the storage of gametes	Where a person chooses to store gametes or embryos for social reasons, this will not be reflective of medical need or capacity to benefit in terms of medical need, particularly given that

Ethical principle	What are the ethical considerations in relation to NHS-funded gamete storage and the duration of storage offered to patients in the following groups for the purpose of preserving fertility?		
	the storage of gametes and embryos will reflect medical need. Given that use of stored gametes and embryos for IVF is effective, the storage of gametes and embryos and the IVF/ICSI treatment will reflect capacity to benefit. Given that we did not identify evidence to suggest significant deterioration in the quality of stored gametes or embryos and hence reduction in the effectiveness of IVF/ICSI with increased duration of storage, longer duration of storage for those who have not yet been able to attempt conception will reflect need and capacity to benefit, particularly if the delay is for a medical reasons.	and embryos and, if required, extended duration of storage, will reflect medical need. Given that use of stored gametes and embryos for IVF is effective in this group, and for other groups where there is evidence that it is effective, the storage of gametes and embryos and the IVF/ICSI treatment will reflect capacity to benefit.	earlier conception without storage is safer for the woman and the baby. The evidence suggesting that the majority of people who store gametes or embryos for social reasons do not return to use them, regardless of the age of storage [28], implies that for many the need and capacity to benefit is limited.
Avoiding discrimination except where this is relevant to capacity to benefit from the treatment	Provision according to medical need and capacity to benefit will avoid discrimination. People with iatrogenic infertility are not a protected group under the Equalities Act 2010.	For people where the underlying condition requires postponement of conception, provision of gamete and embryo storage would be according to medical need and capacity to benefit and would avoid discrimination. Not providing gamete and embryo storage for those where there is no medical need to postpone conception and hence no medical benefit from postponing conception is not likely to constitute discrimination. People with premature infertility are not a protected group under the Equalities Act 2010.	Where there is no medical need and hence no medical benefit from postponing conception, not providing storage of gametes and embryos is not likely to constitute discrimination. People who choose to postpone conception for social reasons are not a group that is protected under the Equalities Act 2010.

Ethical principle	What are the ethical considerations in relation to NHS-funded gamete storage and the duration of storage offered to patients in the following groups for the purpose of preserving fertility?		
Absolute costs, affordability in relation to the overall ICB resources for healthcare, and hence anticipated impact on the rest of the patient population	Storage of gametes and embryos prior to treatment that is likely to reduce fertility is currently funded by ICBs. Although the data received from ICBs does not include sufficient detail to understand current durations of storage and usage rates and times, they suggest that there were many more sperm storage episodes than egg storage episodes in the four years from 2019/20 to 2022/23 (280,170, 55 and 60 for sperm storage episodes versus 31, 44, 51 and 46 for oocyte storage episodes respectively). However, it is not clear how accurate these data are.[43] In addition, it is not clear how many of the episodes relate to retrieval of sperm or oocytes vs extension of storage. The reason for the large fall in sperm storage in 2021/22 and 2022/23 compared to the previous 2 years would be worth exploring with clinicians. Given this, it is not possible, from the available data, to predict the increased cost that might arise from increasing the duration of NHS-funded gamete and embryo storage for people with iatrogenic infertility.	It has not been possible to estimate the number of females with endometriosis who may request storage or extended storage of gametes or embryos, or to estimate the cost and affordability to the ICB is this was funded by the NHS.	It has not been possible to estimate the number of individuals who would request gamete or embryo storage for social reasons if this was funded by the NHS. However, the number requesting this privately is increasing [29]. The HFEA reported that egg and embryo storage cycles are the fastest growing fertility treatments in the UK, with egg storage cycles increasing from 373 in 2011 to 4,215 cycles in 2021 and embryos storage cycles from 230 in 2011 to 10,719 cycles in 2021 [6].

[43] Please see section on activity data which explains why these data may be inaccurate or incomplete.

Summary

People about to undergo treatments that are likely to result in infertility (e.g. treatment for cancer or gender reassignment)

Storage of gametes or embryos for future use in this group is a relatively clinically effective and safe procedure, reflects clinical need and capacity to benefit, and avoids discrimination, provided that the process of gamete retrieval (including ovulation induction) and the time required for this, does not impact negatively on prognosis (e.g. for a patient with cancer). No evidence was identified to suggest that longer duration of storage of gametes or embryos reduces effectiveness, particularly given that otherwise the individual may have little or no chance of conception. It was not possible, from available data, to estimate the cost per ICB of increasing the NHS-funded duration of storage of gametes or embryos for this group. The other costs associated with IVF/ICSI would still be incurred in due course (provided the individual meets future criteria (e.g. age and BMI) for access to IVF/ICSI).

People with conditions that may result in earlier than average loss of fertility (e.g. endometriosis)

Although IVF/ICSI is a relatively clinically effective, safe and cost-effective procedure for this group if they suffer from infertility, postponing these treatments by storing gametes or embryos for future use increases the risks to the mother and child and reduces cost-effectiveness compared to having fertility treatments at a younger age. However, if for medical reasons the individual is not able to attempt to conceive at a younger age, storage of gametes or embryos for future use may be considered cost-effective and to reflect need and capacity to benefit. It was not possible to estimate the number of women and associated costs that might be incurred by each ICB if storage of gametes and embryos for this group was funded by the NHS.

People with social reasons for postponing having a child

Although IVF/ICSI is a relatively clinically effective and safe procedure, it is safer for the mother and child not to postpone pregnancy by storing gametes and embryos for future use. Doing this for social reasons does not reflect medical need or capacity to benefit, and is not cost-effective compared to having a child at a younger age. It was not possible from the data available to estimate the number of women who wish to store gametes and embryos and postpone having a child for non-medical reasons, but this is reported to be one of the fastest growing fertility treatments in the UK [6]. The cost impact for ICBs will not be insignificant.

6 ACTIVITY

Each ICB contract lead provided anonymised data, either directly or through their provider, for all assisted conception activity in 2019/20 to 2022/23. Following discussions with information governance leads, it was agreed that the data provided would include, for each patient, their:

- ICB
- GP practice – to assess inequalities in access (it was not possible to obtain patient postcodes because of the risk of patient identification)
- Year and month of treatment (invoice month)
- Age group
- Treatment type – particularly IVF/ICSI, DI/IUI, egg freeze and storage, and sperm freeze and storage
- Outcome – whether the treatment was cancelled and whether pregnancy was achieved (data on live births were not available)

Unfortunately, one major provider was not able to provide outcome data and other outcome data received were difficult to interpret. The analysis therefore excludes outcomes. Outcomes were analysed separately across the whole of the East Midlands using data provided by the HFEA through a freedom of information (FOI) request.[44]

Some of the data were received late in non-standard formats, making data validation difficult. However, comments on the draft report suggested that the large differences in IUI activity rates between ICBs was not likely to be substantially affected by missing data. In addition, due to information governance concerns within ICBs and the HFEA, it was not possible to obtain sufficient data to assess inequalities in access, for example in relation to ethnicity.

Analyses carried out include:

- Activity for the whole of the East Midlands
- Activity by ICB
- Activity by provider
- Activity by age group
- Activity by deprivation quintile (Index of Multiple Deprivation (IMD)) quintile, based on the average deprivation level of the patients registered with their GP practice (because patient postcode/deprivation quintile was not available due to information governance concerns)
- Outcomes for IVF/ICSI across the East Midlands (live births)
- Cost

6.1 Total activity across East Midlands ICBs

Table 13 provides a breakdown by year for all the treatment categories for which data were provided, with some categories, such as IVF and ICSI combined.[45]

Table 13: Number of treatments for East Midlands ICBs by treatment category and year

[44] Detailed discussions with the HFEA and two earlier requests which were deemed to be requesting more than was possible within FOI rules, meant that the HFEA data received were combined for all providers.
[45] Treatment categories were combined because the decision of which to use is a clinical decision and the cost to the NHS is the same (e.g. IVF and ICSI), or because the data were not clear on which were used (e.g. IUI vs DI).

Treatment Category	2019/20	2020/21	2021/22	2022/23	All Years
IVF/ICSI	765	632	710	689	**2,796**
AI/DI/IUI	229	140	193	152	**714**
FER	458	414	496	520	**1,888**
Luteal Support	254	237	276	278	**1,045**
Cancelled IVF/ICSI	7	1	5	16	**29**
Cancelled FER	0	6	0	21	**27**
Cancelled DI/IUI	12	37	56	45	**150**
Cancelled cycle, treatment not known	30	29	36	19	**114**
Egg Freeze / Storage	31	44	51	46	**172**
Sperm Freeze / Storage	280	170	55	60	**565**
Consultation	712	687	850	741	**2,990**
Cryo (details not provided)	9	3	4	6	**22**
Donor Sperm	3	1	4	3	**11**
Surgical Sperm Retrieval	26	10	16	8	**60**
Other	0	5	0	0	**5**
Not Stated	3	2	5	9	**19**
Total	**2,819**	**2,418**	**2,757**	**2,613**	**10,607**

Note: Consultations were only recorded by UHL and not by the other providers.

Excluding consultations, because the number of consultations was only provided by UHL, IVF/ICSI was the most common procedure reported. The number was lower in 2020/21, presumably due to the Covid-19 pandemic, but over 600 IVF/ICSI cycles were carried out in that year nevertheless. The number of IVF/ICSI cycles carried out in 2021/22 and 2022/23 (710 and 689) was higher than in the main year of the Covid-19 pandemic (2020/21), but remained lower than before the pandemic (765 IVD/ICSI cycles in 2019/20).[46] A similar pattern was seen with AI/DI/IUI, with a significant fall in 2020/21 compared to the previous year and the next two years' numbers remaining lower than before the pandemic.

The number of cancelled IVF/ICSI cycles was relatively low at 7, 1 and 5 in 2019/20, 2020/21 and 2021/22 respectively, but was significantly higher at 16 in 2022/23. However there were another 30, 29, 36 and 19 cancelled cycles in these years respectively for which the type of treatment that was cancelled (IVF/ICSI, AI/DI/IUI or FER) was not recorded.

The number of reported episodes of egg freezing or egg storage each year (31 to 51) was much lower than the number of reported episodes of sperm freezing or sperm storage each year (55 to 280 in 2019/20 to 2022/23). Whereas the number of egg freeze / egg storage episodes reported did not appear to change significantly over the four years for which data were received, the number for sperm fell significantly after the Covid-19 pandemic from 280 in 2019/20 and 170 in 2020/21 to only 55 and 60 in 2021/22 and 2022/23 respectively. It is not clear from the data received whether all the episodes marked as egg or sperm freezing or storage were for people seeking to preserve their fertility prior to treatments such as chemotherapy or radiotherapy that are likely to permanently damage fertility. It is also not clear whether an episode relates to freezing for one or three years.

6.2 Activity by ICB

Table 14 provides the numbers of the main assisted conception procedures carried out between April 2019 and March 2023 inclusive for each of the five East Midlands ICBs. According to the data

[46] This is likely to be due to delays in access to GPs and fertility clinics / waiting times in some ICBs, as a referral from a fertility clinic is needed for accessing IVF (communication from clinician).

provided, the main activity by far in all ICBs related to IVF/ICSI except at NHS Leicester, Leicestershire and Rutland ICB where there were similar numbers of AI/DI/IUI procedures carried out as well as a relatively large number of episodes related to egg and sperm freezing and storage.

It is not clear why the numbers of reported AI/DI/IUI and gamete freezing and storage procedures were so much higher for patients registered with NHS Leicester, Leicestershire and Rutland ICB compared to other ICBs and why no AI/DI/IUI procedures were reported over the four years for NHS Nottingham and Nottinghamshire ICB. Although this might be in part due to missing data, comments on the draft version of this report suggest that the higher activity rate for IUI at Leicester, Leicestershire and Rutland ICB is because they have traditionally had a separate funding pot and policy for this, unlike the other ICBs. Regarding the differences in gamete freezing and storage rates, a separate communication from the Northamptonshire ICB lead stated that there were approximately 50 gamete storage cases last year of which about 25% to 30% were for females. This suggests that the figures of five egg freeze / storage and 31 sperm freeze and storage over the four years is not accurate and data are likely to be missing. Possible data issues need to be investigated further before interpreting these data. However, the data for IVF/ICSI procedures are likely to be more reliable and some of the further analyses below have been limited to IVF/ICSI and associated procedures.

Table 14: Number of selected assisted conception treatments across East Midlands ICB registered patients, 2019/20 to 2022/23 combined

ICB	IVF/ICSI	AI/DI/IUI	Egg Freeze / Storage	Sperm Freeze / Storage	Total
NHS Derby and Derbyshire ICB	681	7	22	26	736
NHS Leicester, Leicestershire and Rutland ICB	642	632	91	443	1,808
NHS Lincolnshire ICB	340	67	9	14	430
NHS Northamptonshire ICB	460	8	5	31	504
NHS Nottingham and Nottinghamshire ICB	673	0	45	51	769
Total	**2,796**	**714**	**172**	**565**	**4,247**

See comments in narrative regarding data issues.

To assess the degree to which this variation reflects the number of women of childbearing age in each of the ICBs, crude rates for each of the groups of procedures were calculated (Table 15). This suggests that the highest rate of IVF/ICSI provision was 4.0 per 1000 women aged 18 to 42 years in Derby and Derbyshire ICB, which was 33% higher than the lowest rate of 2.9 per 1,000 women aged 18 to 42 in Lincolnshire ICB. The average rate of IVF/ICSI provision across the East Midlands was 3.3 per 1,000 women aged 18 to 42.

Table 15: Crude rate of IVF/ICSI per 1,000 women aged 18 to 42 years by ICB (2019/20 to 2022/23 combined)

ICB Name	IVF/ICSI	AI/DI/IUI	Egg Freeze / Storage	Sperm Freeze / Storage	Female Pop aged 18 to 42
NHS Derby and Derbyshire ICB	4.0	0.0	0.1	0.2	169,269
NHS Leicester, Leicestershire and Rutland ICB	3.2	3.1	0.4	2.2	202,650
NHS Lincolnshire ICB	2.9	0.6	0.1	0.1	116,352
NHS Northamptonshire ICB	3.4	0.1	0.0	0.2	134,653
NHS Nottingham and Nottinghamshire ICB	3.1	0.0	0.2	0.2	218,081
Total	3.3	0.8	0.2	0.7	**841,005**

See comments in narrative regarding data issues.

6.3 Activity across East Midlands providers

The main providers of assisted conception for the ICBs in 2019/20 to 2022/23 were as follows:

- Leicester, Leicestershire and Rutland ICB: United Hospitals Leicester (UHL), Care Fertility (Nottingham and Northampton) and Nurture (Nottingham)
- Northamptonshire ICB: Care Northampton (plus a small amount through TFP Oxford, part of Nurture)
- Nottingham and Nottinghamshire ICB: Nurture Nottingham and Care Fertility Nottingham
- Derby and Derbyshire ICB: Care Fertility, Nurture, Sheffield Teaching Hospital (Jessops)
- Lincolnshire ICB: Care Fertility (Nottingham, Northampton and Sheffield) and Nurture

Other providers with which contracts for assisted conception are held by East Midlands ICBs but where there was little or no activity reported are Bourne Hall, IVI Wimpole London, and Cambridge University Hospitals.

The majority of IVF/ICSI provision for Derby and Derbyshire, Lincolnshire and Northamptonshire ICBs is by Care Fertility, a private provider with clinics in Nottingham, Northampton and Sheffield within the East Midlands. For Nottingham and Nottinghamshire ICB, the main provider is Nurture, a private provider based in Nottingham that also provides a significant amount of IVF/ICSI provision for Derby and Derbyshire, Lincolnshire and Leicester, Leicestershire and Rutland ICBs. The main provider of IVF/ICSI for Leicester, Leicestershire and Rutland ICB patients is UHL, which is an NHS provider that also provides secondary care fertility services. Jessop Fertility is the Fertility unit within Sheffield Teaching Hospital, that provides some IVF/ICSI procedures for Derby and Derbyshire and Lincolnshire ICBs.

Table 16 provides a breakdown of provision by these main providers for the whole of the East Midlands in 2019/20 to 2022/23. More than 50% of the IVF/ICSI procedures in these four years were carried out by Care Fertility.

Table 16: Number of treatments by provider and treatment category (East Midlands ICBs, 2019/20 to 2022/23 combined)

Provider	IVF/ICSI	AI/DI/IUI	Egg Freeze / Storage	Sperm Freeze / Storage
Care Fertility	1425	73	11	3
Nurture	723	0	64	79
UHL	540	641	97	482
Sheffield Teaching Hospital (Jessops Fertility)	73	0	0	1
Total	**2761**	**714**	**172**	**565**

A breakdown of providers by ICB is shown in Table 17.

Table 17: Number of treatments by ICB, provider and treatment category (2019/20 to 2022/23 combined)

ICB/Provider	IVF/ICSI	AI/DI/IUI	Egg Freeze / Storage	Sperm Freeze / Storage	Total
NHS Derby and Derbyshire ICB	*681*	*7*	*22*	*26*	*736*
Care Nottingham	309	6	9	1	325
Care Sheffield	105	1	1	0	107
Sheffield Teaching Hosp (Jessop Fertility)	73	0	0	1	74
Nurture LLP	194	0	12	21	227
UHL	0	0	0	3	3
NHS Leicester, Leicestershire and Rutland ICB	*642*	*632*	*91*	*443*	*1808*
Nurture	85	0	0	0	85
UHL	527	630	91	443	1691
Care Fertility (LLR ICB)*	30	2	0	0	32
NHS Lincolnshire ICB	*340*	*67*	*9*	*14*	*430*
Cambridge IVF	3	0	0	0	3
Care Northampton	42	0	0	0	42
Care Nottingham	211	64	1	1	277
Care Sheffield	20	0	0	0	20
Nurture LLP	61	0	7	12	80
Oxford IVF	1	0	0	0	1
UHL	2	3	1	1	7
NHS Northamptonshire ICB	*460*	*8*	*5*	*31*	*504*
Care Northampton	419	0	0	0	419
Oxford IVF	30	0	0	0	30
UHL	11	8	5	31	55
NHS Nottingham and Nottinghamshire ICB	*673*	*0*	*45*	*51*	*769*
Care Nottingham	288	0	0	1	289
Care Sheffield	1	0	0	0	1
Nurture LLP	383	0	45	46	474
Oxford IVF	1	0	0	0	1
UHL	0	0	0	4	4
Total	**2796**	**714**	**172**	**565**	**4247**

* For Leicester, Leicestershire and Rutland (LLR) ICB, data received on provision by Care Fertility was not split by Care Fertility site.

6.4 Age group

Table 18 shows the number of IVF/ICSI cycles carried out in the four years from 2019/20 to 2022/23 by age group. Figure 5 provides rates per 1,000 women. The age group with the highest rate of NHS-funded IVF/ICSI cycles in the East Midlands was the 30 to 34 year age group (5.2 to 7.1 per 1,000 women aged 30 to 34). This was most marked for Derby and Derbyshire ICB (7.1 per 1,000). Derby and Derbyshire ICB also had the highest rate of provision of IVF/ICSI cycles per 1,000 women for the 40 to 42 year age group (3.3 per 1,000 women aged 40 to 42 compared to a range of 1.8 to 2.8 per 1,000 across the other four ICBs for this age group).

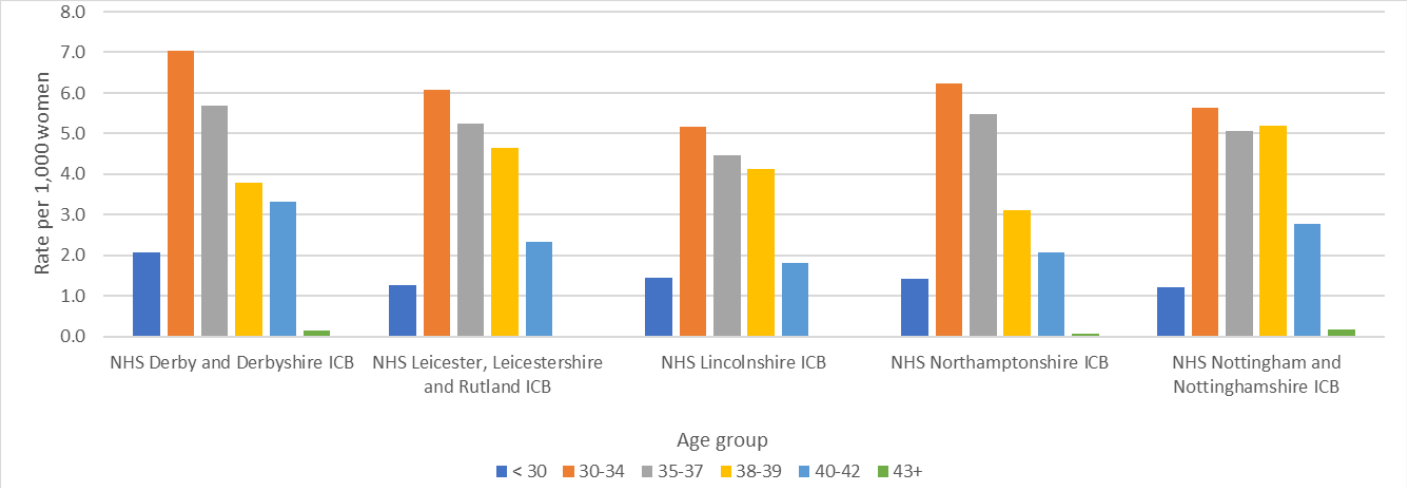
The 30 to 34 year age group was the age group that received the most IVF/ICSI cycles in 2019/20 to 2022/23 at each of the main East Midlands providers.

Note that although the data suggest that a small number of women (eight in the four years from 2019/20 to 2022/23) received IVF/ICSI at the age of 43, this may be because the age provided in the dataset may not have been the age at commencement of the treatment cycle.

Table 18: Number of IVF/ICSI cycles by ICB and age band (2019/20 to 2022/23 combined)

IVF/ICSI	Age Band						
	< 30	30-34	35-37	38-39	40-42	43+	Unknown
Total number	*557*	*1,096*	*565*	*296*	*255*	*8*	*19*
NHS Derby and Derbyshire ICB	152	268	128	55	70	3	5
NHS Leicester, Leicestershire and Rutland ICB	121	255	133	77	56	0	0
NHS Lincolnshire ICB	75	129	68	40	26	0	2
NHS Northamptonshire ICB	79	192	103	37	36	1	12
NHS Nottingham and Nottinghamshire ICB	130	252	133	87	67	4	0

Figure 5: IVF/ICSI age specific rate per 1,000 women (2019/20 to 2022/23 combined)



6.5 Deprivation quintile

In order to assess inequalities in access to assisted conception by deprivation level, the average deprivation level (IMD 2019[47] score) of all individuals registered at the patient's general practice was used, based on published National General Practice profiles [30]. This is because, for information governance reasons, individual patient postcodes, or IMD scores based on these, were not available.

Figure 6 shows how the number of IVF/ICSI cycles in each ICB varies by practice deprivation quintile,[48] and Figure 7 shows the proportion of total IVF/ICSI cycles in each deprivation quintile by ICB. In 2019/20 to 2022/23, for all ICBs, there were fewer IVF/ICSI cycles provided for women in the most deprived quintile of GP practices compared to those in the least deprived quintile of practices. This appears to be particularly marked for Leicester, Leicestershire and Rutland ICB and least marked for Nottingham and Nottinghamshire ICB.

[47] IMD 2019 is a deprivation score that is a composite of multiple weighted components of deprivation (essentially a measure of poverty) for lower super output areas in the UK. English Indices of Deprivation 2019: technical report (publishing.service.gov.uk)

[48] GP practices in each ICB are grouped using national GP practice IMD quintiles based on the average of the deprivation scores of all patients registered with the practice. Source: National General Practice Profiles - OHID (phe.org.uk)

Figure 6: Number of IVF/ICSI cycles by ICB and Index of Multiple Deprivation (IMD 2019) quintile (2019/20 to 2022/23 combined)

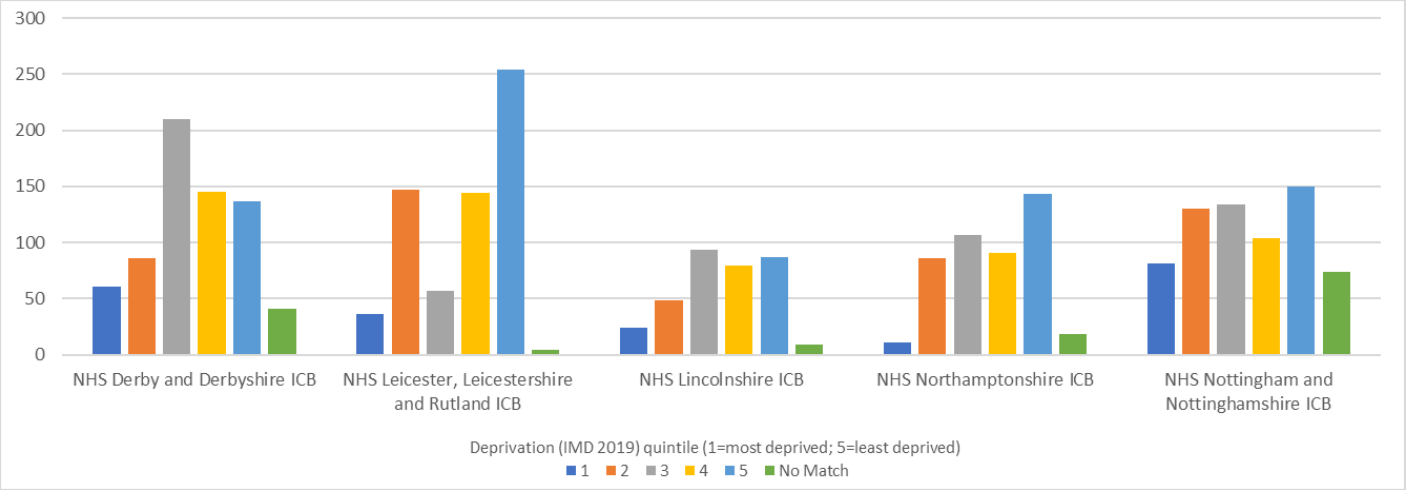
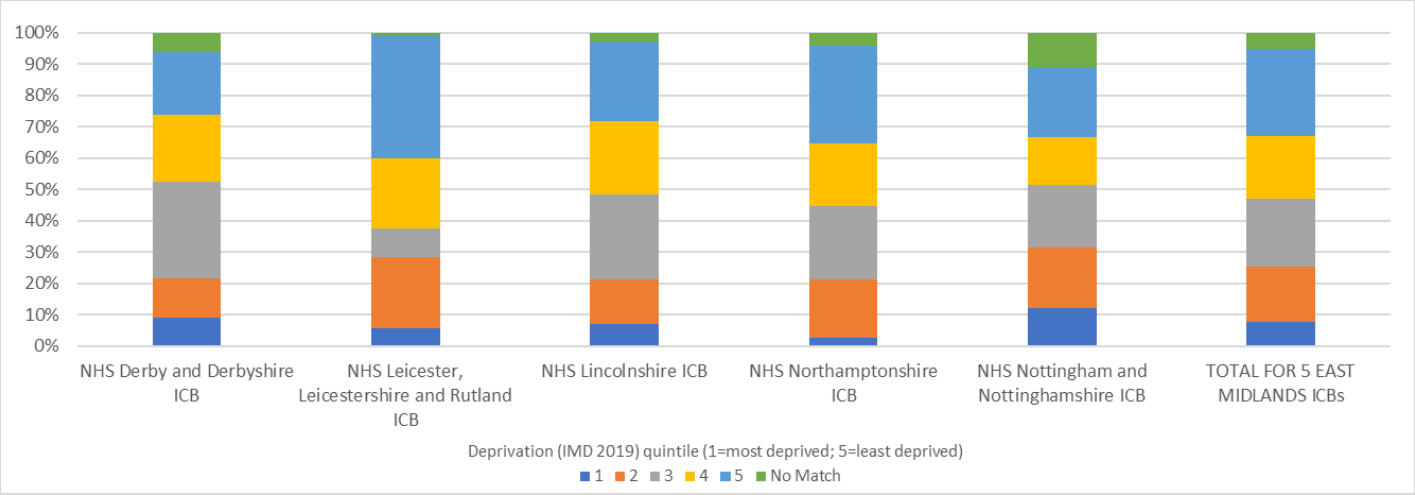
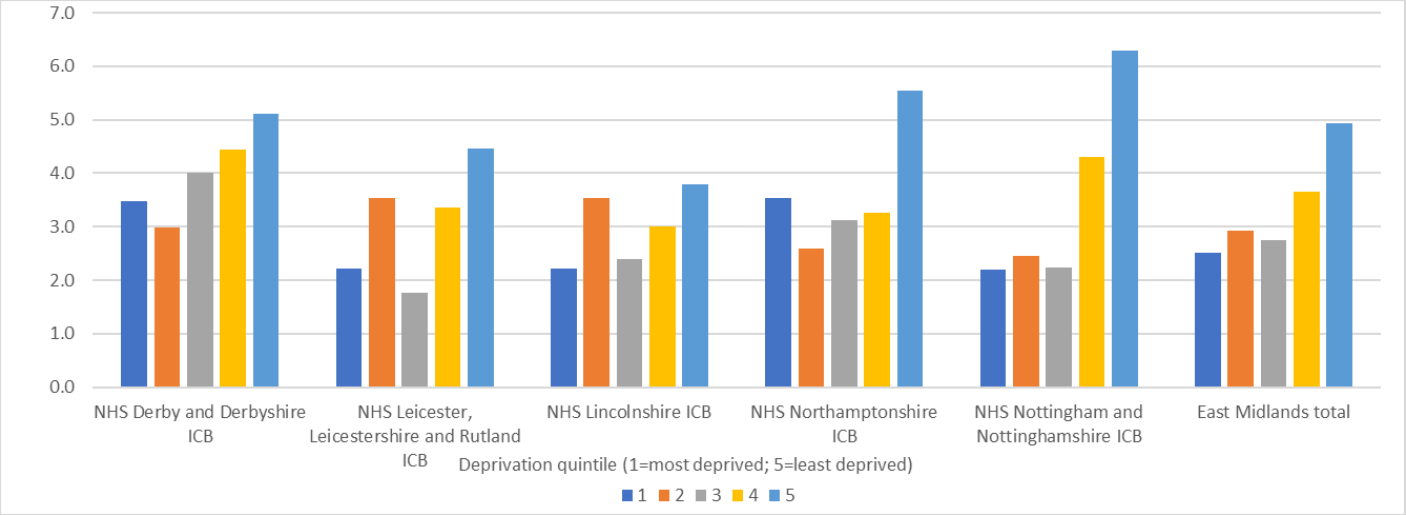


Figure 7: Percent IVF/ICSI cycles by Index of Multiple Deprivation (IMD 2019) quintile for each ICB (2019/20 to 2022/23 combined)



Differences in IVF/ICSI activity by practice deprivation quintile could reflect the number of women of childbearing age in each deprivation quintile in the ICB. We therefore calculated the rate of IVF/ICSI activity per 1,000 women aged 18 to 42 years in each GP practice deprivation quintile for each ICB. This shows that there are higher rates of provision of IVF/ICSI cycles in the least deprived GP practice quintile compared to the most deprived quintile in all the ICBs and overall for the East Midlands (Figure 8). The gradient appears most marked for Nottingham and Nottinghamshire ICB. Reasons for this may include factors such as higher rates of smoking, obesity and fuel/transport poverty in more deprived groups, and being more likely to have had previous children at a younger age [31, 32, 33].

Figure 8: Crude rate of IVF/ICSI cycles (2019/20 to 2022/23 combined) per 1,000 18 to 42 year old female population registered with ICB GP practices in each IMD quintile



GP practices in each ICB are grouped by national GP practice IMD quintiles based on the average of the deprivation scores of all patients registered with the practice. Source: OHID GP practice profiles (National General Practice Profiles - OHID (phe.org.uk))
Missing data (not able to match to a GP practice IMD quintile) for 41 IVF/ICSI cycles in Derby and Derbyshire ICB, 9 in Lincolnshire ICB, 18 in Northamptonshire ICB, 74 in Nottingham and Nottinghamshire ICB and 4 in Leicester, Leicestershire and Rutland ICB.

6.6 Outcomes

Outcomes were analysed across the whole of the East Midlands using data provided by the HFEA through a freedom of information (FOI) request. Detailed discussions with the HFEA and two earlier requests which were deemed to be requesting more than was possible within FOI rules, meant that the HFEA data that we were able to obtain were combined for all providers. So as to reflect outcomes within the East Midlands, we requested that providers that are used relatively infrequently by patients from the East Midlands were excluded from these data because a large proportion of patients at those providers are likely to not be from the East Midlands. Nevertheless, the providers that were included (Care Fertility Sheffield, Care Fertility Nottingham, Care Fertility Northampton, Jessop Fertility (part of Sheffield Teaching Hospital), Leicester Fertility Centre (part of United Hospitals Leicester) and TFP Nurture Fertility Clinic Nottingham) are likely to also treat patients from ICBs outside the East Midlands. These data should therefore not be used as an indicator of IVF activity for East Midlands ICBs, but they do provide an indication of IVF outcomes.

Outcomes were provided separately by age group and for NHS-funded and privately funded IVF cycles for 2016, 2017 and 2018 (the most recent year for which data had been validated). These included numbers of pregnancies, live births, multiple birth occurrences, preterm births, low birth weight births and miscarriages.

Table 19 shows the number of IVF cycles provided by the main East Midlands providers for the years 2016, 2017 and 2018 combined, together with the numbers of live births and the live birth rate (LBR) by age group and whether NHS or privately funded. These data include IVF treatment cycles begun with the intention of having a live birth only and include fresh and frozen embryo transfers (one cycle of IVF includes one episode of ovarian stimulation and transfer of all fresh and frozen embryos that result). Treatments in which a pregnancy was recorded and no birth outcome recorded have been excluded. Treatments that involved preimplantation genetic testing and treatments using donor eggs or surrogacy have been excluded. Smaller numbers in the tables are an underestimate because to avoid the risk of patient identification, numbers under 5 in any age group/year were suppressed and counted as zero.

These data confirm for the NHS what is known from the published evidence, that LBRs reduce substantially with increasing age of the mother. The rates were slightly lower for NHS funded

cycles compared to privately funded cycles for most age groups except for women under 35 years where the LBR was slightly higher for NHS funded cycles. Overall, however, LBRs are higher for NHS funded cycles (35%) than for privately funded cycles (32%) because older women, for whom LBRs from IVF are the lowest, are not provided with NHS funded IVF but are provided with IVF treatments in the private sector.

Table 19: Live birth rates for IVF cycles by age group for the main East Midlands providers (including patients not registered with East Midlands ICBs), 2016 to 2018 inclusive

Patient age	IVF cycles	Live birth occurrences	Live birth rate
NHS funded			
Under 35	3,018	1,220	40%
35-37	1,023	316	31%
38-39	468	111	24%
40-42	353	55	16%
43-44	21	0*	0%
Over 44	0	0	
Total	**4,883**	**1,702**	**35%**
Privately funded			
Under 35	3,702	1,454	39%
35-37	2,168	751	35%
38-39	1,279	343	27%
40-42	1,213	207	17%
43-44	286	36	13%
Over 44	88	0*	0%
Total	**8,736**	**2,791**	**32%**

Includes some patients from outside the East Midlands.
One IVF cycle includes ovarian stimulation and insertion of all fresh and frozen live births.
Preimplantation genetic testing, cycles using donor eggs and surrogacy are excluded.
* An underestimate because to avoid the risk of patient identification, numbers under 5 in any age group/year were suppressed and counted as zero. In 2017, <5 live births were reported for 43-44 year old NHS-funded patients.
Source: HFEA FOI request, data received August 2023

Table 20 provides an indication of the frequency of multiple births and a range of adverse events for the NHS funded IVF cycles by age group. However, exact numbers of each adverse event are not known because, to avoid the risk of patient identification, numbers under 5 in any age group/year were suppressed and counted as zero. In addition, there is no comparison with rates of adverse events associated with natural conception.

Among the 4,883 NHS funded IVF cycles in 2016 to 2018 recorded by the HFEA for the main IVF providers for East Midlands ICBs, there were just over 218 miscarriages, which were the most common adverse event. The number of miscarriages was highest in the youngest age group. However, the miscarriage rate as a percentage of NHS funded IVF cycles was lowest in the youngest age group (under 35s) and there was a suggestion from the data that miscarriage rates increase with increasing age of the mother (Table 21).

Table 20: Numbers of multiple births and adverse events for NHS-funded IVF cycles by age group for the main East Midlands providers (including patients not registered with East Midlands ICBs), 2016 to 2018 inclusive

Patient age	IVF cycles	Multiple birth occurrences	Extremely preterm (less than 28 weeks)	Very preterm (28 to 32 weeks)	Moderate to late preterm (33 to 36 weeks)	Low birth weight (under 2.5 kg)	Miscarriages	Terminations	Congenital abnormalities	Reductions	Stillbirths
Under 35	**3,018**	86	6*	33	129	184	107	6	8*	0*	0*
35-37	**1,023**	24	0*	0*	39	50	59	0*	0*	0	0*
38-39	**468**	0*	0*	0*	5*	10*	35	0*	0	0	0
40-42	**353**	5*	0*	0*	0*	0*	17*	0*	0*	0*	0
43-44	**21**	0	0	0	0	0	0	0	0	0	0
Over 44	**0**	0	0	0	0	0	0	0	0	0	0
Total	**4,883**	115	6	33	173	244	218	6	8	0	0

Includes some patients from outside the East Midlands.
Includes IVF treatment cycles begun with the intention of having a live birth only and includes fresh and frozen embryo transfers. Treatments in which a pregnancy was recorded and no birth outcome recorded have been excluded. Preimplantation genetic treatments and treatments using donor eggs or surrogacy have been excluded. Counts of preterm births and low birth weights are provided as occurrences based on the presence of 1-3 foetal heartbeats identified by ultrasound during pregnancy. Miscarriages, reductions, still births, terminations and congenital abnormalities are total counts which include outcomes for all foetal heartbeats identified (1-3 heartbeats) by ultrasound during pregnancy.
* An underestimate because to avoid the risk of patient identification, numbers under 5 in any age group/year were suppressed and counted as zero (e.g. there were 8, 9 and <5 miscarriages in 40-42 year olds in 2016, 2017 and 2018 respectively).
Source: HFEA FOI request, data received August 2023

Table 21: Miscarriage rates for NHS-funded IVF cycles by age group for the main East Midlands providers (including patients not registered with East Midlands ICBs), 2016 to 2018 inclusive

Patient age	IVF cycles	Miscarriages	Rate of miscarriage (per IVF cycle)
Under 35	**3,018**	107	3.5%
35-37	**1,023**	59	5.8%
38-39	**468**	35	7.5%
40-42	**353**	17*	4.8%*
43-44	**21**	0	0.0%
Total	**4,833**	218	4.5%

Includes some patients from outside the East Midlands.
Includes IVF treatment cycles begun with the intention of having a live birth only and includes fresh and frozen embryo transfers. Treatments in which a pregnancy was recorded and no birth outcome recorded have been excluded. Preimplantation genetic treatments and treatments using donor eggs or surrogacy have been excluded. Counts of preterm births and low birth weights are provided as occurrences based on the presence of 1-3 foetal heartbeats identified by ultrasound during pregnancy. Miscarriages, reductions, still births, terminations and congenital abnormalities are total counts which include outcomes for all foetal heartbeats identified (1-3 heartbeats) by ultrasound during pregnancy.
* An underestimate because to avoid the risk of patient identification, numbers under 5 in any age group/year were suppressed and counted as zero (there were 8, 9 and <5 miscarriages in 40-42 year olds in 2016, 2017 and 2018 respectively).
Source: HFEA FOI request

6.7 Cost

Using tariffs we were provided by contract leads, we have estimated the total cost of IVF/ICSI and AI/DI/IUI for each ICB for each year from 2019/20 to 2022/23. The actual costs to the ICB may be different due to confidential agreements with providers. For IVF/ICSI, we have reflected the different tariff for women aged 37 and under vs women aged 38 and over. For AI/DI/IUI, it is not always clear whether the data received reflects the number of episodes for which donor sperm were used, as opposed to partner sperm. We have therefore not included the cost of donor sperm in these cost estimates. For egg and sperm freezing and storage, it was not always clear from the data whether the episode related to the initial collection and freezing or to follow up contacts and

continued storage, each of which incurs a very different tariff. We have therefore not attempted to estimate costs for these procedures.

Table 22 provides the total estimated costs of IVF/ICSI and of AI/DI/IUI (excluding costs of donor sperm) for each ICB using these baseline tariffs for the four years from 2019/20 to 2022/23. Figure 9 shows how costs for IVF/ICSI varied by year for each ICB over the four years.

Overall, excluding the costs of donor sperm, frozen embryo transfer, luteal support and cancelled cycles, each ICB spent between about £1 million and £2 million pounds on IVF/ICSI over the last four years; Lincolnshire ICB spent the least (around £1 million), Northamptonshire ICB spent about £1.4 million, and the other three ICBs spending around £2 million each over the four years. The variation from year to year varied between ICBs with no clear pattern (Table 22).

Table 23 provides the cost per 1,000 women aged 18 to 42 by ICB to provide an indication of the extent to which the differences in ICB costs reflect population differences.

Assuming that all the frozen embryo transfer episodes and luteal support episodes reported were associated with IVF/ICSI cycles and that half of the cancelled IVF/ICSI cycles reported were cancelled after ovarian stimulation and before oocyte retrieval,[49] we applied the tariffs received to estimate the total costs of IVF/ICSI including frozen embryo transfer, luteal support and cancelled cycles (Table 24).

The estimated costs from the data we received for AI, DI and IUI vary to a much greater extent, from £0 over the four years (Nottingham and Nottinghamshire ICB) to over £500,000 over the four years for Leicester, Leicestershire and Rutland ICBs (Table 22). This variation should be investigated as part of future policy development.

Table 22: Costs of IVF/ICSI cycles and AI/DI/IUI cycles by ICB and year 2019/20 to 2022/23)

	2019/20	2020/21	2021/22	2022/23	Total
IVF/ICSI cost*					
NHS Derby and Derbyshire ICB	£584,800	£479,600	£472,800	£542,000	£2,079,200
NHS Leicester, Leicestershire and Rutland ICB	£417,600	£523,400	£522,800	£515,400	£1,979,200
NHS Lincolnshire ICB	£281,000	£260,400	£254,600	£251,200	£1,047,200
NHS Northamptonshire ICB	£472,000	£218,200	£352,000	£372,200	£1,414,400
NHS Nottingham and Nottinghamshire ICB	£596,800	£473,200	£571,200	£441,000	£2,082,200
TOTAL FOR 5 EAST MIDLANDS ICBs	**£2,352,200**	**£1,954,800**	**£2,173,400**	**£2,121,800**	**£8,602,200**
AI/DI/IUI cost					
NHS Derby and Derbyshire ICB	£825	£2,475	£825	£1,650	£5,775
NHS Leicester, Leicestershire and Rutland ICB	£172,425	£94,875	£141,900	£112,200	£521,400
NHS Lincolnshire ICB	£14,025	£16,500	£14,025	£10,725	£55,275
NHS Northamptonshire ICB	£1,650	£1,650	£2,475	£825	£6,600
NHS Nottingham and Nottinghamshire ICB	£0	£0	£0	£0	£0
TOTAL FOR 5 EAST MIDLANDS ICBs	**£188,925**	**£115,500**	**£159,225**	**£125,400**	**£589,050**

* These figures do not include the costs of frozen embryo transfer, luteal support or cancelled cycles

[49] This assumption was made because the reason for or timing of cancellation was poorly recorded in the data and only cycles IVF/ICSI cycles cancelled after ovarian stimulation and before oocyte retrieval are associated with a tariff. There were also a number of cancelled cycles reported (114 cycles over the four years) for which the type of treatment was not reported. These have not been included in these figures.

Table 23: Costs of IVF/ICSI cycles and AI/DI/IUI cycles per 1,000 women aged 18 to 42 by ICB and year (2019/20 to 2022/23) (based on GP registered populations, July 2023)

	2019/20	2020/21	2021/22	2022/23	4 year average
IVF/ICSI cost*					
NHS Derby and Derbyshire ICB	£3,455	£2,833	£2,793	£3,202	£3,071
NHS Leicester, Leicestershire and Rutland ICB	£2,061	£2,583	£2,580	£2,543	£2,442
NHS Lincolnshire ICB	£2,415	£2,238	£2,188	£2,159	£2,250
NHS Northamptonshire ICB	£3,505	£1,620	£2,614	£2,764	£2,626
NHS Nottingham and Nottinghamshire ICB	£2,737	£2,170	£2,619	£2,022	£2,387
TOTAL FOR 5 EAST MIDLANDS ICBs	**£2,797**	**£2,324**	**£2,584**	**£2,523**	**£2,557**
AI/DI/IUI cost					
NHS Derby and Derbyshire ICB	£5	£15	£5	£10	£9
NHS Leicester, Leicestershire and Rutland ICB	£791	£435	£651	£514	£598
NHS Lincolnshire ICB	£69	£81	£69	£53	£68
NHS Northamptonshire ICB	£14	£14	£21	£7	£14
NHS Nottingham and Nottinghamshire ICB	£0	£0	£0	£0	£0
TOTAL FOR 5 EAST MIDLANDS ICBs	**£225**	**£137**	**£189**	**£149**	**£175**

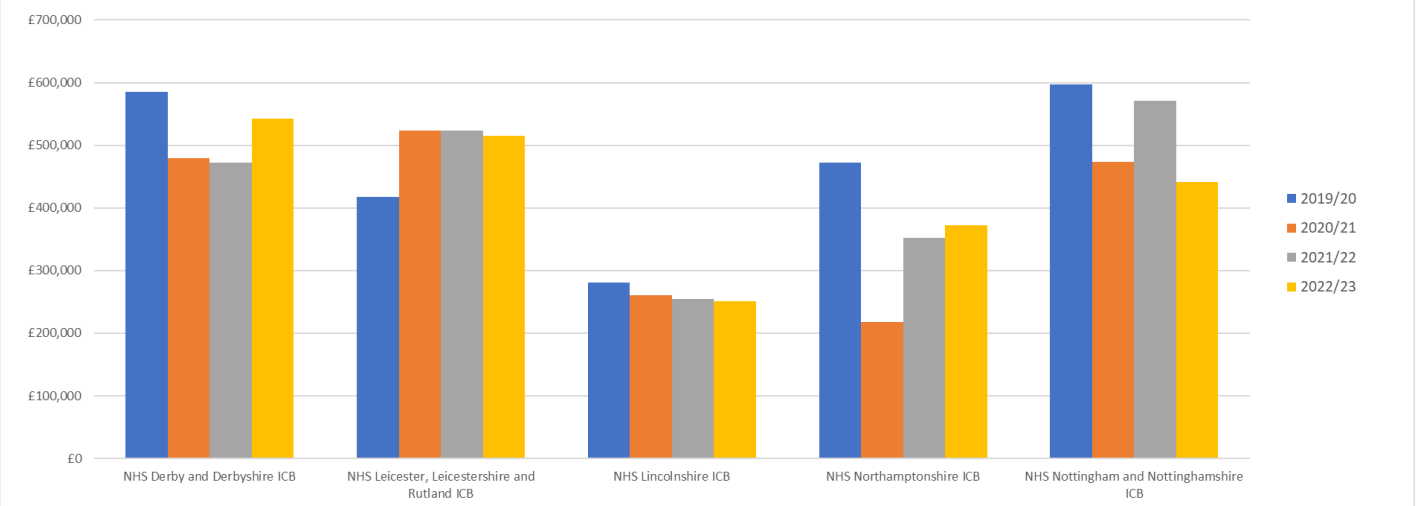
* These figures do not include the costs of frozen embryo transfer, luteal support or cancelled cycles

Table 24: Costs of IVF/ICSI cycles including estimated costs of frozen embryo transfer, luteal support and cancelled cycles by ICB and year 2019/20 to 2022/23)

ICB	2019/20	2020/21	2021/22	2022/23	Total
NHS Derby and Derbyshire ICB	£688,390	£592,360	£602,430	£668,650	£2,551,830
NHS Leicester, Leicestershire and Rutland ICB	£536,600	£612,392	£635,850	£605,288	£2,390,130
NHS Lincolnshire ICB	£327,120	£304,130	£307,940	£305,992	£1,245,182
NHS Northamptonshire ICB	£526,260	£255,780	£410,570	£461,750	£1,654,360
NHS Nottingham and Nottinghamshire ICB	£698,690	£575,810	£676,850	£570,512	£2,521,862
TOTAL FOR 5 EAST MIDLANDS ICBs	**£2,777,060**	**£2,340,472**	**£2,633,640**	**£2,612,192**	**£10,363,364**

Assumes all reported frozen embryo transfer and luteal support episodes related to IVF/ICSI cycles and that half of the reported cancelled IVF/ICSI cycles were cancelled between ovarian stimulation and oocyte collection. (Cancelled cycles with treatment type not reported and not included.)

Figure 9: Costs of IVF/ICSI cycles by ICB and year (2019/20 to 2022/23)



Assumes all reported frozen embryo transfer and luteal support episodes related to IVF/ICSI cycles and that half of the reported cancelled IVF/ICSI cycles were cancelled between ovarian stimulation and oocyte collection. (Cancelled cycles with treatment type not reported and not included.)

7 Modelling IVF cost scenarios

A model providing estimated costs to commissioners of offering different numbers of cycles of IVF (with or without ICSI) to infertile women of different age ranges and with different ranges of BMI registered with GP practices in each of the five ICBs in the East Midlands is described below.

7.1 Modelling Methodology

We have developed a spreadsheet model to estimate, for each ICB, for a range of commissioning scenarios, the:

- number of women that might receive IVF/ICSI treatment
- total number of IVF/ICSI cycles provided
- direct costs of IVF/ICSI treatment
- number of live births that may result from treatment
- average cost per live birth

Consistent with the main body of this report, a full cycle of IVF, with or without ICSI, comprises one episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s).

The scenarios considered by the model vary widely in terms of the number of cycles provided for different age groups and the BMI criteria, so as not to pre-empt ICB policy decisions, but instead act as a starting point for discussions.

The scenarios considered by the model are shown in Table 25 below. The range includes a scenario that reflects the level of provision of IVF treatment suggested by the 2013 NICE clinical guideline (Scenario 11) and a scenario that reflects the existing policy in most ICBs (Scenario 4). The additional scenarios were based on rational criteria that emerged from the evidence outcomes reported. For instance, there was a noticeable difference in live birth rate associated with increased age, particularly at higher ages, and a lower live birth rate associated with obesity (see Appendix 4).

Table 25: Scenarios included in the IVF model

Number	Patient age band (a)	Number of cycles (a)	Patient age band (b)	Number of cycles (b)	Patient age band (c)	Number of cycles (c)
Scenario 1	18 to 39	1	40 to 42	0	not applicable	not applicable
Scenario 2	18 to 39	2	40 to 42	0	not applicable	not applicable
Scenario 3	18 to 39	3	40 to 42	0	not applicable	not applicable
Scenario 4	18 to 39	1	40 to 42	1	not applicable	not applicable
Scenario 5	18 to 39	2	40 to 42	1	not applicable	not applicable
Scenario 6	18 to 39	3	40 to 42	1	not applicable	not applicable
Scenario 7	18 to 37	3	38 to 39	2	40 to 42	1
Scenario 8	18 to 37	3	38 to 39	0	not applicable	not applicable
Scenario 9	18 to 37	2	38 to 39	1	40 to 42	0
Scenario 10	18 to 37	1	38 to 39	0	40 to 42	0
Scenario 11	18 to 39	3	40 to 42	1	not applicable	not applicable

Scenario 4 represents the current policy in most ICBs.
Scenario 6 represents the current policy in what was NHS Bassetlaw CCG (now part of NHS Nottingham and Nottinghamshire ICB).
Scenario 11 represents NICE guidance where additional criteria for access to IVF, such as being non-smoking and childless are not applied.

In addition, each of the 11 scenarios were re-run based on different assumptions with respect to the woman's BMI as follows:

- BMI of 18.5 kg/m^2 to <30 kg/m^2 (this is the BMI range that equates most closely to current East Midlands ICB policies; a lower BMI boundary of 18.5 kg/m^2 was used rather than 19 kg/m^2 because this is the limit of what is generally considered a normal weight [34], and matches population BMI available from the Health Survey for England)
- BMI of 18.5 kg/m^2 to <35 kg/m^2 (this BMI range is less restrictive than current ICB policies; the upper limit of 35 kg/m^2 is the limit beyond which oocyte retrieval is likely to require a general anaesthetic and would therefore not be provided by most local providers)[50]

For each scenario the model calculates:

- The number of women likely to receive IVF
- The number of cycles of IVF provided and the number of these including ICSI
- The cost of the estimated cycles (using a general East Midlands tariff provided by contract leads)
- The number of live births resulting from IVF treatment
- The total cost per live birth.

For precision, the calculations throughout the model are not rounded.

The model uses a number of parameters to estimate the number of infertile women likely to receive IVF, the number of cycles of IVF, the number of live births and the costs of treatment for the different scenarios.

The data used to populate the parameters has been drawn from various sources including East Midlands ICB assisted fertility leads and contract managers (tariff), the HFEA through a freedom of information request (live birth rates by age), the Health Survey for England (obesity rates) [33], and a number of the published papers used to inform this rapid evidence review.

Table 26 below lists the parameters included in the model and the values for each parameter as well as the source used to inform the value. The model has been designed so that the values can be overwritten by updated or more local data if appropriate.

Table 26: Parameters, values and sources used in scenario modelling

Parameter	Value	Source
Female population registered with GP practices in each ICB, by age group	2023 population by age	NHS Digital CCG to ICB listing, July 2023 [35]
Incidence of infertility by age group	Patient age — Infertility inc. 15-19 — 0.07% 20-24 — 0.46% 25-29 — 0.94% 30-34 — 0.109% 35-39 — 0.70% 40-42 — 0.24%	Dhalwani 2013 [36]
Proportion likely to have IVF/ICSI	33%	Wilkes 2009 [37]

[50] Communication from clinicians.

Parameter	Value	Source
Proportion who have a live birth after first cycle	Patient age — Live birth rate Under 35 — 40% 35-37 — 31% 38-39 — 24% 40-42 — 16% 43-44 — 0%	HFEA freedom of information request, August 2023
Proportion who continue to a second cycle after one unsuccessful cycle	78.2%	Gameiro 2021 [38]
Proportion who have a live birth after second cycle	Patient age — Live birth rate Under 35 — 28% 35-37 — 19% 38-39 — 14% 40-42 — 13%	HFEA freedom of information request, August 2023 live birth rate for first cycle reduced by proportion reported by Wang 2022 [38] for second cycle live birth rate compared to first cycle live birth rate by age group
Proportion who continue to a third cycle after two unsuccessful cycles	71.5%	Gameiro 2021 [38]
Proportion who have a live birth after third cycle	Patient age — Live birth rate Under 35 — 22% 35-37 — 17% 38-39 — 13% 40-42 — 9%	HFEA freedom of information request, August 2023 live birth rate for first cycle reduced by proportion reported by Wang 2022 [39] for third cycle live birth rate compared to second cycle live birth rate by age group
Proportion underweight, normal weight, overweight, obese and morbidly obese	Patient age 25 to 34 years (used for 18-37 and 18-39 age groups) Underweight — 2.0% Normal — 44.0% Overweight — 28.0% BMI ≥30, <35 — 16.2% BMI ≥35, <40 — 3.8% Patient age 35 to 44 years (used for 38-39, 40-42 and 40-45 age groups) Underweight — 1.0% Normal — 38.0% Overweight — 28.0% BMI ≥30, <35 — 21.9% BMI ≥35, <40 — 5.1%	Health Survey for England 2019 [33] with adjustment for proportion with BMI 30-35 kg/m^2 vs 35-40 kg/m^2 based on proportion in Stival 2022 [40]
Live birth rate for BMI 30-35 and 35-40 kg/m^2	BMI 30-35 kg/m^2 — RR 0.82 BMI 35-40 kg/m^2 — RR 0.7	Tang 2021 [41]
Cost of a cycle of IVF/ICSI	Age 37 and under — £3,000 Age 38 and older — £3,400	East Midlands tariff from ICB assisted conception contract managers
Cost of a cycle of IVF/ICSI	Age under 39 years — £3,047	IVF/ICSI tariff from contract leads adjusted based on ratio of women aged 37 and under vs 38-39 year olds in local activity data received from ICB contract leads

Parameter	Value	Source
Total cost of a cycle of IVF/ICSI including cost of frozen embryo transfer, luteal support and cancelled cycles	Uplift of above IVF/ICSI tariff by a factor of 1.2	Activity data and tariffs received from ICB assisted conception contract managers. Used the whole of East Midlands activity data received from ICB contract managers. Calculated the ratio of overall East Midlands costs of IVF/ICSI with vs without inclusion of data for frozen embryo transfer, luteal support and cancelled cycles (because not all patients receive these)
ICB policy adjustment: reduction of all scenario costs to reflect real life costs where other criteria for IVF also apply e.g. non-smoking, childlessness, ovarian reserve, etc.	NHS Derby and Derbyshire ICB 62% NHS Leicester, Leicestershire and Rutland ICB 74% NHS Lincolnshire ICB 45% NHS Northampton ICB 54% NHS Nottingham and Nottinghamshire ICB 49%	The ratio of total cost for IVF/ICSI plus associated procedures based on ICB contracting data and tariffs or actual costs compared to modelled cost of scenario 4 (the scenario closest to current policies)

7.2 Modelling Limitations

Data were not available to support all the current East Midlands ICB eligibility criteria to be built individually into the model. These criteria include, for example, maternal and paternal smoking status and the female's ovarian reserve. To account for these, a parameter (ICB policy adjustment) was applied to allow the estimated number of women with infertility likely to take up IVF to be reduced by an appropriate proportion. To determine this proportion, the estimated number of women with infertility likely to take up IVF shown in scenario 4 – the scenario most similar to the majority of current policies – was compared with the actual number of women receiving treatment per year. This showed that the latter was, depending on the ICB, between 45% and 74% of the former (see Table 26 above). Accordingly, the default value for this ICB policy adjustment was set to the corresponding percentage value for each ICB. This parameter was applied to all scenarios. An additional scenario (Scenario 11) was added without this adjustment, to reflect the 2013 NICE Clinical Guideline CG156, where adjustments for childlessness, smoking status, etc. are not relevant.

Data giving the proportion of women in the relevant age bands in each ICB who are underweight or obese were not available. Proportions from the Health Survey for England 2019 data were therefore applied to the East Midlands populations [33].

The model estimates, within each scenario, the number of women in the population with a BMI of 18.5 to 30 kg/m^2, a BMI of 18.5 to 35 kg/m^2 and a BMI under 40 kg/m^2. The model also reflects the evidence identified in the evidence section of this report on the difference in live birth rates in these BMI groups.

It should be noted that the model does not take into account either maternal or perinatal complications such as gestational diabetes, pre-term delivery, birth weight or the need for

caesarean section that can be associated with maternal obesity [42]. This means that the cost per live birth may be underestimated, particularly for obese mothers relative to non-obese mothers.

The model does not take account of maternal and perinatal complications, and hence underestimates the true costs of provision of IVF/ICSI.

The model also does not take into account the number that might come forward for IVF/ICSI if policies were changed regarding access for groups such as

- same-sex couples
- single women
- couples where a partner already has a child
- transgender individuals
- individuals/couples for whom it is very difficult/impossible to have vaginal intercourse
- couples where a partner has previously been sterilised

Relatively little of the current IVF/ICSI provision is for these groups.

Other limitations include the number of parameters and assumptions that need to be included in the model. These were based on the local data that we received and on generalisations based on the results of published studies. This means that the model outputs provide an indication of possible numbers and costs for different scenarios but are likely to be more useful for comparing the different scenarios in relative terms.

7.3 Modelling Results

The tables below show the results of the modelling for each of the 11 scenarios and three BMI ranges for all five East Midlands ICBs combined and for each ICB separately.

Table 27a: Modelling results for five East Midlands ICBs combined, BMI 18.5 to <30

Women with BMI 18.5 to <30											
All East Midlands ICBs											
Number	**Patient age band (a)**	**Number of cycles (a)**	**Patient age band (b)**	**Number of cycles (b)**	**Patient age band (c)**	**Number of cycles (c)**	**Total cost**	**Cost per live birth**	**Number of live births**	**Number of women treated**	**Number of cycles**
Scenario 1	18 to 39	1	40 to 42	0	not applicable	not applicable	**£2,787,953**	£10,050	277	759	759
Scenario 2	18 to 39	2	40 to 42	0	not applicable	not applicable	**£4,171,779**	£11,086	376	759	1,136
Scenario 3	18 to 39	3	40 to 42	0	not applicable	not applicable	**£4,901,673**	£11,732	418	759	1,335
Scenario 4	18 to 39	1	40 to 42	1	not applicable	not applicable	**£2,924,719**	£10,343	283	793	793
Scenario 5	18 to 39	2	40 to 42	1	not applicable	not applicable	**£4,308,545**	£11,289	382	793	1,170
Scenario 6	18 to 39	3	40 to 42	1	not applicable	not applicable	**£5,038,439**	£11,907	423	793	1,369
Scenario 7	18 to 37	3	38 to 39	2	40 to 42	1	**£4,917,038**	£11,671	421	793	1,342
Scenario 8	18 to 37	3	38 to 39	0	not applicable	not applicable	**£4,343,071**	£11,018	394	693	1,202
Scenario 9	18 to 37	2	38 to 39	1	40 to 42	0	**£3,990,555**	£10,713	372	759	1,095
Scenario 10	18 to 37	1	38 to 39	0	40 to 42	0	**£2,502,986**	£9,508	263	693	693
Scenario 11	18 to 39	3	40 to 42	1	not applicable	not applicable	**£8,708,765**	£11,906	731	1370	2,366

Note: The model does not take into account either maternal or perinatal complications such as gestational diabetes, pre-term delivery, birth weight or the need for caesarean section. This means that the cost per live birth may be an underestimate.

Table 27b: Modelling results for five East Midlands ICBs combined, BMI 18.5 to <35

Women with BMI 18.5 to <35											
All East Midlands ICBs											
Number	**Patient age band (a)**	**Number of cycles (a)**	**Patient age band (b)**	**Number of cycles (b)**	**Patient age band (c)**	**Number of cycles (c)**	**Total cost**	**Cost per live birth**	**Number of live births**	**Number of women treated**	**Number of cycles**
Scenario 1	18 to 39	1	40 to 42	0	not applicable	not applicable	**£3,416,764**	£10,394	329	931	940
Scenario 2	18 to 39	2	40 to 42	0	not applicable	not applicable	**£5,145,038**	£11,490	448	931	1,416
Scenario 3	18 to 39	3	40 to 42	0	not applicable	not applicable	**£6,068,238**	£12,177	498	931	1,671
Scenario 4	18 to 39	1	40 to 42	1	not applicable	not applicable	**£3,584,377**	£10,698	335	972	981
Scenario 5	18 to 39	2	40 to 42	1	not applicable	not applicable	**£5,312,651**	£11,699	454	972	1,458
Scenario 6	18 to 39	3	40 to 42	1	not applicable	not applicable	**£6,235,851**	£12,357	505	972	1,712
Scenario 7	18 to 37	3	38 to 39	2	40 to 42	1	**£6,084,807**	£12,109	503	972	1,678
Scenario 8	18 to 37	3	38 to 39	0	not applicable	not applicable	**£5,379,296**	£11,439	470	849	1,504
Scenario 9	18 to 37	2	38 to 39	1	40 to 42	0	**£4,920,813**	£11,101	443	931	1,365
Scenario 10	18 to 37	1	38 to 39	0	40 to 42	0	**£3,067,525**	£9,834	312	849	857
Scenario 11	18 to 39	3	40 to 42	1	not applicable	not applicable	**£10,778,452**	£12,356	872	1680	2,962

Note: The model does not take into account either maternal or perinatal complications such as gestational diabetes, pre-term delivery, birth weight or the need for caesarean section. For obese women, doses and costs of drugs for ovarian stimulation will also be higher (communication from clinician). This means that the cost per live birth may be an underestimate, particularly for obese mothers.

Table 28a: Modelling results for NHS Derby and Derbyshire ICB, BMI 18.5 to <30

Women with BMI 18.5 to <30											
Derby and Derbyshire ICB											
Number	**Patient age band (a)**	**Number of cycles (a)**	**Patient age band (b)**	**Number of cycles (b)**	**Patient age band (c)**	**Number of cycles (c)**	**Total cost**	**Cost per live birth**	**Number of live births**	**Number of women treated**	**Number of cycles**
Scenario 1	18 to 39	1	40 to 42	0	not applicable	not applicable	**£607,508**	£10,050	60	165	165
Scenario 2	18 to 39	2	40 to 42	0	not applicable	not applicable	**£909,050**	£11,086	82	165	248
Scenario 3	18 to 39	3	40 to 42	0	not applicable	not applicable	**£1,068,097**	£11,732	91	165	291
Scenario 4	18 to 39	1	40 to 42	1	not applicable	not applicable	**£637,958**	£10,350	62	173	173
Scenario 5	18 to 39	2	40 to 42	1	not applicable	not applicable	**£939,500**	£11,294	83	173	255
Scenario 6	18 to 39	3	40 to 42	1	not applicable	not applicable	**£1,098,547**	£11,910	92	173	298
Scenario 7	18 to 37	3	38 to 39	2	40 to 42	1	**£1,072,171**	£11,685	92	173	292
Scenario 8	18 to 37	3	38 to 39	0	not applicable	not applicable	**£944,493**	£11,018	86	151	261
Scenario 9	18 to 37	2	38 to 39	1	40 to 42	0	**£869,179**	£10,719	81	165	239
Scenario 10	18 to 37	1	38 to 39	0	40 to 42	0	**£544,327**	£9,508	57	151	151
Scenario 11	18 to 39	3	40 to 42	1	not applicable	not applicable	**£1,782,512**	£11,910	150	281	484

Note: The model does not take into account either maternal or perinatal complications such as gestational diabetes, pre-term delivery, birth weight or the need for caesarean section. This means that the cost per live birth may be an underestimate.

Table 28b: Modelling results for NHS Derby and Derbyshire ICB, BMI 18.5 to <35

Women with BMI 18.5 to <35											
Derby and Derbyshire ICB											
Number	**Patient age band (a)**	**Number of cycles (a)**	**Patient age band (b)**	**Number of cycles (b)**	**Patient age band (c)**	**Number of cycles (c)**	**Total cost**	**Cost per live birth**	**Number of live births**	**Number of women treated**	**Number of cycles**
Scenario 1	18 to 39	1	40 to 42	0	not applicable	not applicable	**£744,529**	£10,394	72	203	203
Scenario 2	18 to 39	2	40 to 42	0	not applicable	not applicable	**£1,121,127**	£11,490	98	203	305
Scenario 3	18 to 39	3	40 to 42	0	not applicable	not applicable	**£1,322,297**	£12,177	109	203	360
Scenario 4	18 to 39	1	40 to 42	1	not applicable	not applicable	**£781,846**	£10,704	73	212	212
Scenario 5	18 to 39	2	40 to 42	1	not applicable	not applicable	**£1,158,445**	£11,703	99	212	315
Scenario 6	18 to 39	3	40 to 42	1	not applicable	not applicable	**£1,359,615**	£12,360	110	212	369
Scenario 7	18 to 37	3	38 to 39	2	40 to 42	1	**£1,326,782**	£12,123	109	212	362
Scenario 8	18 to 37	3	38 to 39	0	not applicable	not applicable	**£1,169,841**	£11,439	102	185	324
Scenario 9	18 to 37	2	38 to 39	1	40 to 42	0	**£1,071,787**	£11,107	96	203	294
Scenario 10	18 to 37	1	38 to 39	0	40 to 42	0	**£667,098**	£9,834	68	185	185
Scenario 11	18 to 39	3	40 to 42	1	not applicable	not applicable	**£2,206,123**	£12,360	178	344	599

Note: The model does not take into account either maternal or perinatal complications such as gestational diabetes, pre-term delivery, birth weight or the need for caesarean section. For obese women, doses and costs of drugs for ovarian stimulation will also be higher (communication from clinician). This means that the cost per live birth may be an underestimate, particularly for obese mothers.

Table 29a: Modelling results for NHS Leicester, Leicestershire and Rutland ICB, BMI 18.5 to <30

Women with BMI 18.5 to <30											
Leicester, Leicestershire and Rutland ICB											
Number	Patient age band (a)	Number of cycles (a)	Patient age band (b)	Number of cycles (b)	Patient age band (c)	Number of cycles (c)	Total cost	Cost per live birth	Number of live births	Number of women treated	Number of cycles
Scenario 1	18 to 39	1	40 to 42	0	not applicable	not applicable	**£858,148**	£10,050	85	234	234
Scenario 2	18 to 39	2	40 to 42	0	not applicable	not applicable	**£1,284,098**	£11,086	116	234	350
Scenario 3	18 to 39	3	40 to 42	0	not applicable	not applicable	**£1,508,764**	£11,732	129	234	411
Scenario 4	18 to 39	1	40 to 42	1	not applicable	not applicable	**£900,000**	£10,342	87	244	244
Scenario 5	18 to 39	2	40 to 42	1	not applicable	not applicable	**£1,325,950**	£11,288	117	244	360
Scenario 6	18 to 39	3	40 to 42	1	not applicable	not applicable	**£1,550,616**	£11,906	130	244	421
Scenario 7	18 to 37	3	38 to 39	2	40 to 42	1	**£1,513,235**	£11,668	130	244	413
Scenario 8	18 to 37	3	38 to 39	0	not applicable	not applicable	**£1,337,137**	£11,018	121	213	370
Scenario 9	18 to 37	2	38 to 39	1	40 to 42	0	**£1,228,380**	£10,712	115	234	337
Scenario 10	18 to 37	1	38 to 39	0	40 to 42	0	**£770,615**	£9,508	81	213	213
Scenario 11	18 to 39	3	40 to 42	1	not applicable	not applicable	**£2,082,945**	£11,906	175	328	566

Note: The model does not take into account either maternal or perinatal complications such as gestational diabetes, pre-term delivery, birth weight or the need for caesarean section. This means that the cost per live birth may be an underestimate.

Table 29b: Modelling results for NHS Leicester, Leicestershire and Rutland ICB, BMI 18.5 to <35

Women with BMI 18.5 to <35											
Leicester, Leicestershire and Rutland ICB											
Number	**Patient age band (a)**	**Number of cycles (a)**	**Patient age band (b)**	**Number of cycles (b)**	**Patient age band (c)**	**Number of cycles (c)**	**Total cost**	**Cost per live birth**	**Number of live births**	**Number of women treated**	**Number of cycles**
Scenario 1	18 to 39	1	40 to 42	0	not applicable	not applicable	**£1,051,700**	£10,394	101	287	287
Scenario 2	18 to 39	2	40 to 42	0	not applicable	not applicable	**£1,583,673**	£11,490	138	287	431
Scenario 3	18 to 39	3	40 to 42	0	not applicable	not applicable	**£1,867,840**	£12,177	153	287	509
Scenario 4	18 to 39	1	40 to 42	1	not applicable	not applicable	**£1,102,991**	£10,696	103	299	299
Scenario 5	18 to 39	2	40 to 42	1	not applicable	not applicable	**£1,634,964**	£11,697	140	299	444
Scenario 6	18 to 39	3	40 to 42	1	not applicable	not applicable	**£1,919,131**	£12,356	155	299	521
Scenario 7	18 to 37	3	38 to 39	2	40 to 42	1	**£1,872,625**	£12,107	155	299	511
Scenario 8	18 to 37	3	38 to 39	0	not applicable	not applicable	**£1,656,167**	£11,439	145	261	458
Scenario 9	18 to 37	2	38 to 39	1	40 to 42	0	**£1,514,735**	£11,100	136	287	416
Scenario 10	18 to 37	1	38 to 39	0	40 to 42	0	**£944,424**	£9,834	96	261	261
Scenario 11	18 to 39	3	40 to 42	1	not applicable	not applicable	**£2,577,972**	£12,356	209	402	700

Note: The model does not take into account either maternal or perinatal complications such as gestational diabetes, pre-term delivery, birth weight or the need for caesarean section. For obese women, doses and costs of drugs for ovarian stimulation will also be higher (communication from clinician). This means that the cost per live birth may be an underestimate, particularly for obese mothers.

Table 30a: Modelling results for NHS Lincolnshire ICB, BMI 18.5 to <30

Women with BMI 18.5 to <30											
Lincolnshire ICB											
Number	**Patient age band (a)**	**Number of cycles (a)**	**Patient age band (b)**	**Number of cycles (b)**	**Patient age band (c)**	**Number of cycles (c)**	**Total cost**	**Cost per live birth**	**Number of live births**	**Number of women treated**	**Number of cycles**
Scenario 1	18 to 39	1	40 to 42	0	not applicable	not applicable	**£296,330**	£10,050	29	81	81
Scenario 2	18 to 39	2	40 to 42	0	not applicable	not applicable	**£443,416**	£11,086	40	81	121
Scenario 3	18 to 39	3	40 to 42	0	not applicable	not applicable	**£520,996**	£11,732	44	81	142
Scenario 4	18 to 39	1	40 to 42	1	not applicable	not applicable	**£311,296**	£10,352	30	84	84
Scenario 5	18 to 39	2	40 to 42	1	not applicable	not applicable	**£458,381**	£11,295	41	84	124
Scenario 6	18 to 39	3	40 to 42	1	not applicable	not applicable	**£535,961**	£11,912	45	84	146
Scenario 7	18 to 37	3	38 to 39	2	40 to 42	1	**£523,080**	£11,682	45	84	143
Scenario 8	18 to 37	3	38 to 39	0	not applicable	not applicable	**£461,092**	£11,018	42	74	128
Scenario 9	18 to 37	2	38 to 39	1	40 to 42	0	**£424,046**	£10,717	40	81	116
Scenario 10	18 to 37	1	38 to 39	0	40 to 42	0	**£265,735**	£9,508	28	74	74
Scenario 11	18 to 39	3	40 to 42	1	not applicable	not applicable	**£1,199,520**	£11,912	101	189	326

Note: The model does not take into account either maternal or perinatal complications such as gestational diabetes, pre-term delivery, birth weight or the need for caesarean section. This means that the cost per live birth may be an underestimate.

Table 30b: Modelling results for NHS Lincolnshire ICB, BMI 18.5 to <35

Women with BMI 18.5 to <35											
Lincolnshire ICB											
Number	**Patient age band (a)**	**Number of cycles (a)**	**Patient age band (b)**	**Number of cycles (b)**	**Patient age band (c)**	**Number of cycles (c)**	**Total cost**	**Cost per live birth**	**Number of live births**	**Number of women treated**	**Number of cycles**
Scenario 1	18 to 39	1	40 to 42	0	not applicable	not applicable	**£363,166**	£10,394	35	99	99
Scenario 2	18 to 39	2	40 to 42	0	not applicable	not applicable	**£546,863**	£11,490	48	99	149
Scenario 3	18 to 39	3	40 to 42	0	not applicable	not applicable	**£644,989**	£12,177	53	99	176
Scenario 4	18 to 39	1	40 to 42	1	not applicable	not applicable	**£381,507**	£10,707	36	103	103
Scenario 5	18 to 39	2	40 to 42	1	not applicable	not applicable	**£565,204**	£11,705	48	103	153
Scenario 6	18 to 39	3	40 to 42	1	not applicable	not applicable	**£663,330**	£12,362	54	103	180
Scenario 7	18 to 37	3	38 to 39	2	40 to 42	1	**£647,299**	£12,120	53	103	177
Scenario 8	18 to 37	3	38 to 39	0	not applicable	not applicable	**£571,106**	£11,439	50	90	158
Scenario 9	18 to 37	2	38 to 39	1	40 to 42	0	**£522,895**	£11,105	47	99	144
Scenario 10	18 to 37	1	38 to 39	0	40 to 42	0	**£325,671**	£9,834	33	90	90
Scenario 11	18 to 39	3	40 to 42	1	not applicable	not applicable	**£1,484,580**	£12,362	120	231	403

Note: The model does not take into account either maternal or perinatal complications such as gestational diabetes, pre-term delivery, birth weight or the need for caesarean section. For obese women, doses and costs of drugs for ovarian stimulation will also be higher (communication from clinician). This means that the cost per live birth may be an underestimate, particularly for obese mothers.

Table 31a: Modelling results for NHS Northamptonshire ICB, BMI 18.5 to <30

Women with BMI 18.5 to <30											
Northamptonshire ICB											
Number	**Patient age band (a)**	**Number of cycles (a)**	**Patient age band (b)**	**Number of cycles (b)**	**Patient age band (c)**	**Number of cycles (c)**	**Total cost**	**Cost per live birth**	**Number of live births**	**Number of women treated**	**Number of cycles**
Scenario 1	18 to 39	1	40 to 42	0	not applicable	not applicable	**£422,990**	£10,050	42	115	115
Scenario 2	18 to 39	2	40 to 42	0	not applicable	not applicable	**£632,945**	£11,086	57	115	172
Scenario 3	18 to 39	3	40 to 42	0	not applicable	not applicable	**£743,685**	£11,732	63	115	203
Scenario 4	18 to 39	1	40 to 42	1	not applicable	not applicable	**£445,000**	£10,361	43	121	121
Scenario 5	18 to 39	2	40 to 42	1	not applicable	not applicable	**£654,955**	£11,301	58	121	178
Scenario 6	18 to 39	3	40 to 42	1	not applicable	not applicable	**£765,695**	£11,917	64	121	208
Scenario 7	18 to 37	3	38 to 39	2	40 to 42	1	**£747,419**	£11,708	64	121	204
Scenario 8	18 to 37	3	38 to 39	0	not applicable	not applicable	**£655,464**	£11,018	59	105	181
Scenario 9	18 to 37	2	38 to 39	1	40 to 42	0	**£604,747**	£10,730	56	115	166
Scenario 10	18 to 37	1	38 to 39	0	40 to 42	0	**£377,755**	£9,508	40	105	105
Scenario 11	18 to 39	3	40 to 42	1	not applicable	not applicable	**£1,417,545**	£11,917	119	223	385

Note: The model does not take into account either maternal or perinatal complications such as gestational diabetes, pre-term delivery, birth weight or the need for caesarean section. This means that the cost per live birth may be an underestimate.

Table 31b: Modelling results for NHS Northamptonshire ICB, BMI 18.5 to <35

Women with BMI 18.5 to <35											
Northamptonshire ICB											
Number	**Patient age band (a)**	**Number of cycles (a)**	**Patient age band (b)**	**Number of cycles (b)**	**Patient age band (c)**	**Number of cycles (c)**	**Total cost**	**Cost per live birth**	**Number of live births**	**Number of women treated**	**Number of cycles**
Scenario 1	18 to 39	1	40 to 42	0	not applicable	not applicable	**£518,394**	£10,394	50	141	150
Scenario 2	18 to 39	2	40 to 42	0	not applicable	not applicable	**£780,609**	£11,490	68	141	227
Scenario 3	18 to 39	3	40 to 42	0	not applicable	not applicable	**£920,677**	£12,177	76	141	269
Scenario 4	18 to 39	1	40 to 42	1	not applicable	not applicable	**£545,368**	£10,716	51	148	157
Scenario 5	18 to 39	2	40 to 42	1	not applicable	not applicable	**£807,583**	£11,711	69	148	234
Scenario 6	18 to 39	3	40 to 42	1	not applicable	not applicable	**£947,651**	£12,367	77	148	276
Scenario 7	18 to 37	3	38 to 39	2	40 to 42	1	**£924,883**	£12,148	76	148	270
Scenario 8	18 to 37	3	38 to 39	0	not applicable	not applicable	**£811,853**	£11,439	71	128	241
Scenario 9	18 to 37	2	38 to 39	1	40 to 42	0	**£745,704**	£11,118	67	141	219
Scenario 10	18 to 37	1	38 to 39	0	40 to 42	0	**£462,957**	£9,834	47	128	136
Scenario 11	18 to 39	3	40 to 42	1	not applicable	not applicable	**£1,754,404**	£12,367	142	274	510

Note: The model does not take into account either maternal or perinatal complications such as gestational diabetes, pre-term delivery, birth weight or the need for caesarean section. For obese women, doses and costs of drugs for ovarian stimulation will also be higher (communication from clinician). This means that the cost per live birth may be an underestimate, particularly for obese mothers.

Table 32a: Modelling results for NHS Nottingham and Nottinghamshire ICB, BMI 18.5 to <30

Women with BMI 18.5 to <30											
Nottingham and Nottinghamshire ICB											
Number	**Patient age band (a)**	**Number of cycles (a)**	**Patient age band (b)**	**Number of cycles (b)**	**Patient age band (c)**	**Number of cycles (c)**	**Total cost**	**Cost per live birth**	**Number of live births**	**Number of women treated**	**Number of cycles**
Scenario 1	18 to 39	1	40 to 42	0	not applicable	not applicable	**£602,977**	£10,050	60	164	164
Scenario 2	18 to 39	2	40 to 42	0	not applicable	not applicable	**£902,270**	£11,086	81	164	246
Scenario 3	18 to 39	3	40 to 42	0	not applicable	not applicable	**£1,060,131**	£11,732	90	164	289
Scenario 4	18 to 39	1	40 to 42	1	not applicable	not applicable	**£630,466**	£10,323	61	171	171
Scenario 5	18 to 39	2	40 to 42	1	not applicable	not applicable	**£929,759**	£11,275	82	171	253
Scenario 6	18 to 39	3	40 to 42	1	not applicable	not applicable	**£1,087,620**	£11,894	91	171	296
Scenario 7	18 to 37	3	38 to 39	2	40 to 42	1	**£1,061,133**	£11,628	91	171	290
Scenario 8	18 to 37	3	38 to 39	0	not applicable	not applicable	**£944,885**	£11,018	86	151	261
Scenario 9	18 to 37	2	38 to 39	1	40 to 42	0	**£864,203**	£10,695	81	164	237
Scenario 10	18 to 37	1	38 to 39	0	40 to 42	0	**£544,554**	£9,508	57	151	151
Scenario 11	18 to 39	3	40 to 42	1	not applicable	not applicable	**£2,226,243**	£11,894	187	350	605

Note: The model does not take into account either maternal or perinatal complications such as gestational diabetes, pre-term delivery, birth weight or the need for caesarean section. This means that the cost per live birth may be an underestimate.

Table 32b: Modelling results for NHS Nottingham and Nottinghamshire ICB, BMI 18.5 to <35

Women with BMI 18.5 to <35											
Nottingham and Nottinghamshire ICB											
Number	**Patient age band (a)**	**Number of cycles (a)**	**Patient age band (b)**	**Number of cycles (b)**	**Patient age band (c)**	**Number of cycles (c)**	**Total cost**	**Cost per live birth**	**Number of live births**	**Number of women treated**	**Number of cycles**
Scenario 1	18 to 39	1	40 to 42	0	not applicable	not applicable	**£738,976**	£10,394	71	201	201
Scenario 2	18 to 39	2	40 to 42	0	not applicable	not applicable	**£1,112,766**	£11,490	97	201	303
Scenario 3	18 to 39	3	40 to 42	0	not applicable	not applicable	**£1,312,435**	£12,177	108	201	358
Scenario 4	18 to 39	1	40 to 42	1	not applicable	not applicable	**£772,665**	£10,677	72	210	210
Scenario 5	18 to 39	2	40 to 42	1	not applicable	not applicable	**£1,146,455**	£11,684	98	210	311
Scenario 6	18 to 39	3	40 to 42	1	not applicable	not applicable	**£1,346,124**	£12,344	109	210	366
Scenario 7	18 to 37	3	38 to 39	2	40 to 42	1	**£1,313,219**	£12,065	109	210	359
Scenario 8	18 to 37	3	38 to 39	0	not applicable	not applicable	**£1,170,328**	£11,439	102	185	324
Scenario 9	18 to 37	2	38 to 39	1	40 to 42	0	**£1,065,692**	£11,082	96	201	293
Scenario 10	18 to 37	1	38 to 39	0	40 to 42	0	**£667,376**	£9,834	68	185	185
Scenario 11	18 to 39	3	40 to 42	1	not applicable	not applicable	**£2,755,373**	£12,344	223	429	749

Note: The model does not take into account either maternal or perinatal complications such as gestational diabetes, pre-term delivery, birth weight or the need for caesarean section. For obese women, doses and costs of drugs for ovarian stimulation will also be higher (communication from clinician). This means that the cost per live birth may be an underestimate, particularly for obese mothers.

7.4 Modelling Discussion

In order to validate the model and the parameters used for estimating outcomes for women with a BMI of 18.5 to 30 kg/m^2, the outputs of the model for scenario 4 (which most closely resembles most current ICB policies), were compared with the actual IVF activity and costs for recent years (based on cost and activity data received from ICB contract leads). Overall for the East Midlands, this suggested a total spend per year of just over £2.9 million for provision of 793 IVF/ICSI cycles to 793 women (most current policies offer one cycle to women of any age up to 42 years). This was estimated to result in 283 live births at a cost of £10,343 per live birth.

As expected, the number of live births is directly related to:

- the number of women for whom IVF/ICSI is made available
- the age of women at the time of the IVF/ICSI cycle
- the number of cycles offered
- the BMI of the mother

Note that the scenario closest to implementation of the full NICE guideline did not include women with a BMI >35 kg/m^2 because of clinical advice that most local providers would not be able to provide IVF for women with a BMI >35.

Live Births

The model gives some insight into the range of differences in live birth rates when these factors are changed. For example, when three full cycles are offered to all East Midlands women aged 18-39 (scenario 3) (no cycles offered to women aged 40 to 42), the estimated number of live births is 418. When 2 full cycles are available for the same group of women (scenario 2), the estimated number of live births is 376. This falls to 277 live births if one full cycle is offered to the same group of women (scenario 1). A full cycle as defined in the NICE guideline CG156 is one that includes ovarian stimulation and transfer into the womb of any resultant fresh and frozen embryos.

The highest estimated number of live births (872) is seen in scenario 11 for women with a BMI of 18.5 to <35 kg/m^2 (close to NICE Clinical Guideline CG156 with limited further criteria for access to IVF such as smoking status, non-obese BMI, childlessness, etc). This would involve provision of around 2,962 cycles to 1,680 women at a total cost of just under £10.8 million and a cost per live birth of around £12,356. However, with the NICE guideline criteria relating to age and number of cycles but including current more restrictive ICB criteria for other aspects such as BMI, smoking status and childlessness (Scenario 6 for women with a BMI of 18.5 to <30 kg/m^2), the model estimates that there would be a lower number of live births (423), associated with a total of 1,369 cycles provided, a total cost of around £5 million, and a cost per cycle of around £11,907. This also represents a considerably higher total cost, total number of cycles provided and cost per cycle than most other scenarios and current provision.

The lowest estimated numbers of live births are seen in scenarios 10 and 1 (BMI 18.5 to <30 kg/m^2) (263 and 277 live births respectively), which do not include provision of IVF/ICSI to women aged over 37 and over 39 respectively.

Total Costs

The estimated total cost for each scenario varies from around £10.8 million for near full implementation of the 2014 NICE Clinical Guideline (CG156) (scenario 11, BMI 18.5 to <35 kg/m^2) to just over £2.5 million for scenario 10 which prioritises one IVF/ICSI cycle for 18 to 37 year old women with a BMI between 18.5 and 30 kg/m^2. Scenario 11 (near to full NICE guideline implementation) suggests significantly higher total costs than for any of the other modelled scenarios. For example, scenario 6 (NICE guideline for age and number of cycles but including

non-NICE guideline criteria for factors such as BMI, smoking status and childlessness) is estimated to incur a total cost to the five East Midlands ICBs of just over £5.0 million. This is most likely to be due to the absolute number of women treated in each of these scenarios (ranging from 1,680 for the near full NICE guideline implementation to 312 women for the most restrictive scenario, Scenario 10; for scenario 6 for women with a BMI of 18.5 to <30 kg/m^2 the number of women treated would be around 972).

Cost per live birth

The model indicates that the most cost effective strategy in terms of cost per live birth is to prioritise treatment for women aged 18-37 years who are not obese (Scenario 10; BMI 18.5 to <30 kg/m^2). The estimated cost per live birth for these women was £9,508, which was the lowest cost per live birth of all modelled scenarios. The estimated cost per live birth for women aged 18-39 years who are not obese and receive 1 IVF/ICSI cycle (Scenario 1; BMI 18.5 to <30 kg/m^2) was £10,394.

The highest estimated cost per live birth was £12,357 for Scenario 6 (three cycles of IVF/ICSI for women aged 18 to 39 and one cycle for women aged 40 to 42; BMI 18.5 to 35 kg/m^2) which included women who were obese. This reflected the lower live birth rates per IVF/ICSI cycle for women aged 40 years or more and obese women and is consistent with the evidence findings that maternal age is the key predictor of success following IVF treatment, with BMI also affecting success. Note that because of the higher cost of drugs and maternal and neonatal complications in obese women, the true cost per live birth is likely to be higher than this.

As well as taking into account the cost per live birth estimates for the different scenarios, commissioners will wish to note the predicted number of women treated, number of IVF/ICSI cycles offered, number of live births and total costs for each scenario.

Total number of cycles provided

The total number of cycles provided will indicate the pressure on services that might result from a policy change. For Scenario 4 for non-obese women (the closest to most current policies) there are roughly 793 cycles provided per year in total across the East Midlands. A policy that provided IVF/ICSI in line with NICE guidelines for age and number of cycles (but only to women who are not obese, non-smokers and childless, etc. as per other current criteria for most ICBs) (Scenario 6) would result in a need for services to be expanded to provide around 1,369 cycles per year, a 72% increase in provision. This is likely to require a substantial increase in need for trained staff, premises, equipment and other resources.

The above results of the model pertain to the five East Midlands ICBs combined. **Corresponding figures for each of the five ICBs are provided in the tables above.**

8 Summary and discussion

Solutions for Public Health (SPH) was commissioned to review existing fertility policies across the five East Midlands ICBs, to provide information to support a collaborative approach to ICB policy making. The work included a comparison of assisted conception policies; evidence enquiries; a discussion of the ethical considerations (for policy areas where evidence is not helpful); collation and analysis of data on activity, costs and outcomes; and modelling of a range of policy scenarios.

Some of the key differences between local policies were in the number of IVF cycles offered to women aged 40 and under (one vs three; NICE recommends three), the number of funded IUI cycles for people who have had six unsuccessful AI attempts (varies from one to six; NICE recommends six) and whether factors such as BMI are criteria for access to IVF or are simply prompts for advice from the provider (NICE recommends the latter). Table 33 provides live birth rates, by age group for a first, second and third IVF cycle for two different ranges of BMI.

Table 33: Estimated/predicted live birth rates for 1st, 2nd, 3rd NHS funded IVF cycles by BMI and age group

Patient age	BMI 18.5 to 18.5 <30 kg/m^2			BMI 30-35 kg/m^2		
	LBR 1st cycle	LBR 2nd cycle	LBR 3rd cycle	LBR 1st cycle	LBR 2nd cycle	LBR 3rd cycle
18-37	38%	28%	22%	31%	23%	18%
38-39	24%	14%	13%	20%	12%	11%
40-42	16%	13%	9%	13%	11%	8%

See main report for source of data, assumptions and data issues. LBR = live birth rate.

The modelled scenarios for IVF/ICSI policy provision represent a range of possible policy options in terms of the age and BMI of the patient and the number of IVF/ICSI cycles provided, so as not to prejudge which options may be selected within the East Midlands in future. Table 34 provides the results for a selection of the modelled scenarios for all five East Midlands ICBs combined. Scenarios higher in the table provide more cycles of IVF to more people and more live births, but with lower overall cost effectiveness (higher cost per live birth) and higher overall costs for ICBs. They range from nearly full NICE guideline implementation to scenarios closer to current policies in East Midlands ICBs (bearing in mind that they do not include all policy criteria due to data constraints). Separate tables for each ICB are provided in the main report. Separate tables for each ICB are provided in the main report.

In making decisions, ICBs need to consider the potential impact of the different scenarios in terms of numbers treated, outcomes and costs, as well as the capacity of local services to deliver higher numbers of assisted fertility treatments at the same or better quality because for fertility treatments in particular, timing of treatments is crucial and waiting lists will have a major impact on quality and outcomes. High quality provision is very important to patients and providers.

Note that the model does not take into account maternal or perinatal complications or higher costs of drugs associated with higher BMI. This means that the cost per live birth may be an underestimate, particularly for obese mothers. See main report for model assumptions and limitations.

Table 34: A selection of modelled scenarios for IVF provision for the five East Midlands ICBs combined

Scenario		Number of women treated	Total number of IVF cycles	Live births (LBs)	Cost	Cost per live birth (LB)	Comments
1	**Close to full NICE guideline implementation**: *BMI 18.5 to <35 kg/m^2 3 IVF cycles for women <40 1 IVF cycle for 40 to 42 year olds No other restrictions	1,680	2,962	872	£10.8 million	£12,356	• Least restrictive • Highest number treated • Most live births • Highest cost • Highest cost per LB
2	**Close to current Bassetlaw policy**: *BMI 18.5 to <35 kg/m^2 3 IVF cycles for women <40 1 IVF cycle for 40 to 42 year olds Other restrictions e.g. re smoking, childlessness, etc.	972	1,712	505	£6.2 million	£12,357	• Highest cost per LB • Similar to NICE for BMI and number of IVF cycles but includes some restrictions
3	**Current Glossop policy**: BMI 18.5 to 30 kg/m^2 3 IVF cycles for women <40 1 IVF cycle for 40 to 42 year olds Other restrictions e.g. re smoking, childlessness, etc.	793	1,369	423	£5.0 million	£11,907	• Similar to NICE and Bassetlaw re number of IVF cycles, but additional BMI criteria and other restrictions
4	**Between Bassetlaw/Glossop and other East Midlands policies, closer to Glossop:** BMI 18.5 to 30 kg/m^2 3 IVF cycles for women ≤37 2 IVF cycles for 38-39 year olds 1 IVF cycle for 40 to 42 year olds Other restrictions e.g. re smoking, childlessness, etc.	793	1,342	421	£4.9 million	£11,671	• Reducing number of IVF cycles (3, 2, 1) with increasing age of woman • Little change in numbers treated, LBs or cost compared to Glossop policy
5	**Between Bassetlaw/Glossop and other East Midlands policies, closer to latter:** BMI 18.5 to 30 kg/m^2 2 IVF cycles for women <40 1 IVF cycle for 40 to 42 year olds Other restrictions e.g. re smoking, childlessness, etc.	793	1,170	382	£4.3 million	£11,289	• Same number of women treated, but 1.3x more LBs, higher cost per LB and 1.5x higher overall cost compared to most current East Midlands policies
6	**Wider BMI criteria than most current East Midlands ICB policies:** 1 IVF cycles for women ≤42 BMI 18.5 to 35 kg/m^2 Other restrictions e.g. re smoking, childlessness, etc.	972	981	335	£3.6 million	£10,698	• Less restrictive BMI criteria than most East Midlands policies except Bassetlaw • Fewer cycles for women <40 than Bassetlaw and Glossop
7	**Close to most current East Midlands ICB policies:** 1 IVF cycles for women ≤42 BMI 18.5 to 30 kg/m^2 Other restrictions e.g. re smoking, childlessness, etc.	793	793	283	£2.9 million	£10,343	• Most current East Midlands policies except more restrictive than Bassetlaw and Glossop
8	**Most restrictive:** BMI 18.5 – 30 kg/m^2 1IVF cycle for women <38 Other restrictions e.g. re smoking, childlessness, etc.	693	693	263	£2.5 million	£9,508	• Most restrictive • Lowest number treated • Lowest live births • Lowest cost • Lowest cost per LB

For some potential policy criteria, such as those relating to same-sex couples, single women, transgender individuals, and couples where one partner already has a child, there were insufficient data available for modelling, and evidence on clinical effectiveness of IVF will not be helpful. The model therefore does not take potential expansions in IVF access relating to these population groups into account. For these groups, some of the **ethical considerations** that ICBs need to take into account when making policy decisions include:

1. Whether it is the role of the NHS to treat clinical (medical and psychological) conditions only and hence only treat infertility, or to support people to conceive who are not able to conceive because of non-clinical reasons (such as single women and same-sex couples). Similar decisions need to be made for people who delay having a child for non-clinical reasons and request gamete/embryo storage in the interim
2. Whether it is the role of the NHS to provide IUI for people who are not able to have vaginal sexual intercourse to conceive because of a clinical condition (physical or psychosexual condition) other than infertility
3. Whether childlessness of one individual in a couple reflects a need that must be addressed by ICBs
4. ICB ethical frameworks allow for policies to prioritise funding of clinically and cost-effective treatments for groups of individuals with the greatest capacity to benefit
5. The total cost of providing more cycles of IUI or IVF (e.g. three cycles instead of one) will be less than the multiple of the individual cycle cost because not all patients will be eligible for, or take up, later cycles
6. Expansion of policies to provide assisted conception for some groups (such as single women, same-sex couples and couples where one or both partners already have a child) could potentially have a large impact on service capacity, quality, inequalities, waiting times, budgets, opportunity costs and other parameters, and research should be carried out to understand the potential numbers involved as part of policy development
7. It is assumed that exceptional circumstances would be considered by ICBs in the usual way

Policy changes to widen access to NHS funded assisted conception services need to be informed by these ethical considerations and also take account of the potential numbers of new patients. In the absence of published epidemiological data, we recommend that *local population surveys and/or sampling of a selection of GP practice populations* may be useful. Updating the model with data for these additional populations is essential in order to fully understand the impact that such policy changes may have on service delivery, quality and outcomes as well as costs/affordability.

The overview of current activity, outcomes and costs highlighted that across all five ICBs, people who were registered with a GP practice in an area with high levels of deprivation, had the lowest access to IVF/ICSI and vice versa, with the difference being more marked in some ICBs. *ICBs should consider the likely reasons for this inequity in access and how it could be addressed.* This may include addressing fuel/transport poverty, smoking rates and obesity rates in more deprived groups and possibly considering how best to encourage people not to wait till their late 30s to start their families.

9 Conclusion

This report and the model outputs support ICB policy considerations by providing an indication of clinical effectiveness, ethical considerations, potential activity, costs and outcomes associated with a range of policy scenarios/options. For some groups (such as single women, same-sex couples and couples where one or both partners already have a child), further data need to be collected to understand potential demand. For all options, there is also a need for public consultation, inequalities impact assessments and financial impact assessments.

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Glossary

Adapted from Kent and Medway ICB[51] Abandoned IVF cycle	An abandoned IVF cycle is one where an egg collection procedure has not been undertaken.
Artificial insemination (AI)	AI is the introduction of sperm into the cervix or uterine cavity for the purpose of achieving pregnancy. Intrauterine insemination (IUI) is a type of AI undertaken at a fertility clinic where sperm is filtered to produce a concentrated 'healthy' sample which is placed directly into the uterus (womb). AI undertaken at home would normally be intra-vaginal insemination, usually by means of a needleless syringe.
Assisted reproduction treatment (ART)	The collective name for treatments designed to lead to conception by means other than sexual intercourse. Includes: intrauterine insemination (IUI), in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI) and donor insemination (DI).
Azoospermia	Where there are no sperm in the ejaculate.
Cryopreservation	The freezing and storage of embryos, sperm or eggs for future use in assisted conception treatment cycles.
Donor insemination (DI)	Artificial insemination using donated sperm.
Egg (oocyte) donation	The process by which a fertile donor donates eggs to be used in the treatment of others.
Embryo transfer	The procedure in which one or more embryos are placed in the uterus.
Endometriosis	A condition where tissue similar to the lining of the uterus starts to grow in other places, such as the ovaries and fallopian tubes. Endometriosis is a known clinical cause of fertility problems.
Fertilisation	The union of an egg and sperm.
Fertility preservation (FP)	Fertility preservation involves storing eggs, sperm, embryos or reproductive tissue with the aim of having biological children in the future.
Fresh IVF cycle	Comprises an episode of ovarian stimulation and the transfer of embryos created that have not previously been frozen.
Frozen embryo transfer (FET)	Where an excess of embryos is available following a fresh IVF cycle, these embryos may be frozen for future use. Once thawed, these embryos may be transferred to the patient as a 'frozen embryo transfer'. Also known as a 'frozen IVF cycle'.
Full IVF cycle	Defined by NICE as one episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s).
Gonadal dysgenesis	Abnormal development of an ovary or testicle.
HFEA	Human Fertilisation and Embryology Authority. The HFEA is the UK's independent regulator of fertility treatment and research using human embryos. They license and inspect fertility clinics and set standards on best practice.

[51] Schedule of policy statements for assisted reproductive technologies (ART) for Kent and Medway Integrated Care Board. Issued by: South Central and West Commissioning Support Unit (SCW CSU) on behalf of: Kent and Medway Integrated Care Board (ICB), April 2023. https://www.kentandmedway.icb.nhs.uk/application/files/8616/8189/4915/Kent_and_Medway_ART_policy_document_April_2023.pdf

Infertility	The World Health Organisation states infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. NICE indicates that for people trying to conceive using artificial insemination (including, but not limited to, female same sex couples and single women), infertility may be indicated after 6 unsuccessful cycles. In the male reproductive system, infertility is most commonly caused by problems in the ejection of semen, absence or low levels of sperm, or abnormal shape (morphology) and movement (motility) of the sperm; this is commonly called 'male factor infertility'. In the female reproductive system, infertility may be caused by a range of abnormalities of the ovaries, uterus, fallopian tubes, and the endocrine system, among others.
In vitro fertilisation (IVF)	IVF involves ovarian stimulation and then collection of eggs. The eggs are then fertilised with sperm in a laboratory. If fertilisation is successful, the embryo is allowed to develop for 2–6 days and is then transferred to the uterus to hopefully continue to a pregnancy. Ideally 1 embryo is transferred to minimise the risk of multiple pregnancy. Where the woman or person trying to conceive is older, or the quality of the embryos is poor, 2 embryos may be transferred. It is best practice to freeze any remaining good quality embryos to use later on in a frozen embryo transfer if the first transfer is unsuccessful.
Intracytoplasmic sperm injection (ICSI)	IVF with ICSI treatment is similar to standard IVF. However, instead of mixing the sperm with the eggs and leaving them to fertilise in a dish, an embryologist will inject a single sperm into each mature egg. This maximises the chance of fertilisation as it bypasses any potential problems the sperm may have in penetrating the egg.
Intrauterine insemination (IUI)	IUI is a type of fertility treatment in which the better quality sperm are separated from sperm that are sluggish, non-moving or abnormally shaped. This sperm is then placed directly in the uterus. This can either be performed with partner sperm or donor sperm (known as donor insemination).
NICE	National Institute for Health and Care Excellence. NICE provide national guidance and advice to improve health and social care. One of the ways that NICE does so is by publishing clinical guidelines, which are evidence-based recommendations on health and care in England. Organisations commissioning and delivering services are expected to take the recommendations contained within NICE clinical guidelines into account when planning and delivering services. NICE has published a Clinical Guideline (CG 156) on fertility problems.
Oophorectomy	An operation to remove one or both ovaries.
Ovarian Hyper-Stimulation Syndrome (OHSS)	A condition in which the ovarian response to stimulation results in clinical problems, including abdominal distension, dehydration and potentially serious complications due to thrombosis and lung and kidney dysfunction. It is more likely in patients who are excessively sensitive to medicines used for ovarian stimulation.
Ovarian reserve	Ovarian reserve tests were developed by fertility clinics to predict how a person having IVF treatment would respond to the medication used to stimulate the ovaries and ultimately how many eggs they may produce.
Ovarian stimulation	Stimulation of the ovary to achieve growth and development of ovarian follicles with the aim of increasing the number of eggs released.
Pre-implantation genetic diagnosis	A technique used to identify inherited genetic defects in embryos created through IVF. Only embryos with a low genetic risk for the condition are then transferred to the uterus. Any resulting pregnancy should be unaffected by the condition for which the diagnosis is performed.
Sperm donation	The process by which a fertile donor donates sperm to be used in the treatment of others. The HFEA regulates sperm donation undertaken at UK fertility clinics.

Sperm washing	Sperm washing is used to reduce the viral load (for example, of HIV) in prepared sperm to a very low or undetectable level. The washed sperm can then be transferred to the uterus using IUI or used to fertilise eggs in IVF or ICSI.
Surgical sperm retrieval (SSR)	SSR is a technique for collecting sperm directly from the testicles or epididymis (where sperm is stored, after it is formed in the testicles).
Surrogacy	Surrogacy is where a person carries and gives birth to a baby for another person or couple. This may involve the eggs of the surrogate, the intended parent, or a donor.
Unsuccessful cycle of IVF/ ICSI	Includes failure of fertilisation, failure of development of embryos and failure to become pregnant following transfer of embryos.

Appendix 1: Policy comparison

Comparison of East Midlands ICBs assisted conception policies and NICE assisted conception guideline CG156
See end of table for abbreviations and included policies.

Criteria	Comparison between ICB policies	NICE guideline
Access criteria for IVF		
Age	All except B and G: 1 cycle of IVF for women <42 years, G: 3 cycles B: Policy statement (front page) says 3 cycles "for patients who meet the access criteria set out in the shared policy" (age not mentioned). Under Background, it also says that IFR submission could be considered for 4th cycle and that CCGs should exercise discretion re number of funded cycles up to the max recommended by NICE. Under Clinical Effectiveness heading, states that NICE considers the following to be clinically effective: 18-39y: 3 cycles 40-42y: 1 cycle (also stated in Female Age section)	Under 40 years offer 3 full cycles of IVF+/-ICSI (if reaches 40 during a cycle, complete that cycle only). 40-42 years: offer 1 full cycle provided no previous IVF, no evidence of low ovarian reserve, and implications discussed
BMI	All: Female BMI 19-30 Only B says the provider is expected to provide lifestyle support, interventions and referrals. G: 19-30 unless "exceptionally" a woman with a BMI outside this range can demonstrate that they are not clinically obese or too thin e.g. accurate body fat measurement	Women should be **informed** that before IVF female BMI should ideally be 19-30 and that BMI outside this range reduces success of assisted reproduction. Men with BMI≥30 should be **informed** that likely to take longer to conceive.
Smoking	All except B: both partners must be non-smoking before and during IVF (IVF stops if they restart smoking), except D which does not mention IVF stopping and also says e-cigarettes are not counted as smoking. G specifies that this includes any product containing nicotine. B: GP needs to discuss effect of smoking on success rates prior to referral.	Women should be **informed** that smoking, and passive smoking, likely to reduce fertility and offered referral. Men should be **informed** of association with reduced semen quality.
Ovarian reserve	All except B and G: Satisfactory ovarian reserve: FSH ≤8.9 B: Low ovarian reserve: FSH ≥9 IU/l using Leeds assay OR antral follicle count ≤4 OR AMH ≤pmol/l G: if AFC, AMH or FSH level suggest low ovarian reserve (as per NICE CG156), donor eggs can be used for 40-42 year olds	Use age as initial indicator of chance of success with natural conception or IVF. Then one of the following as an indicator for low IVF ovarian response: 1) AFC ≤4; 2) AMH ≤5.4pmol/l; 3) FSH ≥8.9 IU/l
Infertility	All except B, D: include people with a medical reason for being unable to conceive or have unexplained infertility and are able to demonstrate this (including same-sex couples). B: Specifies those who have an identified cause for their infertility or who have infertility of at least 2 years duration. D: Need to evidence infertility or a condition leading to infertility is mentioned in relation to single women and to family structure. G: 2 years trying to conceive. For same-sex couples, 6 cycles of self-funded self-reported AI (3 if aged >36 years) then 6 cycles NHS-funded IUI.	Consider IVF if not conceived after 2 years of regular unprotected intercourse or 12 cycles of AI (6 or more by IUI). Where investigations show no chance of pregnancy with expectant management and IVF is the only effective treatment refer women directly to specialist team for IVF.
Other criteria	G: Couple should give assurance that alcohol intake is withing DH guidelines and not using recreational drugs; evidence to the contrary will result in cessation of treatment	Women should be informed that drinking no more than 1 or 2 units of alcohol once or twice per week and avoiding episodes of intoxication reduces the risk of harming a developing fetus.

Criteria	Comparison between ICB policies	NICE guideline
		Men should be informed that 3-4 units/day alcohol consumption is unlikely to affect their semen quality; excessive alcohol intake is detrimental to semen quality. Enquiry should be made and advice given on use of over-the-counter and recreational drugs
IVF/ICSI pathway		
Definition of an IVF cycle	Defined by all except D (not defined by D). One episode of ovarian stimulation plus transfer of all viable fresh and frozen embryos.	1 episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s).
Number of IVF cycles **Female age <40 years**	Age <40 y: All except B and G: 1 cycle if <3 self-funded cycles previously (and no remaining viable frozen embryos). G also includes cycles funded by another CCG in the total limit of 3 cycles. B and G: 3 cycles. Previous self-funded cycles count towards max number of cycles allowed. G specifies that this includes cancelled and abandoned cycles. B: Under Background, also says that IFR submission could be considered for 4th cycle and that CCGs should exercise discretion re number of funded cycles up to the max recommended by NICE.	Under 40 years offer 3 full cycles of IVF+/-ICSI (if reaches 40 during a cycle, complete that cycle only).
Number of IVF cycles **Female age 40-42 years**	All except B and G: Age 40-42y AND no previous IVF AND no low ovarian reserve (AND risks discussed): 1 cycle B: 1 cycle if either an identified cause of infertility or infertility >2years, no evidence of low ovarian reserve G: 1 cycle if no previous IVF; if low ovarian reserve (NICE AFC, AMH or FSH thresholds) donor eggs can be used All say that previous cycles whether self-funded or NHS funded will be taken into consideration.	40-42 years: offer 1 full cycle provided that never previously had IVF and no evidence of low ovarian reserve and implications have been discussed.
Number of embryos	Default of 1 embryo All roughly in line with HFEA guidance though not always worded the same: 2 embryos only if clear clinical justification (no top quality embryos) available; and can consider two in females aged 40-42y. B: says currently only transferring a single embryo for couples who are at high risk. And that they support the HFEA guidance on single embryo transfer.	Women <37 years: first full IVF cycle – single embryo transfer; second cycle – single if 1 or more top quality embryos available, if not consider using 2; 3rd cycle – no more than 2 embryos. Women aged 37-39: 1st and 2nd full IVF cycles – single if there are 1 or more top quality embryos, if not consider double embryo transfer; 3rd cycle – no more than 2 embryos. Women aged 40-42: consider double embryo transfer. For donor eggs use age of donor. If top-quality blastocyst available use single embryo transfer. Advise of risks of double transfer; offer cryopreservation to store remaining good quality embryos.
Fresh vs frozen embryos	All: all fresh and frozen embryos should be used unless a successful live birth	No mention of different effectiveness of fresh vs frozen embryos. Use all viable fresh and frozen embryos in 1 full cycle.
Storage of IVF embryos (and sperm from	All except G: Embryo and sperm (from surgical retrieval) from NHS funded IVF can be stored frozen for up to 3 years or till 6 months after successful live birth, whichever is shorter. Longer storage must be self-funded.	Duration of storage as part of IVF not mentioned.

Criteria	Comparison between ICB policies	NICE guideline
surgical retrieval)	G: Viable embryos remaining after live birth stored for 10 years (duration will change if HFEA guidance changes) or till 43rd birthday, whichever is shorter, available for private treatment. D: will not fund access after live birth. B: if funded privately, will remain privately funded.	
Cancelled/ abandoned cycles	All except G, say one cancelled cycle (egg collection not undertaken) is included as part of NHS treatment. G may allow a 2nd cycle after a cancelled or abandoned cycle – requires individual prior approval. B defines abandoned cycle as <3 mature follicles or excessive response, or failure of fertilisation or cleavage. Only 1 further cycle funded even if latter cycle also abandoned.	Defined as egg collection procedure not undertaken. Cancelled cycles due to low ovarian reserve should be taken into account when considering suitability for further IVF.
Surgical sperm retrieval (SSR)	All except B (not mentioned) and G say SSR is included where couple eligible for IVF, for obstructive azoospermia or ejaculatory failure not corrected by other means, but not if previous vasectomy. G: SSR is NHS England responsibility; need to use NHS England form for funding request.	Surgical sperm recovery before ICSI may be performed depending on the pathology and wishes of the man; facilities for cryopreservation of spermatozoa should be available.
Oocyte donation (OD)	All except B say OD is included in IVF funding for premature ovarian failure, ovarian dysgenesis, bilateral oophorectomy, chemo and radiotherapy and not normally for women in other groups who do not respond to follicular stimulation. G: also includes OD for women aged 40-42 with low ovarian reserve as per NICE CG156 criteria. B: not mentioned except under IUI/DI (see below).	Considered effective in fertility problems due to premature ovarian failure, dysgenesis, bilateral oophorectomy, chemo and radiotherapy and certain cases of IVF treatment failure, and consider in certain cases where high risk of transmitting a genetic disorder.
Access criteria for IUI/DI		
Indications	LLR, D, B, Lincs: Offer IUI if vaginal intercourse difficult or not possible due to physical disability or psychosexual condition, if specific consideration to methods of conception needed e.g. sperm washing for HIV; or if same-sex relationship. G: consider IUI as a treatment option for the groups above and also for single women D: IUI can be considered if cultural or religious (but not social) objections to IVF and have a fertility problem. D: if psychosexual problems, refer to counselling before referral. Unexplained infertility, mild endometriosis or mild male factor infertility: LLR: Algorithm says up to 3 stimulated IUI cycles if minimal/mild endometriosis and tried laparoscopic surgical treatment. Nh: 1 cycle for fully investigated infertility or unexplained subfertility considered amenable to IUI; if not conceived after 2 years of regular sexual intercourse, no previous IUI or IVF in this relationship, no history of tubal surgery or evidence of tubal damage, neither partner has history of sterilisation Notts, Li, G: not mentioned B, D: IUI/DI not funded but exceptional circumstances include social, cultural or religious objections to IVF. B: anovulatory infertility: ovulation induction with gonadotrophin therapy 6 cycles funded with or without IUI.	Consider unstimulated IUI as a treatment option as an alternative to vaginal sexual intercourse in: • people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychosexual problem • people with conditions that require specific consideration in relation to methods of conception (e.g. man is HIV positive) • people in same-sex relationships. For unexplained infertility, mild endometriosis and mild male factor infertility with regular unprotected sexual intercourse do not routinely offer IUI (exceptions may be social, cultural or religious objections to IVF), and advise to try to conceive for 2 years (including up to 1 year before fertility investigations) before IVF is considered.
Age	Woman's age: LLR: 23-42 years Linc: for same-sex couples, 23-42 years; heterosexual couples required to meet criteria in the IVF policy.	Not discussed in terms of criterion for access to IUI

Criteria	Comparison between ICB policies	NICE guideline
	Notts, Nh: 23-39 years (Nh specifies IUI completed before 40th birthday) D: <39 years B: 18-42 years (assuming criteria listed apply to both IVF and IUI) G: not mentioned for IUI Man's age: LLR, Notts, Nh: ≤55 years Others: not mentioned	
BMI	Woman: LLR, Notts, D, Li (for same-sex couples), Nh: BMI 19-30 Li: heterosexual couples required to meet criteria in the IVF policy B: BMI 19-30, assuming criteria listed apply to both IVF and IUI G: not mentioned for IUI Man: Notts: BMI <35 Others: not mentioned	Not discussed in terms of criterion for access to IUI
Smoking	LLR, Notts, Li, D, Nh: both partners must be not smoking. Li, D: both partners not smoking >=28 days (CO validation may be required). Li policy says this for same-sex couples; for heterosexual couples it refers to criteria in IVF policy. D: e-cigs alone considered non-smoking G: not mentioned for IUI B: GP should discuss and refer for support (assuming criteria listed apply to both IVF and IUI)	Not discussed in terms of criterion for access to IUI
Previous treatment	Nh: woman must be rubella immune. Others: not mentioned	Not mentioned
IUI/DI pathway		
Number of cycles	LLR: Max 3 cycles of DI or 3 of IUI. Notts: 6 DI or 3 IUI cycles. Li: number of cycles not specified except in Background section which says current funding for up to 3 IUI cycles (prior approval needed for same-sex couples; heterosexual couples treated in line with IVF/ICSI policy). Policy section says IUI funded in line with NICE guideline (number of cycles not stated); for same-sex couples, DI only funded after 6 cycles of privately funded DI in a clinical setting (number of NHS funded cycles not specified). D: 6 IUI/DI cycles funded only after patient self-funds initial 6 in clinical setting with initial clinical assessment and investigations (for same-sex couples or physical disability or psychosexual condition); if male HIV, NHS also funds initial 6 IUI cycles.	Where criteria for IUI/DI are met, offer 6 cycles of unstimulated IUI/DI. If not conceived after 6 cycles (donor or partner sperm) despite evidence of normal ovulation, tubal patency and semen analysis offer 6 more unstimulated cycles before considering IVF.

Criteria	Comparison between ICB policies	NICE guideline
	B: 6 IUI cycles “where a medical condition exists” e.g. physical disability, and for same-sex couples, followed by further assisted conception if needed. Nh: 1 cycle. G: Number not specified for the indications for IUI listed above. For same-sex couples and single women: 6 cycles after referral in addition to self-funded 6 cycles of self-reported AI prior to referral (considered equivalent of expectant management for heterosexual couples) or 3 cycles if age >36 years.	
Timing	LLR, Notts: Suitable patients should have IUI/DI before being considered for IVF/ICSI. If IVF first and IVF fails, will not be offered IUI. Li: no previous IVF (NHS or private) Nh: no previous IUI or IVF in this relationship G: consider IUI as a treatment option for the groups listed under indications for IUI above. For same-sex couples and single women offer 6 cycles of IUI as above before considering IVF.	See above – where IUI/DI indicated, consider IVF after 12 unstimulated cycles of IUI/DI
Donor sperm	LLR, Notts: Funded for azoospermia, severe oligospermia or to avoid transmission of inherited disorders (where other criteria for IUI are met). Notts adds: up to 6 DI or 3 IUI if required in addition to full IVF entitlement B: 6 cycles of DI where clinically indicated and donor sperm available. If required, place on waiting list for 3 years, then review to assess if criteria still met. If difficulty finding suitable donor is anticipated and exceptionality consider sourcing from alternative providers via IFR. G: implies that it may be funded for the indications listed above but not clearly specified.	Consider donor sperm if obstructive azoospermia, non-obstructive azoospermia, severe deficits in semen quality in couples who do not wish to use ICSI, high risk of transmitting a genetic disorder or infectious disease (to offspring or to woman), severe rhesus isoimmunisation.
Social / ethical factors in relation to IVF and IUI/DI		
Existing children / family structure	IVF: All: no living child from any relationship, including adopted but not fostered. D also says that child given up for adoption previously is not counted as living child. LLR and B are clearer that this means either partner. G: no living child from current relationship and 1 of the partners does not have a living child from a previous relationship. All except B say that eligibility ceases if live birth or adoption. IUI: LLR, Notts, D, Lincs, Nh: not eligible if any living children from any relationship including adopted but not fostered; same for B if assume criteria listed apply to both IUI and IVF G: not stated	Does not suggest that presence of no existing child is a criterion for IVF but says “People should be informed that IVF treatment is more effective in women who have previously been pregnant and/or had a live birth.”
Sterilisation and reversal	All except B and G: IVF and IUI not funded if either partner been sterilised even if reversed. B: IVF not funded if sterilised or unsuccessfully reversed. Same for IUI if criteria listed apply to both IVF and IUI. G: IVF (IUI not mentioned) not funded if infertility results from previous sterilisation for family planning reasons unless sterilisation has been successfully reversed and the other (not previously sterilised) partner has infertility or unexplained infertility.	Not mentioned

Criteria	Comparison between ICB policies	NICE guideline
Same-sex couples	For IVF: All except B and D: eligible for IVF if evidence of subfertility from clinical investigations as per NICE guideline or if AI as per CCG policy is unsuccessful (AI needs to be in licenced setting with initial clinical assessment, tests, etc). D: eligible for 1 cycle of IVF if criteria are met as for heterosexual couples. B: if sexual intercourse is not possible then eligible for 6 cycles IUI and further assisted conception if required. G: access IVF as per policy after 6 cycles of self-funded self-reported AI then 6 cycles NHS-funded IUI, 3 cycles if age >36y. For IUI: B: 6 cycles IUI funded then further assisted conception if required. D: 6 cycles funded only if patient funds initial 6 cycles in clinical setting with initial clinical assessment and investigation. Li: IUI funded only if patient funds initial 6 cycles in a clinical setting; number of funded cycles not specified in policy section, but policy section says IUI funded in line with NICE guideline. Background section says current funding for up to 3 IUI cycles and prior approval needed for same-sex couples; heterosexual couples treated in line with IVF/ICSI policy. G: 6 cycles IUI after 6 cycles of self-funded self-reported AI, 3 cycles if age >36 years.	Not mentioned for IVF; only mentioned for IUI (consider unstimulated IUI as a treatment option; if not conceived after 6 cycles of DI despite evidence of normal ovulation, tubal patency and semen analysis, offer a further 6 cycles of unstimulated IUI before IVF is considered).
Transgender	B only (in background section): if conception by regular sexual intercourse is not possible consider as inability to conceive.	Not mentioned
Single women	D: one IVF cycle funded if criteria are met as for heterosexual couples and can evidence infertility or condition leading to infertility; not mentioned for IUI. G: access IVF as per policy after 6 cycles of self-funded self-reported AI then 6 cycles NHS-funded IUI, 3 cycles if aged >36 years. Lincs: assisted conception not funded Others: not mentioned	Not mentioned
Length of relationship	Only mentioned by B: couples must have been in a stable relationship for a minimum of 2 years and currently co-habiting.	Not mentioned
HIV/HepB/HepC and sperm washing	For IVF: Mentioned in B in relation to IVF: offer testing and if positive offer specialist advice, counselling, management; not sperm washing. For IUI: Included in all policies we were sent in line with NICE guideline except for Nh and G.	Mentioned under investigation of fertility problems and management strategies (not specifically IVF). For man with HIV discuss with specialist and advise risk of transmission negligible if man compliant with HAART and viral load <50/ml and no other infections and unprotected intercourse only at time of ovulation. If not, or if still worried, offer/consider sperm washing. If man has Hep B offer woman vaccine before starting fertility treatment; not sperm washing.

Criteria	Comparison between ICB policies	NICE guideline
		If man has Hep C, discuss with specialist and discuss treatment options to eradicate before conception considered.
Welfare of the child	Mentioned in all IVF and IUI policies.	Not mentioned except for DI and for OD: Couples considering DI and oocyte recipients and donors should be offered independent counselling regarding implications for themselves and potential children.
Cryopreservation for other reasons (not as part of IVF cycle) e.g. prior to cancer treatment, to preserve fertility	Separate policies provided by LLR, D (D's will be revised in the next few weeks), B and Nh. Notts: uses prior approval form with policy stated within the form. EM-wide policy was being developed but now awaiting this review. LLR, D: Funded if about to start treatment that risks permanent infertility. For women having cancer treatment, oocyte cryopreservation only if well enough and time available. Only if pregnancy would still be viable after surgery. Not for non-surgical/non-medical reason e.g. social, sterilised, congenital disorder. Not for ovarian or testicular tissue. Future fertility treatment depends on criteria at the time. Ovarian stimulation before 43rd birthday, no lower age limit, sperm retrieval before 56th birthday (LLR only). D adds that no living children and that male patients have sperm analysis one year after treatment and if in normal range continued storage not funded. Sperm stored for 5 years, 5 further years if criteria still met. Same for oocytes or till 42nd birthday if sooner. (can opt to self-fund further) Notts: Similar to LLLR and D. List of indications includes treatments that may cause permanent infertility including treatments for malignancies, conditions requiring relevant urology/gynae surgery, treatments for gender dysphoria / transgender, specialist endocrine, rare mitochondrial disorders, autoimmune conditions requiring chemotherapy. Up to 43rd birthday for female, 56th birthday for male, no min age. Sperm for 10 years or till age 56, whichever sooner. Eggs and embryos for max 10 years or till age 43, whichever is sooner. Single treatment cycle only. Excludes embryos using donor sperm, and additional costs for transport if needed. B: For patients about to undergo a medically necessary procedure that may permanently impair fertility, impact discussed, able to make an informed choice and aware that cryopreservation does not guarantee funding for future assisted conception. Women: one cycle of egg retrieval funded with or without fertilisation. If <10 eggs, 1 more cycle. Men: store at least 2 semen samples over a week, max 3. Not ovarian or testicular tissue. Testicular sperm retrieval commissioned separately by NHSE. Duration: initially for 10y; more requires IFR and to be in line with HFEA. Nh: Gamete storage funded (not superovulation or associated techniques as considered experimental) for children from sexual maturity, men up to 45y, women to 38y. Duration: until the sooner of fertility restored, man reaches 55y, woman reaches 42y, 10y from retrieval, death of man or woman. Further storage is private. Consultant responsible for care that impairs fertility (oncologist/ haematologist) submits funding request. CCG writes to GP annually for health update and then to patient re wishes re storage. If conception planned, patient approaches GP for fertility test. G: For individuals undergoing treatment for cancer, lifesaving treatment or treatment for a congenital condition resulting in infertility, or gender reassignment offer gamete retrieval and cryopreservation if the procedure or delay does not put them at risk. Storage and use in line with HFEA regulations (at the time these included no lower age, no upper age for men, up to age 43 years for women, storage for up to 10 years, but HFEA could change these). Use will depend on local policy at the time. If age over 42 years, IFR required for oocyte storage – IFR will be dealt	Offer early referral if treatment planned that may result in infertility. Take account of diagnosis, treatment plan, expected outcome of fertility treatment, cancer prognosis, viability of stored material. Don't apply conventional eligibility criteria for cancer patients e.g. no lower age limit. But criteria will apply at point of use. Store sperm, embryos or oocytes. For women with cancer – if well enough for ovarian stimulation and egg collection and this won't worsen the condition and enough time. Store initially for 10 years. Offer continued storage of sperm beyond 10 years if remain at risk of significant infertility.

Criteria	Comparison between ICB policies	NICE guideline
	with as urgent. IFR required for extension of storage of gametes or embryos (up to statutory upper limit - 55 years at the time). Lincs says not in scope of IVF policy.	
PGD / Preimplantation genetic screening / IVF to screen out embryos with a serious inherited disease	LLR mentions separate policy but not received. Others say not within scope of IVF or assisted conception policy or not a fertility treatment. B says requires prior approval. G: PGD is NHS England responsibility; need to use NHS England form for funding request. Also states that IVF/ICSI is not commissioned for recurrent miscarriage unless part of PGD approved by NHS England.	Before considering ICSI people should undergo appropriate investigations re diagnosis and to allow informed discussion, and consideration given to relevant genetic issues. Where a specific genetic defect associated with male infertility is known or suspected couples should be offered genetic counselling and testing e.g. if severe deficit of semen quality or non-obstructive oligospermia. Men undergoing karyotype testing should be offered genetic counselling, Testing for Y chromosome microdeletions not routine before ICSI.
ZIFT and GIFT	LLR, Notts – not recommended Others: not mentioned	Insufficient evidence
Clomifene citrate	LLR and Notts: From IUI/DI policy: all couples e.g. if IUI/DI criteria not met, can have primary or secondary care investigations and if appropriate clomifene in line with NICE Other: not mentioned	Clomifine offered to: Group 2 anovulatory infertility (mainly PCOS) taking into account potential adverse effects, ease of use and woman's BMI, offer ultrasound monitoring during at least the first cycle to minimise risk of multiple pregnancy. (alternative is metformin but not licenced in 2013) Group 3 ovulation disorders resistant to clomifene consider clomifene plus metformin or other alternatives (see NICE)
Investigations for subfertility	All: Available to anyone with a fertility problem	Guidance on which investigations to use and reference values

Abbreviations:

Policies: B - Bassetlaw CCG (now part of Notts); D – NHS Derby and Derbyshire ICB; G - Glossop (part of D but previously part of previously part of Tameside and Glossop CCG); Li – NHS Lincolnshire ICB; LLR – NHS Leicester, Leicestershire and Rutland ICB; Nh – NHS Northamptonshire ICB; Notts – NHS Nottingham and Nottinghamshire ICB

Other abbreviations: AI – artificial insemination; BMI – body mass index; CCG – clinical commissioning group; DI – donor insemination; EM – East Midlands; GIFT – gamete intrafallopian transfer; GP – general practitioner; ICB – integrated care board; HAART – highly active antiretroviral therapy; Hep – hepatitis; HFEA – Human Fertilisation and Embryology Authority; HIV – human immunodeficiency virus; ICSI – intracytoplasmic sperm injection; IFR – individual funding request; IUI – intrauterine insemination; IVF – in vitro fertilization; NICE – National Institute for Health and Care Excellence; OD – oocyte donation; PCOS – polycystic ovary syndrome; PGD – preimplantation genetic diagnosis; ZIFT – zygote intrafallopian transfer

Policies included (* denotes policies received after the scoping workshop):

- NHS Leicester, Leicestershire and Rutland ICB: IVF/ICSI; IUI/DI; Gamete/embryo cryopreservation
- NHS Nottingham and Nottinghamshire ICB: IVF/ICSI; IUI/DI, etc excluding IVF/ICSI; Gamete and embryo storage policy/prior approval form*
- Bassetlaw (formerly NHS Bassetlaw CCG): Infertility treatment policy; Cryopreservation*
- NHS Derby and Derbyshire ICB: IVF/ICSI; IUI; Gamete storage
- Glossop (now part of Derby and Derbyshire ICB): NHS Manchester CCG assisted conception policy*
- NHS Lincolnshire ICB: IVF/ICSI; IUI

Criteria	Comparison between ICB policies	NICE guideline
• NHS Northamptonshire ICB: IVF/ICSI; IUI*; Gamete storage*		

Appendix 2: Questions and PICOS frameworks for evidence enquiries

Questions and PICOS frameworks agreed at May 2023 scoping workshop with ICBs for consideration of evidence.

Questions

Age / IVF

How does the clinical effectiveness of 1 full cycle of IVF vary with the age of the female?

- Population: Women aged 40-42 years
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full IVF cycle
- Comparator: Women aged 25-39, smaller age bands if information available
- Outcomes: Pregnancy rate, live birth rate, adverse events, cost effectiveness

BMI / IVF

What is the effectiveness of IVF/ICSI where the woman has a BMI>=30 compared to <30?

- Population: Women up to 42 years with BMI >= 30
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full IVF cycle
- Comparator: BMI <30
- Outcomes: Pregnancy rate, live birth rate, adverse events, complications of pregnancy, neonatal complications
- Subgroup question re ethnicity

What is the effectiveness of IVF/ICSI where the woman has a BMI <=19 compared to >19?

- Population: Women up to 42 years who have BMI <= 19
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full IVF cycle
- Comparator: BMI >19
- Outcomes: Pregnancy rate, live birth rate, adverse events, complications of pregnancy, neonatal complications
- Subgroup question re ethnicity

What is the effectiveness of IVF/ICSI where the man has a BMI >=30 compared to <30?

- Population: Male partner of couple undergoing IVF with BMI >=30
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full IVF cycle
- Comparator: BMI <30
- Outcomes: Pregnancy rate, live birth rate
- Subgroup question re ethnicity

What is the effectiveness of IVF/ICSI where the man has a BMI <=19 compared to >19?

- Population: Male partner of couple undergoing IVF with BMI <= 19
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full cycle of IVF
- Comparator: BMI >19
- Outcomes: Pregnancy rate, live birth rate
- Subgroup question re ethnicity

Smoking / IVF

What is the clinical effectiveness evidence that betel nut use adversely affects the success of IVF?

- Population: Women who uses betel nut
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full cycle of IVF
- Comparator population: Women who do not use betel nut at time of IVF treatment
- Outcomes: Pregnancy rate, live birth rate, adverse events, complications of pregnancy, neonatal complications

- Population: Where male partner of the couple uses betel nut
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full cycle of IVF
- Comparator population: Where male partner of the couple does not use betel nut at time of IVF treatment
- Outcomes: Pregnancy rate, live birth rate, adverse events, complications of pregnancy, neonatal complication

What is the clinical effectiveness evidence that chewing tobacco adversely affects the success of IVF?

- Population: Women who chews tobacco
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full cycle of IVF
- Comparator population: Women who do not chew tobacco at time of IVF treatment
- Outcomes: Pregnancy rate, live birth rate, adverse events, complications of pregnancy, neonatal complications

- Population: Where male partner of the couple chews tobacco
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full cycle of IVF
- Comparator population: Where male partner of the couple does not chew tobacco at time of IVF treatment
- Outcomes: Pregnancy rate, live birth rate, adverse events, complications of pregnancy, neonatal complication

Ovarian response / IVF

What are the relative values of antral follicle count and FSH levels in predicting ovarian response to ovarian stimulation and effectiveness of IVF/ICSI and what are the optimum thresholds below which response/effectiveness of IVF/ICSI is significantly lower?

- Population: Women aged up to 42 years with FSH<8.9 IU/l
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full cycle of IVF
- Comparator populations: women with antral follicle count > 4, women with antral follicle count <4, women with FSH>=8.9 IU/l
- Outcomes: Pregnancy rate, live birth rate

Number of IVF cycles (woman under 40 years)

For women under 40 years of age, what is the effectiveness of a 2nd and 3rd full cycle compared to the 1st?

- Population: Women aged up to 40 years

- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 2nd and 3rd full cycles of IVF
- Comparator: 1st full IVF cycle
- Outcomes: Pregnancy rate, live birth rate, adverse events, cost effectiveness

Indications for IUI

What is the effectiveness of IUI compared to IVF for women with unexplained infertility, mild endometriosis or mild male factor infertility?

- Population: people with unexplained infertility, mild endometriosis or mild male factor infertility
- Intervention: 1 IUI cycle
- Comparator: 1 IVF cycle
- Outcomes: pregnancy rate, live birth rate

Age / IUI

How does the clinical effectiveness of 1 full cycle of IUI vary with the age of the female?

- Population: Women aged 40-42 years
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full IUI cycle
- Comparator: Women aged 23-39
- Outcomes: Pregnancy rate, live birth rate, adverse events, cost effectiveness

How does the clinical effectiveness of 1 full cycle of IUI vary with the age of the male?

- Population: Male partner of couple undergoing IUI aged over 55 years
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full IUI cycle
- Comparator: Male partner aged up to and including 55 years
- Outcomes: Pregnancy rate, live birth rate

BMI / IUI

What is the effectiveness of IUI where the woman has a BMI >30 compared to <30?

- Population: Women up to 42 years who have BMI over 30
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full cycle of IUI
- Comparator: BMI under 30
- Outcomes: Pregnancy rate, live birth rate, adverse events, complications of pregnancy, neonatal complications
- Subgroup question re ethnicity

What is the effectiveness of IUI where the woman has a BMI ≤19 compared to >19?

- Population: Women up to 42 years who have BMI ≤19
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full IUI cycle
- Comparator: BMI >19
- Outcomes: Pregnancy rate, live birth rate, adverse events, complications of pregnancy, neonatal complications
- Subgroup question re ethnicity

What is the effectiveness of IUI where the man has a BMI over 35 compared to <35?

- Population: Male partner of couple undergoing IVF with BMI over 35
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full cycle of IUI
- Comparator: BMI under 35
- Outcomes: Pregnancy rate, live birth rate
- Subgroup question re ethnicity
- Subgroup question re BMI over and under 30

Smoking / IUI

What is the clinical effectiveness evidence that betel nut use adversely affects the success of IUI?

- Population: Women who use betel nut
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full cycle of IUI
- Comparator population: Women who do not use betel nut at time of IUI treatment
- Outcomes: Pregnancy rate, live birth rate, adverse events, complications of pregnancy, neonatal complications

- Population: Where male partner of the couple uses betel nut
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full cycle of IUI
- Comparator population: Where male partner of the couple does not use betel nut at time of IUI treatment
- Outcomes: Pregnancy rate, live birth rate, adverse events, complications of pregnancy, neonatal complication

What is the clinical effectiveness evidence that chewing tobacco adversely affects the success of IUI?

- Population: Women who chews tobacco
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full cycle of IUI
- Comparator population: Women who do not chew tobacco at time of IUI treatment
- Outcomes: Pregnancy rate, live birth rate, adverse events, complications of pregnancy, neonatal complications

- Population: Where male partner of the couple chews tobacco
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full cycle of IUI
- Comparator population: Where male partner of the couple does not chew tobacco at time of IUI treatment
- Outcomes: Pregnancy rate, live birth rate, adverse events, complications of pregnancy, neonatal complication

Sterilisation and reversal / IUI and IVF

What is the effectiveness of a cycle of **IVF** when the woman undergoing IVF has had a successful reversal of a sterilisation procedure versus in a woman who has never had a sterilisation procedure?

- Population: Women with a history of successful reversal of a sterilisation procedure

- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full IVF cycle
- Comparator population: Women without a history of a sterilisation procedure
- Outcomes: Pregnancy rate, live birth rate, adverse events, cost effectiveness

What is the effectiveness of a cycle of **IUI** when the woman undergoing IUI has had a successful reversal of a sterilisation procedure versus in a woman who has never had a sterilisation procedure?

- Population: Women with a history of successful reversal of a sterilisation procedure
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full IUI cycle
- Comparator population: Women without a history of a sterilisation procedure
- Outcomes: Pregnancy rate, live birth rate, adverse events, cost effectiveness

What is the effectiveness of a cycle of **IVF** when the male partner in the couple has had a reversal of a vasectomy versus when the male partner in the couple has never had a vasectomy?

- Population: Male partner of couple has a history of successful reversal of vasectomy
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full **IVF** cycle
- Comparator population: Male partner of couple without a history of vasectomy
- Outcomes: Sperm quality, pregnancy rate, live birth rate, adverse events, cost effectiveness

What is the effectiveness of a cycle of **IUI** when the male partner in the couple has had a reversal of a vasectomy versus when the male partner in the couple has never had a vasectomy?

- Population: Male partner of couple has a history of successful reversal of vasectomy
- Indication: Infertility, unable to conceive after 2 years of regular unprotected sex (as per NICE GL), regardless of cause
- Intervention: 1 full **IUI** cycle
- Comparator population: Male partner of couple without a history of vasectomy
- Outcomes: Sperm quality, pregnancy rate, live birth rate, adverse events, cost effectiveness

Cryopreservation of gametes and embryos

How is the quality of sperm stored for future use in IVF affected by the duration of cryopreservation?

- Population: Sperm stored for future use in IVF
- Indication: Patient stores sperm because they are about to undergo treatment that is likely to cause infertility
- Intervention: Thawing of sperm for use in IVF after period of cryopreservation
- Comparator population: Different numbers of years duration of cryopreservation
- Outcomes: Quality of thawed sperm, suitability of thawed sperm for use in IVF, pregnancy rate, live birth rate

How is the quality of oocytes stored for future use in IVF affected by the duration of cryopreservation?

- Population: Oocytes stored for future use in IVF
- Indication: Patient stores oocytes because they are about to undergo treatment that is likely to cause infertility
- Intervention: Thawing of oocytes for use in IVF after period of cryopreservation
- Comparator population: Different numbers of years duration of cryopreservation

- Outcomes: Quality of thawed oocytes, suitability of thawed oocytes for use in IVF, pregnancy rate, live birth rate

How is the quality of embryos stored for future use in IVF affected by the duration of cryopreservation?

- Population: Embryos stored for future use in IVF
- Indication: Patient stores embryos because they are about to undergo treatment that is likely to cause infertility
- Intervention: Thawing of embryos for use in IVF after period of cryopreservation
- Comparator population: Different numbers of years duration of cryopreservation
- Outcomes: Quality of thawed embryos, suitability of thawed embryos for use in IVF, pregnancy rate, live birth rate

Appendix 3: Search strategy

Medline search

Systematic Reviews

Ovid MEDLINE(R) ALL <1946 to May 31, 2023>

1	reproductive techniques, assisted/ or exp embryo transfer/ or exp fertilization in vitro/ or exp insemination, artificial/
2	(assist* adj2 (reproduct* or conception*)).ti,kf.
3	(((invitro or "in vitro") adj2 fertili*) or ivf).ti,kf.
4	(intracytoplasmic sperm injection* or intra-cytoplasmic sperm injection* or icsi).ti,af.
5	(intrauterine insemination or intra-uterine insemination or artificial insemination or iui).ti,kf.
6	((egg? or ova or oocyte? or sperm* or embryo?) adj2 (freez* or frozen or cropreserv* or cryo-preserv* or cryostor* or cryo-stor*)).ti,kf.
7	((egg? or ova or oocyte? or sperm* or embryo?) adj2 transfer*).ti,kf.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	limit 8 to (meta analysis or "systematic review" or "reviews (maximizes specificity)")
10	limit 9 to (english language and yr="2013 -Current")
11	exp animals/ not humans.sh.
12	10 not 11

Age Factors

Ovid MEDLINE(R) ALL <1946 to June 06, 2023>

1	reproductive techniques, assisted/ or exp embryo transfer/ or exp fertilization in vitro/ or exp insemination, artificial/
2	(assist* adj2 (reproduct* or conception*)).ti,kf.
3	(((invitro or "in vitro") adj2 fertili*) or ivf).ti,kf.
4	(intracytoplasmic sperm injection* or intra-cytoplasmic sperm injection* or icsi).ti,af.
5	(intrauterine insemination or intra-uterine insemination or artificial insemination or iui).ti,kf.
6	((egg? or ova or oocyte? or sperm* or embryo?) adj2 (freez* or frozen or cropreserv* or cryo-preserv* or cryostor* or cryo-stor*)).ti,kf.
7	((egg? or ova or oocyte? or sperm* or embryo?) adj2 transfer*).ti,kf.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	age factors/ or maternal age/
10	age.ti,kf.
11	((maternal or mother* or wom?n or female? or paternal or father* or m?n or male? or parent*) adj5 age).ab.
12	((("20" or "25" or "26" or "27" or "38" or "29" or twenty or "30" or "31" or "32" or "33" or "34" or "35" or "36" or "37" or "38" or "39" or thirty or "40" or "41" or "42" or "43" or "44" or "45" or "46" or "47" or "48" or "49" or forty or "50" or "51" or "52" or "53" or "54" or "55" or "56" or "57" or "58" or "59" or fifty?) adj (year? or aged)) or (twenties or thirties or forties or fifties)).ti,kf.
13	9 or 10 or 11 or 12
14	8 and 13
15	randomized controlled trial.pt.
16	controlled clinical trial.pt.
17	randomized.ab.
18	placebo.ab.
19	drug therapy.fs.
20	randomly.ab.
21	trial.ab.

22 groups.ab.
23 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24 exp animals/ not humans.sh.
25 23 not 24
26 14 and 25
27 (comment or editorial or letter or news or review).pt.
28 26 not 27
29 limit 28 to (english language and yr="2013 -Current")

Weight

Ovid MEDLINE(R) ALL <1946 to June 06, 2023>

1 reproductive techniques, assisted/ or exp embryo transfer/ or exp fertilization in vitro/ or exp insemination, artificial/
2 (assist* adj2 (reproduct* or conception*)).ti,kf.
3 (((invitro or "in vitro") adj2 fertili*) or ivf).ti,kf.
4 (intracytoplasmic sperm injection* or intra-cytoplasmic sperm injection* or icsi).ti,af.
5 (intrauterine insemination or intra-uterine insemination or artificial insemination or iui).ti,kf.
6 ((egg? or ova or oocyte? or sperm* or embryo?) adj2 (freez* or frozen or cropreserv* or cryo-preserv* or cryostor* or cryo-stor*)).ti,kf.
7 ((egg? or ova or oocyte? or sperm* or embryo?) adj2 transfer*).ti,kf.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 overweight/ or obesity/ or obesity, abdominal/ or obesity, maternal/ or obesity, morbid/
10 Thinness/
11 *Body Weight/
12 Body Mass Index/
13 (weight or obes* or overweight).ti,kf.
14 (underweight or thin or thinness).ti,kf.
15 (weight adj2 (lose or losing or lost or reduc* or decreas* or manag* or high* or low* or increas*)).ab.
16 (bmi or body mass).ti,kf.
17 ((bmi or body mass) adj2 (manag* or reduc* or decreas* or low* or high* or increas*)).ab.
18 ((maternal or mother* or wom?n or female? or paternal or father* or m?n or male? or parent*) adj3 (weight or bodyweight or obes* or overweight or underweight or thin or thinness or bmi or body mass)).ab.
19 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20 8 and 19
21 randomized controlled trial.pt.
22 controlled clinical trial.pt.
23 randomized.ab.
24 placebo.ab.
25 drug therapy.fs.
26 randomly.ab.
27 trial.ab.
28 groups.ab.
29 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 exp animals/ not humans.sh.
31 29 not 30
32 20 and 31
33 (comment or editorial or letter or news or review).pt.
34 32 not 33

35 limit 34 to (english language and yr="2013 -Current")

Smoking

Ovid MEDLINE(R) ALL <1946 to June 07, 2023>

1 reproductive techniques, assisted/ or exp embryo transfer/ or exp fertilization in vitro/ or exp insemination, artificial/
2 (assist* adj2 (reproduct* or conception*)).ti,kf.
3 (((invitro or "in vitro") adj2 fertili*) or ivf).ti,kf.
4 (intracytoplasmic sperm injection* or intra-cytoplasmic sperm injection* or icsi).ti,af.
5 (intrauterine insemination or intra-uterine insemination or artificial insemination or iui).ti,kf.
6 ((egg? or ova or oocyte? or sperm* or embryo?) adj2 (freez* or frozen or cropreserv* or cryo-preserv* or cryostor* or cryo-stor*)).ti,kf.
7 ((egg? or ova or oocyte? or sperm* or embryo?) adj2 transfer*).ti,kf.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 exp smoking/ or "tobacco use"/
10 exp Smoking Devices/
11 (smok* or tobacco or betel or betal or areca).ti,ab,kf.
12 9 or 10 or 11
13 8 and 12
14 exp animals/ not humans.sh.
15 13 not 14
16 (comment or editorial or letter or news or review).pt.
17 15 not 16
18 limit 17 to (english language and yr="2013 -Current")

Ovarian response

Ovid MEDLINE(R) ALL <1946 to June 07, 2023>

1 reproductive techniques, assisted/ or exp embryo transfer/ or exp fertilization in vitro/ or exp insemination, artificial/
2 (assist* adj2 (reproduct* or conception*)).ti,kf.
3 (((invitro or "in vitro") adj2 fertili*) or ivf).ti,kf.
4 (intracytoplasmic sperm injection* or intra-cytoplasmic sperm injection* or icsi).ti,af.
5 (intrauterine insemination or intra-uterine insemination or artificial insemination or iui).ti,kf.
6 ((egg? or ova or oocyte? or sperm* or embryo?) adj2 (freez* or frozen or cropreserv* or cryo-preserv* or cryostor* or cryo-stor*)).ti,kf.
7 ((egg? or ova or oocyte? or sperm* or embryo?) adj2 transfer*).ti,kf.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 (ovar* adj2 respons*).ti,kf.
10 ((follicle adj3 (count? or threshold? or level?)) or ((fsh or follicle stimulating hormone) adj3 (count? or threshold? or level?))).ti,kf.
11 ((low or poor) adj2 (response or responder?)).ti,kf.
12 9 or 10 or 11
13 8 and 12
14 exp animals/ not humans.sh.
15 13 not 14
16 (comment or editorial or letter or news or review).pt.
17 15 not 16
18 limit 17 to (english language and yr="2013 -Current")

Cycles

Ovid MEDLINE(R) ALL <1946 to June 07, 2023>

1 reproductive techniques, assisted/ or exp embryo transfer/ or exp fertilization in vitro/ or exp insemination, artificial/
2 (assist* adj2 (reproduct* or conception*)).ti,kf.
3 (((invitro or "in vitro") adj2 fertili*) or ivf).ti,kf.
4 (intracytoplasmic sperm injection* or intra-cytoplasmic sperm injection* or icsi).ti,af.
5 (intrauterine insemination or intra-uterine insemination or artificial insemination or iui).ti,kf.
6 ((egg? or ova or oocyte? or sperm* or embryo?) adj2 (freez* or frozen or cropreserv* or cryo-preserv* or cryostor* or cryo-stor*)).ti,kf.
7 ((egg? or ova or oocyte? or sperm* or embryo?) adj2 transfer*).ti,kf.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 (("1" or 1st or one or first or "2" or 2nd or two or second or "3" or 3rd or three or third or "4" or 4th or four or fourth or "5" or 5th or five or fifth) and cycle?).ti,kf.
10 8 and 9
11 exp animals/ not humans.sh.
12 10 not 11
13 (comment or editorial or letter or news or review).pt.
14 12 not 13
15 limit 14 to (english language and yr="2013 -Current")

IUI

Ovid MEDLINE(R) ALL <1946 to June 07, 2023>

1 exp insemination, artificial/
2 (intrauterine insemination or intra-uterine insemination or artificial insemination or iui).ti,kf.
3 1 or 2
4 exp embryo transfer/ or exp fertilization in vitro/
5 (assist* adj2 (reproduct* or conception*)).ti,kf.
6 (((invitro or "in vitro") adj2 fertili*) or ivf).ti,kf.
7 ((egg? or ova or oocyte? or sperm* or embryo?) adj2 transfer*).ti,kf.
8 4 or 5 or 6 or 7
9 3 and 8
10 Endometriosis/
11 endometriosis.ti,ab,kf.
12 10 or 11
13 3 and 12
14 9 or 13
15 exp animals/ not humans.sh.
16 14 not 15
17 (comment or editorial or letter or news or review).pt.
18 16 not 17
19 limit 18 to (english language and yr="2013 -Current")

Sterilisation

Ovid MEDLINE(R) ALL <1946 to June 07, 2023>

1 reproductive techniques, assisted/ or exp embryo transfer/ or exp fertilization in vitro/ or exp insemination, artificial/
2 (assist* adj2 (reproduct* or conception*)).ti,kf.
3 (((invitro or "in vitro") adj2 fertili*) or ivf).ti,kf.

4 (intracytoplasmic sperm injection* or intra-cytoplasmic sperm injection* or icsi).ti,af.
5 (intrauterine insemination or intra-uterine insemination or artificial insemination or iui).ti,kf.
6 ((egg? or ova or oocyte? or sperm* or embryo?) adj2 (freez* or frozen or cropreserv* or cryo-preserv* or cryostor* or cryo-stor*)).ti,kf.
7 ((egg? or ova or oocyte? or sperm* or embryo?) adj2 transfer*).ti,kf.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 sterilization, reproductive/ or sterilization reversal/ or sterilization, tubal/ or vasectomy/
10 sterili?ation.ti,kf.
11 ((male or female) adj sterili?ation?).ab.
12 (vasectom* or Vasovasotom* or Vasoepididymostom*).ti,ab,kf.
13 (tubal adj2 (sterili?ation? or ligation?)).ti,ab,kf.
14 9 or 10 or 11 or 12 or 13
15 8 and 14
16 exp animals/ not humans.sh.
17 15 not 16
18 (comment or editorial or letter or news or review).pt.
19 17 not 18
20 limit 19 to (english language and yr="2013 -Current")

Cryopreservation

Ovid MEDLINE(R) ALL <1946 to June 07, 2023>

1 (reproductive techniques, assisted/ or exp embryo transfer/ or exp fertilization in vitro/ or exp insemination, artificial/) and cryopreservation/
2 ((egg? or ova or oocyte? or sperm* or embryo?) adj2 (freez* or frozen or cropreserv* or cryo-preserv* or cryostor* or cryo-stor*)).ti,kf.
3 1 or 2
4 time/ or time factors/
5 (time or timing or duration or day? or week? or month? or year?).ti,kf.
6 ((freez* or frozen or cropreserv* or cryo-preserv* or cryostor* or cryo-stor*) adj5 (time or timing or duration or day? or week? or month? or year?)).ab.
7 4 or 5 or 6
8 3 and 7
9 exp animals/ not humans.sh.
10 8 not 9
11 (comment or editorial or letter or news or review).pt.
12 10 not 11
13 limit 12 to (english language and yr="2013 -Current")

Appendix 4: Evidence summary tables

How does the clinical effectiveness of one full cycle of IVF vary with the age of the female and the number of IVF cycles?

Table A1: Summary of studies for maternal age and number of cycles

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td colspan="4">No systematic reviews identified</td></tr>
<tr><td colspan="4">Other studies</td></tr>
<tr><td>Wang et al 2022 [A9]</td><td>Retrospective cohort study

20,687 women undergoing IVF cycles (using freeze-all IVF strategy) at a single centre in China between 2007 to 2016

An IVF cycle was defined as all attempts at frozen–thawed embryo transfer resulting from one episode of ovarian stimulation.

IVF cycles for fertility preservation or using donor semen were excluded.</td><td>CLBR estimates by age of conceiving female at 1st ovarian stimulation and by cycle number
Proportions in the narrative are shown rounded to the nearest percentage point.
Live birth rates decline steeply with age between 31 to 40 years, from 53% after the first cycle in females aged 31-34 years to 22% in females aged 38-40 and 5% in females >40.

LBR shows a comparable gradient of decline across sequential cycles, though without evidence of a precipitate drop after any particular cycle.
CLBR estimates vary depending on the assumptions made regarding expected prognosis in females who discontinued IVF cycles.
For females aged <37, over 50% achieved a live birth after 3 IVF cycles, for females aged 38-40, 31-40% achieved a live birth after 3 IVF cycles.
In females aged >40 years, 8-11% achieved a live birth after 3 IVF cycles.

<table><tr><td>Age group[1] (y)</td><td></td><td colspan="5">Cycle number</td></tr><tr><td></td><td></td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr><tr><td><31</td><td>LBR within each cycle, % (95% CI)</td><td>63.81 (62.80, 64.81)</td><td>43.85 (41.68, 46.04)</td><td>37.58 (33.75, 41.52)</td><td>22.57 (17.29, 28.58)</td><td>16.67 (9.83, 25.65)</td></tr><tr><td></td><td>Optimal estimated CLBR, % (95% CI)</td><td>63.81 (62.80, 64.81)</td><td>79.68 (78.71, 80.63)</td><td>87.32 (86.32, 88.28)</td><td>90.18 (89.12, 91.17)</td><td>91.82 (90.64, 92.89)</td></tr><tr><td></td><td>Change in CLBR per additional cycle, %[2]</td><td></td><td>+16</td><td>+8</td><td>+3</td><td>+2</td></tr></table></td><td>Generalisability of CLBRs from a Chinese study cohort to the UK may be impacted by differences in the prevalence of different types of infertility between these populations (depending on the degree of variation in IVF effectiveness by type of infertility) and by differences in the prevalence of demographic factors that impact on IVF effectiveness (such as obesity).

With respect to differences in IVF protocols compared to UK clinical practice, only females in whom a freeze-all IVF strategy was used were included in the study population.
This strategy is used to reduce the risk of ovarian hyperstimulation</td></tr>
</table>

Reference	Study details	Outcomes							Comments
	Causes of infertility, non-exclusive (% prevalence of cause of infertility in the UK based on NICE estimates [1]): Tubal 68% (20%) Ovulatory 12% (25%) Endometriosis 10% (10% uterine or peritoneal) Male cause 32% (30%)		Conservative estimated CLBR, % (95% CI)	63.81 (62.80, 64.81)	73.76 (72.84, 74.67)	76.36 (75.47, 77.24)	76.93 (76.05, 77.80)	77.11 (76.23, 77.98)	syndrome (OHSS) and improve IVF outcomes and the authors report that this strategy was more likely to be used in patients with higher risk of developing OHSS, of advanced maternal age, with diminished ovarian reserve, with polycystic ovary syndrome or poor ovarian response. The freeze-all strategy was used in 85% of IVF cycles performed at the centre from which the study dataset was derived. The cohort selected for inclusion in the study may therefore be expected to have a worse IVF prognosis compared to the IVF-seeking patient population as a whole. Information on previous parity in the women receiving IVF was not provided, however 49% of the study cohort had secondary infertility. Though not defined within the study, secondary infertility typically implies previous pregnancy/pregnancies. If the parity in the study
			Change in CLBR per additional cycle, %[2]		+10	+3	+1	+0	
		31-34	LBR within each cycle, % (95% CI)	53.02 (51.78, 54.25)	37.58 (35.35, 39.84)	27.91 (24.58, 31.42)	24.15 (19.37, 29.46)	23.49 (16.94, 31.12)	
			Optimal estimated CLBR, % (95% CI)	53.02 (51.78, 54.25)	70.67 (69.37, 71.96)	78.86 (77.48, 80.20)	83.96 (82.47, 85.39)	87.73 (86.12, 89.24)	
			Change in CLBR per additional cycle, %[2]		+18	+8	+5	+4	
			Conservative estimated CLBR, % (95% CI)	53.02 (51.78, 54.25)	63.80 (62.61, 64.98)	66.82 (65.65, 67.98)	67.94 (66.78, 69.09)	68.49 (67.33, 69.63)	
			Change in CLBR per additional cycle, %[2]		+11	+3	+1	+1	
		35-37	LBR within each cycle, % (95% CI)	39.23 (37.36, 41.13)	24.44 (21.77, 27.26)	21.93 (18.08, 26.18)	18.78 (13.37, 25.25)	16.47 (9.31, 26.09)	
			Optimal estimated CLBR, % (95% CI)	39.23 (37.36,41.13)	54.08 (51.94,56.26)	64.16 (61.68,66.62)	70.89 (68.00,73.72)	75.68 (72.31,78.93)	
			Change in CLBR per additional cycle, %[2]		+15	+10	+7	+5	

Reference	Study details	Outcomes							Comments
			Conservative estimated CLBR, % (95% CI)	39.23 (37.36, 41.13)	48.29 (46.37, 50.22)	51.82 (49.89, 53.74)	53.11 (51.18, 55.03)	53.64 (51.71, 55.56)	cohort exceeded that typically seen in the ICB IVF eligible population then, given IVF treatment is known to be more effective in women who have previously been pregnant and/or had a live birth [1], LBRs in the study cohort would overestimate those in the ICB patient population. It does not appear that IVF cycles for all non-infertility indications (e.g. PGT) or using donor oocytes were excluded from the study cohort which impacts on generalisability of the LBRs to autologous IVF cycles performed for infertility indications. Either 1-2 embryos were transferred at one time which is broadly comparable with current practice in the UK. The study outcomes examined live births, defined as any birth event in which at least one infant was born alive. We do not know if these
			Change in CLBR per additional cycle, %[2]		+9	+4	+1	+1	
		38-40	LBR within each cycle, % (95% CI)	21.67 (19.58, 23.87)	13.03 (10.64, 15.74)	11.85 (8.71, 15.62)	8.63 (5.11, 13.46)	8.00 (3.52, 15.16)	
			Optimal estimated CLBR, % (95% CI)	21.67 (19.58,23.87)	31.88 (29.28,34.63)	39.95 (36.76,43.30)	45.13 (41.42,49.02)	49.52 (45.06,54.16)	
			Change in CLBR per additional cycle, %[2]		+10	+8	+5	+4	
			Conservative estimated CLBR, % (95% CI)	21.67 (19.58, 23.87)	27.96 (25.67, 30.33)	30.90 (28.53, 33.33)	32.06 (29.67, 34.52)	32.60 (30.20, 35.07)	
			Change in CLBR per additional cycle, %[2]		+6	+3	+1	+1	
		>40	LBR within each cycle, % (95% CI)	4.71 (3.61, 6.02)	3.80 (2.56, 5.41)	2.76 (1.48, 4.67)	2.63 (1.06, 5.35)	0.62 (0.02, 3.41)	
			Optimal estimated CLBR, % (95% CI)	4.71 (3.61, 6.02)	8.33 (6.78, 10.21)	10.86 (8.90, 13.21)	13.20 (10.74, 16.17)	13.74 (11.12, 16.92)	
			Change in CLBR per additional cycle, %[2]		+4	+3	+2	+1	

Reference	Study details	Outcomes	Comments

	Conservative estimated CLBR, % (95% CI)	4.71 (3.61, 6.02)	6.99 (5.65, 8.53)	8.01 (6.58, 9.63)	8.56 (7.08, 10.23)	8.63 (7.15, 10.31)
	Change in CLBR per additional cycle, %[2]		+2	+1	+1	+0

[1] Age of female at time of 1st ovarian stimulation
[2] Change in CLBR per additional cycle was calculated by the report authors based on the published information and is presented rounded to the nearest percentage point.

CLBR Cumulative live birth rate. CLBR was defined as the probability of having at least one live birth up to and including a given cycle divided by the number of women who ever received IVF treatment during these cycles. Optimal CLBR assumes that the cumulative live-birth rate in women who discontinued IVF without a live birth would, had they had continued, have been equal to the rate in those who continued to have further cycles. Conservative CLBR assumes that those who discontinue IVF would have had a live birth rate of 0 in any subsequent IVF cycles (i.e. discontinuation was the result of poor prognosis in all cases).

Odds Ratios for probability of live birth for age and number of completed cycles from a multivariate model:

Predictors	Odds ratio (95% CI)[1]	*p* value
Number of complete cycles		
1 (reference)	1	
2	0.45 (0.41, 0.49)	< 0.001
3	0.35 (0.31, 0.39)	< 0.001
4	0.25 (0.21, 0.31)	< 0.001
5	0.24 (0.18, 0.32)	< 0.001
6	0.29 (0.20, 0.42)	< 0.001
7	0.15 (0.08, 0.27)	< 0.001

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td colspan="3">Patient characteristic</td></tr>
<tr><td>Woman’s age</td><td></td><td></td></tr>
<tr><td>≤ 30 years (reference)</td><td>1</td><td></td></tr>
<tr><td>31–34</td><td>0.68 (0.63, 0.73)</td><td>< 0.001</td></tr>
<tr><td>35–37</td><td>0.38 (0.34, 0.42)</td><td>< 0.001</td></tr>
<tr><td>38–40</td><td>0.17 (0.15, 0.20)</td><td>< 0.001</td></tr>
<tr><td>≥ 41</td><td>0.04 (0.03, 0.05)</td><td>< 0.001</td></tr>
</table>
[1]The multivariate model adjusted for cause of infertility and infertility type (primary versus secondary infertility). Odds ratios represent odds of a live birth in the relevant group compared to the reference group.
</td><td></td></tr>
<tr><td>Gu et al 2021 [A10]</td><td>Retrospective single centre cohort study

3486 women in China who underwent 5088 complete IVF/ICSI cycles (an ovarian stimulation and all subsequent fresh and frozen</td><td>Proportions in the narrative are shown rounded to the nearest percentage point.

Results for the ‘non-POSEIDON’ good ovarian response study group (N=1473)[52]
(inclusion criteria: females aged ≥35 years, AFC ≥5 and/or AMH ≥1.2 ng/ml, ovarian response >9 oocytes retrieved during ovarian stimulation)

In females aged 35-37 years, the CLBR after the 3rd cycle was 62-81% (compared to 54% after the 1st cycle).
In females aged 38-39 years, the CLBR after the 3rd cycle was 56-75% (compared to 44% after the 1st cycle).
<table>
<tr><td rowspan="2">Maternal age group (y)</td><td colspan="4">Cycle number</td></tr>
<tr><td>1</td><td>2</td><td>3[3]</td><td>4[3]</td></tr>
</table>
</td><td>The optimal and conservative estimates of CLBR represent two extremes, the true CLBR is likely to lie between these estimates.

CLBRs decreased with age across the age groups examined in both study subgroups.</td></tr>
</table>

[52] The POSEIDON classification criteria divide patients with low ART prognosis into 4 subgroups based on factors including conceiving female age, ovarian reserve biomarkers and ovarian response to stimulation [16,17]. In their results, Gu et al 2021 present LBR/CLBR by POSEIDON criteria subgroups to improve comparability between patients within each subgroup. Results for POSEIDON group 4 are not shown here, as these individuals would have had an AFC<5 and so would not meet IVF ovarian reserve-related eligibility criteria under NICE guidelines [1] and inclusion of LBRs from these patients would be expected to lead to underestimation of CLBR.

Reference	Study details	Outcomes						Comments
	embryo transfers) initiated between 2009-2015 Median duration of infertility 5y Causes of infertility in study cohort, % (% prevalence of cause of infertility in the UK based on NICE estimates [1]): Ovulatory disorders 1.4% (25%) Male factor 23% (30%) Unexplained 1% (25%) Combined 22% (40%) Tubal, uterine or peritoneal 53% (35%) The study population excluded IVF cycles for preimplantation genetic testing and fertility preservation	35-37[1]	Optimal estimated CLBR, % (95% CI)	53.8 (50.6, 56.9)	73.1 (68.3, 77.8)	81.0 (71.3, 90.6)	81.0 (71.3, 90.6)	Over sequential treatment cycles, the probability of achieving a live birth increased by 7-20% after a 2nd IVF cycle, and by 1-12% after the 3rd IVF cycle (encompassing optimal and conservative LBR estimates), which appeared comparable across different maternal age groups. Generalisability of CLBRs from a Chinese study cohort to the UK may be impacted by differences in the prevalence of different types of infertility between these populations (depending on the degree of variation in IVF effectiveness by type of infertility) and by differences in the prevalence of demographic factors that impact on IVF effectiveness. In the overall study cohort, 27% of females had a parity ≥1, this proportion increased with age (from 21% in those aged 35-37 years to 38% in those aged 40-42 years). Multiparity does not
			Change in CLBR per additional cycle[4], %		+19	+8	+0	
			Conservative estimated CLBR, % (95% CI)	53.8 (50.6, 56.9)	61.0 (57.7, 64.3)	61.7 (58.4, 65.0)	61.7 (58.4, 65.0)	
			Change in CLBR per additional cycle[4], %		+7	+1	+0	
		38-39[2]	Optimal estimated CLBR, % (95% CI)	43.6 (38.3, 49.0)	62.60 (57.0, 68.3)	74.5 (66.9, 82.1)	74.5 (66.9, 82.1)	
			Change in CLBR per additional cycle[4], %		+19	+12	+0	
			Conservative estimated CLBR, % (95% CI)	43.6 (38.3, 49.0)	53.0 (48.0, 58.1)	55.7 (50.7, 60.7)	55.7 (50.7, 60.7)	
			Change in CLBR per additional cycle[4], %		+9	+3	+0	
		40-42	Optimal estimated CLBR, % (95% CI)	27.0 (20.1, 33.9)	46.7 (40.9, 52.6)	53.0 (46.4, 59.6)	76.5 (70.0, 83.1)	
			Change in CLBR per additional cycle[4], %		+20	+6	+24	
			Conservative estimated CLBR, % (95% CI)	27.0 (20.1, 33.9)	39.4 (33.4, 45.5)	41.1 (35.2, 47.1)	43.3 (37.5, 49.1)	
			Change in CLBR per additional cycle[4], %		+12	+2	+2	
		[1, 2] The CLBR estimates provided for the 35-37 year and the 38-39 year age groups differ in the main paper narrative and figures compared to those presented in the supplementary materials. We have assumed the data presented in the main paper are correct given consistency within the narrative and graphs of the main paper, and with the results for the overall study cohort (the non-POSEIDON and POSEIDON group 2 subgroups made up 81% of the overall study population) and have therefore displayed these data here. [3] Note the estimates for cycle 3 and 4 were based on a small number of live births so are more subject to random error							

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr>
<td></td>
<td></td>
<td>
[4] Change in CLBR per additional cycle was calculated by the report authors based on the published information and is presented rounded to the nearest percentage point.

CLBR Cumulative live birth rate. CLBR was defined as the probability of having at least one live birth during any of the preceding IVF cycles.
Optimal CLBR assumes that the cumulative live-birth rate in women who discontinued IVF without a live birth would, had they had continued, have been equal to the rate in those who continued to have further cycles.
Conservative CLBR assumed that those who discontinued IVF would have had a subsequent live birth rate of 0 in further IVF cycles (i.e. discontinuation was the result of poor prognosis in all cases).

Results for ‘POSEIDON group 2’ poor ovarian response subgroup (N=1246)
(inclusion criteria: females aged ≥35 years, AFC ≥5 and/or AMH ≥ 1.2 ng/ml, ovarian response <9 oocytes)

In females aged 35-37 years, the CLBR after the 3rd cycle was 42-63% (compared to 32% after the 1st cycle).
In females aged 38-39 years, the CLBR after the 3rd cycle was 35-47% (compared to 21% after the 1st cycle).

<table>
<tr><th colspan="2" rowspan="2">Age group (y)</th><th colspan="4">Cycle number</th></tr>
<tr><th>1</th><th>2</th><th>3[3]</th><th>4[4]</th></tr>
<tr><td rowspan="4">35-37[1]</td><td>Optimal estimated CLBR, % (95% CI)</td><td>32.0 (28.6, 35.4)</td><td>50.7 (47.5, 54.0)</td><td>62.5 (58.2, 66.8)</td><td>70.0 (60.9, 79.0)</td></tr>
<tr><td>Change in CLBR per additional cycle[4], %</td><td></td><td>+19</td><td>+12</td><td>+8</td></tr>
<tr><td>Conservative estimated CLBR, % (95% CI)</td><td>32.0 (28.6, 35.4)</td><td>40.0 (36.7, 43.1)</td><td>41.8 (38.7, 44.9)</td><td>42.0 (38.9, 45.1)</td></tr>
<tr><td>Change in CLBR per additional cycle[4], %</td><td></td><td>+8</td><td>+2</td><td>+0</td></tr>
<tr><td rowspan="4">38-39[2]</td><td>Optimal estimated CLBR, % (95% CI)</td><td>21.3 (16.6, 25.9)</td><td>39.3 (35.4, 43.2)</td><td>46.7 (42.6, 50.8)</td><td>57.3 (52.9, 61.8)</td></tr>
<tr><td>Change in CLBR per additional cycle[4], %</td><td></td><td>+18</td><td>+7</td><td>+11</td></tr>
<tr><td>Conservative estimated CLBR, % (95% CI)</td><td>21.3 (16.6, 25.9)</td><td>32.7 (28.6, 36.8)</td><td>34.5 (30.5, 38.6)</td><td>35.3 (31.4, 39.3)</td></tr>
<tr><td>Change in CLBR per additional cycle[4], %</td><td></td><td>+11</td><td>+2</td><td>+1</td></tr>
<tr><td>40-42</td><td>Optimal estimated CLBR, % (95% CI)</td><td>15.4 (10.7, 20.0)</td><td>27.4 (23.3, 31.6)</td><td>39.5 (35.7, 43.4)</td><td>39.5 (35.7, 43.4)</td></tr>
</table>
</td>
<td>
equate to a live birth or a living child so would not necessarily exclude a patient from IVF based on current ICB guidelines. However, if the parity in the study cohort exceeds that in the ICB IVF eligible population, then given IVF treatment is known to be more effective in women who have previously been pregnant and/or had a live birth [1], LBRs from this study cohort may overestimate those that could be achieved in the ICB patient population.

The study included patients who had received 3 or less embryo transfers at one time but the prevalence of multiple embryo transfer use was not explicitly stated.

The study outcomes examine live births, defined as an infant born showing any sign of life after 28 weeks gestation. We do not know if these children survived or were healthy.
</td>
</tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td>Change in CLBR per additional cycle[4], %</td><td></td><td>+12</td><td>+12</td><td>+0</td></tr>
<tr><td></td><td>Conservative estimated CLBR, % (95% CI)</td><td>15.4 (10.7, 20.0)</td><td>23.6 (19.3, 27.9)</td><td>27.3 (23.2, 31.4)</td><td>27.3 (23.2, 31.4)</td></tr>
<tr><td></td><td>Change in CLBR per additional cycle[4], %</td><td></td><td>+8</td><td>+4</td><td>+0</td></tr>
</table>
[1, 2] The CLBR estimates provided for the 35-37 year and the 38-39 year age groups differ in the main paper narrative and figures compared to those presented in the supplementary materials. We have assumed the data presented in the main paper are correct given consistency within the narrative and graphs of the main paper, and with the results for the overall study cohort (the non-POSEIDON and POSEIDON group 2 subgroups made up 81% of the overall study population) and these are displayed here.
[3] Note the estimates for cycle 3 and 4 are based on a small number of live births so are more subject to random error
[4] Change in CLBR per additional cycle was calculated by the report authors based on the published information and is presented rounded to the nearest percentage point.</td><td></td></tr>
<tr><td>Law et al. (2019) [A11]</td><td>Retrospective cohort study using registry data

116,677 women who received autologous ART (221,221 cycles) in Australia or New Zealand, initiated between 2009-2015

Cause of infertility (prevalence of causes in the UK [1]):
Tubal disease 8.9% (20%)
Male factor 35% (30%)</td><td>
Odds ratio for cumulative live birth by age group from a multivariable logistic regression model
The odds of cumulative live birth per aspiration decrease with greater maternal age: compared to females aged 30-34 years, the odds of cumulative live birth were 0.62-fold lower in females aged 35-39 years and 0.22-fold lower in females aged 40-44 years (to 2 decimal places).
<table>
<tr><th>Age group (y)</th><th>OR (95% CI)</th><th>P value</th></tr>
<tr><td><30</td><td>1.85 (1.79–1.91)</td><td><0.001</td></tr>
<tr><td>30–34</td><td>1.62 (1.58–1.66)</td><td><0.001</td></tr>
<tr><td>35–39</td><td>1.00</td><td></td></tr>
<tr><td>40–44</td><td>0.35 (0.33–0.36)</td><td><0.001</td></tr>
<tr><td>≥45</td><td>0.05 (0.04–0.07)</td><td><0.001</td></tr>
</table>
ORs are adjusted for the number of oocytes retrieved, cycle count and parity
ORs represent the likelihood of cumulative live birth per aspiration and were calculated as the proportion of IVF cycles that achieved at least one cumulative live birth (at ≥20 weeks gestation).

Odds ratio for cumulative live birth by cycle count from a multivariable logistic regression model
The odds of CLBR decrease steadily across the first 5 IVF cycles, with no precipitate drop after any particular cycle.
<table>
<tr><th>Cycle count</th><th>OR (95% CI)</th><th>P value</th></tr>
<tr><td>1</td><td>1.00</td><td></td></tr>
</table>
</td><td>IVF cycles where no oocytes were retrieved (which made up 10% of cycles in the initial study cohort) were not included in the calculation of CLBRs, with the study authors citing that this was due to the probability of live births from these cycles being zero. This leads to higher LBR estimates and is likely to overestimate ORs at greater maternal ages as the proportion of cycles resulting in 0 oocytes being retrieved is likely to be higher in higher maternal age groups.

Assumptions made relating to reasons for IVF</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr>
<td></td>
<td>Endometriosis 12% (uterine or peritoneal 10%)
Unexplained 31% (25%)

An IVF cycle was defined to include fresh and all subsequent frozen embryo transfers following a single ovarian stimulation.

IVF cycles for preimplantation genetic screening, fertility preservation and natural cycle IVF/ICSI were excluded</td>
<td>
<table>
<tr><td>2</td><td>0.89 (0.87–0.91)</td><td><0.001</td></tr>
<tr><td>3</td><td>0.80 (0.78–0.83)</td><td><0.001</td></tr>
<tr><td>4</td><td>0.76 (0.73–0.79)</td><td><0.001</td></tr>
<tr><td>5</td><td>0.76 (0.72–0.80)</td><td><0.001</td></tr>
<tr><td>≥6</td><td>0.72 (0.69–0.76)</td><td><0.001</td></tr>
</table>
ORs are adjusted for the number of oocytes retrieved, age group and parity.

Odds ratios for CLBR by age and cycle count from a multivariable logistic regression model
<table>
<tr><td colspan="2" rowspan="2"></td><td rowspan="2"></td><td colspan="6">Cycle count</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>≥6</td></tr>
<tr><td colspan="2"></td><td>adjusted OR[1]</td><td>1.00</td><td>0.89</td><td>0.80</td><td>0.76</td><td>0.76</td><td>0.72</td></tr>
<tr><td rowspan="5">Age group</td><td><30 years</td><td>1.85</td><td>1.85</td><td>1.65</td><td>1.48</td><td>1.41</td><td>1.41</td><td>1.33</td></tr>
<tr><td>30–34 years</td><td>1.62</td><td>1.62</td><td>1.44</td><td>1.30</td><td>1.23</td><td>1.23</td><td>1.17</td></tr>
<tr><td>35–39 years</td><td>1.00</td><td>1.00</td><td>0.89</td><td>0.80</td><td>0.76</td><td>0.76</td><td>0.72</td></tr>
<tr><td>40–44 years</td><td>0.35</td><td>0.35</td><td>0.31</td><td>0.28</td><td>0.27</td><td>0.27</td><td>0.25</td></tr>
<tr><td>≥45 years</td><td>0.05</td><td>0.05</td><td>0.04</td><td>0.04</td><td>0.04</td><td>0.04</td><td>0.04</td></tr>
</table>
[1]ORs are adjusted for the number of oocytes retrieved and parity and were calculated from the product of ORs by age group and by cycle count by the report authors. 95% CI cannot be recalculated for these ORs from the published data available.
</td>
<td>discontinuation can have a substantial impact on CLBR estimates [9], however handling of discontinuation between IVF cycles in the multivariable model was not described in the paper.

CLBRs calculated from an Australian/New Zealand-based study cohort may not be generaliseable to the UK context given differences in population demographic factors such as obesity that may impact on IVF outcomes and in IVF clinical practice (for example number of embryos transferred at one time).
Prevalences of different types of infertility amongst those in the study cohort differed from those seen in the UK and 22% of the study cohort had had a previous pregnancy until at least 20 weeks.

The study outcomes examine live births, defined as at least one liveborn baby of ≥20 weeks gestation. We do</td>
</tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>not know if these children survived or were healthy.</td></tr>
<tr><td>Smith et al 2015 [12]</td><td>Observational cohort study

153,360 women (all ages) in the UK who had 250,175 autologous IVF cycles (defined as an ovarian stimulation and all subsequent fresh and frozen embryo transfers) initiated between 2003-2010.

The study excluded IVF cycles for the purpose of storage, donation or surrogacy. Women were included in the cohort up until the first live birth.</td><td>Proportions in the narrative are shown rounded to the nearest percentage point.

CLBR estimates by age of conceiving female and cycle number
LBR in the first cycle decreases steeply with increasing age from 32% in females aged <40 years to 4% in females aged >42.
CLBR estimates vary depending on the assumptions made regarding expected prognosis in females who discontinued IVF cycles.
For females aged <40 years, 32% achieved a live birth after 1 IVF cycle and between 49-63% after 3 IVF cycles.
For females aged 40-42 years, 12% achieved a live birth after 1 IVF cycle and between 19-28% after 3 IVF cycles.

LBR shows a gentler gradient of decline across sequential cycles, without evidence of a substantial drop after any particular cycle. Nonetheless, in females aged <40 years, conservative estimated CLBR continued to increase over at least 5 IVF cycles.

<table>
<tr><th colspan="2" rowspan="2">Age group[1] (y)</th><th colspan="5">Cycle number</th></tr>
<tr><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th></tr>
<tr><td rowspan="3"><40</td><td>LBR within each cycle, % (95% CI)</td><td>32.3 (32.0-32.5)</td><td>27.1 (26.8-27.5)</td><td>24.3 (23.7-24.9)</td><td>21.4 (20.4-22.4)</td><td>19.0 (17.5-20.6)</td></tr>
<tr><td>Optimal estimated CLBR, % (95% CI)</td><td>32.3 (32.0-32.5)</td><td>50.6 (50.3-50.9)</td><td>62.6 (62.3-63.0)</td><td>70.6 (70.1-71.1</td><td>76.2 (75.6-76.8)</td></tr>
<tr><td>Change in CLBR per additional cycle[3], %</td><td></td><td>+18</td><td>+12</td><td>+8</td><td>+6</td></tr>
</table></td><td>This is a retrospective cohort study rather than prospective as reported by the authors.
The study used UK HFEA data, the causes of infertility being treated using IVF and prevalence of demographic characteristics that impact on IVF effectiveness in the study population are likely to be more similar to the UK IVF-seeking population (although HFEA data includes data from both NHS and also private patients who may not fulfil NHS IVF eligibility criteria).

The study uses data from cycles initiated between 2003-2010, IVF technological advancements may mean presented CLBR underestimate CLBR achieved in current clinical practice. NICE</td></tr>
</table>

Reference	Study details	Outcomes							Comments
			Prognostic-adjusted estimated CLBR, % (95% CI)	32.3 (32.0-32.5	48.7 (48.4-49.0)	58.0 (57.7-58.4)	63.3 (62.9-63.7)	66.4 (66.0-66.9)	recommendations to use single embryo transfer in the majority of cases and a maximum of double embryo transfer for women over 40 were published in February 2013. The study cohort did not exclude women who received multiple embryo transfers which may lead to an overestimation of CLBRs achieved in current UK practice. Live birth was defined as an infant born alive after 24 weeks' gestation surviving more than one month. We do not know if all of these children survived and if they were healthy.
			Change in CLBR per additional cycle[3], %		+16	+9	+5	+3	
			Conservative estimated CLBR, % (95% CI)	32.3 (32.0-32.5)	44.3 (44.0-44.5)	48.6 (48.4-48.9)	50.1 (49.8-50.3)	50.6 (50.3-50.8)	
			Change in CLBR per additional cycle[3], %		+12	+4	+2	+1	
		40-42	LBR within each cycle, % (95% CI)	12.3 (11.8-12.8)	10.1 (9.3-10.8)	8.6 (7.6-9.7)	7.8 (6.0-9.6)	5.3 (2.8-7.9)	
			Optimal estimated CLBR, % (95% CI)	12.3 (11.8-12.8)	21.1 (20.3-21.9)	27.9 (26.8-29.1)	33.6 (31.9-35.2)	37.4 (34.8-39.4)	
			Change in CLBR per additional cycle[3], %		+9	+7	+6	+4	
			Prognostic-adjusted estimated CLBR, % (95% CI)	12.3 (11.8-12.8)	19.8 (19.1-20.6)	24.7 (23.8-25.6)	28.0 (26.9-29.2)	29.7 (28.3-31.1)	
			Change in CLBR per additional cycle[3], %		+8	+5	+3	+2	
			Conservative estimated CLBR, % (95% CI)	12.3 (11.8-12.8)	16.8 (16.3-17.4)	18.5 (17.8-19.1)	19.0 (18.4-19.6)	19.1 (18.5-19.8)	
			Change in CLBR per additional cycle[3], %		+5	+2	+1	+0	
		>42	LBR within each cycle, % (95% CI)	3.7 (3.2-4.3)	3.3 (2.4-4.2)	3.3 (1.8-4.9)	1.3[2]	4.5[2]	
			Optimal estimated CLBR, % (95% CI)	3.7 (3.2-4.3)	6.9 (5.9-7.9)	10.0 (8.2-11.7)	11.1 (8.8-13.4)	15.1 (10.2-20.0)	
			Change in CLBR per additional cycle[3], %		+3	+3	+1	+4	
			Prognostic-adjusted estimated CLBR, % (95% CI)	3.7 (3.2-4.3)	6.3 (5.4-7.2)	8.3 (7.1-9.6)	8.9 (7.4-10.5)	10.7 (8.2-13.2)	

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td>Change in CLBR per additional cycle[3], %</td><td></td><td>+3</td><td>+2</td><td>+1</td><td>+2</td></tr>
<tr><td></td><td>Conservative estimated CLBR, % (95% CI)</td><td>3.7 (3.2-4.3)</td><td>4.9 (4.3-5.6)</td><td>5.4 (4.7-6.0)</td><td>5.5 (4.8-6.2)</td><td>5.5 (4.8-6.2)</td></tr>
<tr><td></td><td>Change in CLBR per additional cycle[3], %</td><td></td><td>+1</td><td>+1</td><td>+0</td><td>+0</td></tr>
</table>
[1] Age of woman at time of 1st ovarian stimulation
[2] Standard errors and CI could not be calculated due to small numbers
[3] Change in CLBR per additional cycle was calculated by the report authors based on the published information and is presented rounded to the nearest percentage point.

LBR Live Birth Rate
CLBR Cumulative Live Birth Rate was calculated as the probability of a live birth from all cycles up to and including the current cycle divided by the number of women who ever received IVF treatment during these cycles.
Conservative CLBR assumes that those who discontinued IVF would have had a subsequent live birth rate of 0.
Optimal CLBR assumes that the cumulative live-birth rate in women who discontinued IVF without a live birth would, had they had continued, have been equal to the rate in those who continued to have further cycles.
Prognosis-adjusted CLBR assumes 30% of those who discontinued did so due to poor prognosis (so would have had a subsequent LBR of 0) whilst the remainder discontinued due to other reasons such as psychological or social factors and so would, had they continued, have had a LBR equal to that seen in those who had further cycles.
The authors estimated that in their study cohort approximately 3% of those who discontinued did so because of poor prognosis, therefore the true CLBR is likely to lie between the optimal and prognostic-adjusted CLBR estimates.
</td><td></td></tr>
<tr><td>Safety</td><td></td><td></td><td></td></tr>
<tr><td>Ribeiro et al 2023 [A14]</td><td>Systematic review up until July 2021

96 ‘articles’ examining IVF/ICSI, no information on characteristics of individual</td><td>
Summary of impact of higher conceiving female age on IVF/ICSI outcomes:
<table>
<tr><td colspan="2">Effectiveness:</td></tr>
<tr><td>cycle cancellation rates</td><td>higher in 2 studies, no different or mixed in 1 study</td></tr>
<tr><td>pregnancy/live birth rates</td><td>lower in 24 studies, no different or mixed in 2 studies, lower in subgroup of women <25 years in 1 study</td></tr>
<tr><td>miscarriage</td><td>higher based on 3 studies</td></tr>
<tr><td>multiple pregnancy/birth</td><td>lower based on 2 studies</td></tr>
<tr><td colspan="2">Safety:</td></tr>
</table>
</td><td>Most reported outcomes were based on the synthesis of findings from a small number of papers, the design and quality of included studies was not considered in the synthesis of results.

The review did not set lower date limits for study selection to exclude</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td></td><td>studies provided in the paper</td><td>
<table>
<tr><td>macrosomia</td><td>higher based on 1 study</td></tr>
<tr><td>congenital birth defects</td><td>no different or mixed based on 1 study</td></tr>
<tr><td>preterm birth</td><td>higher in 1 study, no different in 1 study</td></tr>
<tr><td>low birth weight</td><td>higher in 1 study, no different in 1 study</td></tr>
</table>

In the narrative description of results, the authors noted that one of the included papers had observed considerable interindividual variation in the rate of fertility decline in females by age.</td><td>results from older studies which may not be representative of the outcomes seen with use of newer ART protocols and technologies.

Reasons for heterogeneity in study findings were not explored in detail, though the authors noted differences between studies in the inclusion criteria used for, and age ranges of, study participants and in ovarian stimulation approaches.

The review did not provide a detailed description of the included studies (e.g. study country, IVF protocols and use of single versus multiple embryo transfers) to enable assessment of relevance of findings from the included studies to provision of IVF in the UK context.</td></tr>
<tr><td>Sydsjo et al 2019 [A15]</td><td>Retrospective matched cohort study using registry data

Women who had given birth (as recorded in the</td><td>Prevalence of adverse or unintended outcomes amongst ART and spontaneous deliveries
<table>
<tr><td>Adverse outcome</td><td>Age group (years)[1]</td><td>ART pregnancy cohort, N (%)[2]</td><td>Spontaneous pregnancy cohort, N (%)[2]</td></tr>
<tr><td></td><td></td><td>N=4956</td><td>N=104,4074</td></tr>
<tr><td>Twin</td><td>≤39</td><td>490 (25.9)</td><td>2530 (3.6)</td></tr>
<tr><td></td><td>40-44</td><td>432 (15.4)</td><td>941 (2.9)</td></tr>
</table></td><td>The study was a retrospective matched cohort study, not a case control study as described by the study authors.

Information on indications for ART (e.g. infertility</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr>
<td></td>
<td>national birth register) in Sweden between 2007-2012.
3 study subgroups were formed, one of women aged ≥40 years from the register, one of women aged <40 matched to the ≥40 group for parity and year of birth, and one of women aged ≥45 years when they gave birth.

Women were defined as having received ART versus a spontaneous pregnancy based on medical data.</td>
<td>
<table>
<tr><td></td><td>≥45</td><td>79 (31.7)</td><td>117 (5.9)</td></tr>
<tr><td rowspan="3">Preterm, 32–36 weeks</td><td>≤39</td><td>277 (14.6)</td><td>3593 (5.2)</td></tr>
<tr><td>40-44</td><td>284 (10.1)</td><td>1872 (5.7)</td></tr>
<tr><td>≥45</td><td>49 (19.7)</td><td>138 (7.0)</td></tr>
<tr><td rowspan="3">Low birthweight, 1500g - 2499g</td><td>≤39</td><td>230 (12.2)</td><td>2403 (3.5)</td></tr>
<tr><td>40-44</td><td>228 (8.1)</td><td>1330 (4.1)</td></tr>
<tr><td>≥45</td><td>45 (18.1)</td><td>108 (5.5)</td></tr>
<tr><td rowspan="3">Very low birthweight, < 1500g</td><td>≤39</td><td>44 (2.3)</td><td>490 (0.7)</td></tr>
<tr><td>40-44</td><td>52 (1.9)</td><td>1330 (1.1)</td></tr>
<tr><td>≥45</td><td>10 (4.0)</td><td>38 (1.9)</td></tr>
<tr><td rowspan="3">SGA[3]</td><td>≤39</td><td>42 (2.2)</td><td>1239 (1.8)</td></tr>
<tr><td>40-44</td><td>72 (2.6)</td><td>915 (2.8)</td></tr>
<tr><td>≥45</td><td>10 (4.0)</td><td>53 (2.7)</td></tr>
<tr><td rowspan="3">LGA[3]</td><td>≤39</td><td>64 (3.4)</td><td>3020 (4.3)</td></tr>
<tr><td>40-44</td><td>104 (3.7)</td><td>1628 (5.0)</td></tr>
<tr><td>≥45</td><td>13 (5.2)</td><td>101 (5.1)</td></tr>
</table>
[1]Age of female when they gave birth.
[2]For percentages, the denominator is number of births.
[3]Small for gestational age
[4]Large for gestational age

The study text reports that in both ART and spontaneous pregnancy subgroups, older maternal age was associated with delivering a child preterm, with low birthweight or who was SGA compared to women younger than 40 though the statistical analyses used are not explicitly described in the study methods.

The demographic characteristics of the ART versus spontaneous pregnancy study subgroups was not compared in detail, therefore the prevalence of adverse outcomes in the spontaneous pregnancy subgroup may not be directly comparable to those in the ART subgroup and is provided for reference only.
</td>
<td>versus fertility preservation), type of ART protocol used (multiple embryo transfer versus single) or whether females receiving IUI were included within the ART group was not stated in the paper. The authors also note that women who gave birth after receiving ART abroad would not have been excluded from the study cohort. Single rather than multiple embryo transfers reduce the risk of multiple pregnancies and adverse neonatal outcomes and, since February 2013, NICE has recommended single embryo transfer in the majority of cases and a maximum of double embryo transfer for women over 40. If a higher proportion of women who had IVF involving multiple embryo transfers were included in the study cohort relative to the patient population presenting for IVF in the UK, this would lead to overestimation of the risk of adverse outcomes.</td>
</tr>
</table>

Reference	Study details	Outcomes	Comments
			Parity amongst the ART subgroup was 53% and is known to be a factor that influences the risk of certain adverse neonatal events [A18]. If parity (or other demographic factors that influence the risk of adverse ART outcomes) in the Swedish study cohort differs from that in the UK IVF seeking population, this reduces the generalisability of adverse outcome prevalences from this study cohort to the UK population.

How does the clinical effectiveness of one full cycle of IUI vary with the age of the female and of the male?

Table B1: Summary of studies: Age of female and of male and IUI outcomes

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td>Cohort studies</td><td></td><td></td><td></td></tr>
<tr><td>Ombelet et al 2021 [B3]</td><td>989 couples, 2565 IUI procedures. Most had OS using CC or hMG/rFSH.
17% had natural cycle IUI.

Couples had unexplained infertility or mild or moderate male factor infertility and the female partner had at least one patent fallopian tube. They had been trying to conceive for at least one year.

Data were collected prospectively.
Univariate analyses were carried out examining the relationship between patient characteristics and CPR.
Multivariate analyses were carried out examining the relationship of characteristics found to be significant on univariate analysis with CPR, allowing for</td><td>Summary of IUI outcomes by age

Univariate analyses
<table><tr><td colspan="2">Clinical pregnancy rate per cycle by age of female (years)</td></tr><tr><td><30: 14.1%
30-34.99: 9.9%
35-39.99: 8.0%
≥40: 6.8%
p=0.0025</td><td>The clinical pregnancy rate is significantly lower in older women than in younger women</td></tr></table>
<table><tr><td colspan="2">Clinical pregnancy rate per cycle by age of male (years)</td></tr><tr><td><30: 14.7%
30-34.99: 12.0%
35-39.99: 7.7%
≥40: 8.2%
p=0.0014</td><td>The clinical pregnancy rate is significantly lower in older men than in younger men</td></tr></table>
Multivariate analysis

Clinical pregnancy rate
Female age: no statistically significant differences were found in CPR by age group (details not reported in the paper).

Male age
<table><tr><td colspan="2">Comparison of clinical pregnancy rate per cycle by age of male (years)</td></tr><tr><td><30 vs 35-39.99: p<0.0001
<30 vs ≥40: p=0.0007
30-34.99 vs ≥40: p=0.0313</td><td>Clinical pregnancy rate was significantly lower in men aged ≥40 than in those aged <35 years, and in</td></tr></table></td><td>This study reported prospectively collected data from 2565 IUI procedures (83% with OS). Outcomes were clinical pregnancy rate by female and male age groups between <30 and ≥40 years.

The reported results suggest that CPR may be higher in younger than older females and males in these age groups. This was based on a univariate analysis.
On multivariate analysis, in females no statistically significant differences were found in CPR by age, but in males CPR was higher in some younger age groups than some older age groups.

This study collected data over an 8-year period, and a new approach to insemination using slow rather than bolus release was implemented during the last 3 years. The authors reported that mean CPR was significantly higher during the last three years (13.5% vs 9%). The mean age of the female partners was significantly higher during the last 3 years than the first 5 years, but male age did not differ significantly in the two periods. It therefore appears that more older women received slow</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td></td><td>potential confounding factors.</td><td><table><tr><td></td><td>those aged 35-39.99 than in those aged <30 years.</td></tr></table></td><td>release insemination (reported to be more successful) but it is not clear whether the analysis by age allowed for this. It is possible that there may have been an associated increase in pregnancy rates in older women as a consequence.

The authors concluded that the age of the male partner significantly influenced CPR. The age groups compared for both males and females were between <30 and ≥40 years.</td></tr>
<tr><td>Luo et al 2021 [B4]</td><td>1853 couples, 3,015 treatment cycles of IUI (2216 with OS using hCG+CC, hCG+CC+hMG or hCG+FSH/hMG, 799 (26%) natural cycles).

Females had tubal patency confirmed.

This was a retrospective cohort study.

Univariate analyses were carried out examining the relationship between patient characteristics and pregnancy rate. Multivariate analyses were carried out examining the</td><td>Summary of IUI outcomes by age

<table><tr><td colspan="2">Pregnancy rate per cycle by age of female (years)</td></tr><tr><td><30: 13.7%
30–39: 13.0%
≥40: 4.8%
χ^2 5.395, p= 0.068</td><td>No evidence of a significant difference in pregnancy rate by age of female.</td></tr></table>
<table><tr><td colspan="2">Pregnancy rate per cycle by age of male (years)</td></tr><tr><td><30: 13.6%
30–39: 13.4%
≥40: 8.9%
χ^2 4.899, p=0.086</td><td>No evidence of a significant difference in pregnancy rate by age of male.</td></tr></table>
Multivariate analysis
Female age
<table><tr><td>Comparison of pregnancy rate per cycle by age of female (years)</td></tr></table></td><td>This study reported retrospectively analysed data from 3015 IUI treatment cycles, 2216 with OS and 799 (26% natural cycles). Outcomes were pregnancy rate by female and male age groups between <30 and ≥ 40 years.

There was no evidence of a significant difference in pregnancy rate by cycle by age of female or age of male on univariate analysis.
On multivariate analysis which allowed for confounding factors, women aged ≥40 years had significantly lower pregnancy rates than those aged <30 or 30-39 years.

The authors concluded that pregnancy rate after IUI is significantly higher in women aged</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td></td><td>relationship of selected characteristics with pregnancy rate, allowing for potential confounding factors.</td><td>
<table>
<tr><td><30 vs ≥40: OR 3.238 (95% CI 1.16–9.036), p= 0.025

30–39 vs ≥40: OR 3.084 (95% CI 1.113–8.544), p= 0.03</td><td>Pregnancy rate was significantly lower in women aged ≥40 than in those aged <30 or 30-39 years.</td></tr>
</table>

Male age: no statistically significant differences were found in pregnancy rate by age group (details not reported in the paper).</td><td>under 40 years than in those aged 40 or more. They did not find any evidence of an association between pregnancy rate and male age.

The age groups compared for both males and females were from <30 to ≥40 years.</td></tr>
<tr><td>Immediata et al 2020 [B5]</td><td>2901 couples, 7359 IUI cycles started, 6323 IUI procedures. Most cycles which were stopped were because of either excessive or no ovarian response. OS was carried out with hMG/rFSH.

Couples had been trying to conceive for at least one year, women had at least one patent fallopian tube and men had a total progressive motile sperm concentration post-preparation of at least 1 × 10^6/mL.

Analysis was carried out retrospectively. Univariate analyses were carried out examining the relationship between</td><td>Summary of IUI outcomes by age

Female age
<table>
<tr><td colspan="2">Pregnancy rate per cycle by age of female (years)</td></tr>
<tr><td>≤ 35: 11.25%
36–38: 11.45%
39–40 9.03%
> 40 7.17%

OR 0.96 (95% CI 0.95-0.98), p=0.001</td><td>The pregnancy rate is lower in older women than in younger women. On univariate analysis this difference was statistically significant.</td></tr>
</table>
<table>
<tr><td colspan="2">Live birth rate per cycle by age of female (years)</td></tr>
<tr><td>≤ 35: 9.11%
36–38: 8.61%
39–40: 5.49%
> 40: 4.03%

OR 0.95 (95% CI 0.93–0.97), p<0.001</td><td>The live birth rate is lower in older women than in younger women. On univariate analysis this difference was statistically significant.</td></tr>
</table>
Male age
Association between male age and pregnancy rate: OR 0.98 (95% CI 0.96-1.00), p=0.014</td><td>This study reported retrospectively analysed data from 7359 cycles (6323 completed procedures) of IUI with OS. Outcomes reported were pregnancy rate and live birth rate by female and male age groups between ≤35 and >40 years.

The reported results suggest that pregnancy rate and live birth rate may be higher in younger than older females in these age groups. This was based on a univariate analysis which does not allow for potential confounding factors which may also be associated with differences in age (for example, the age of the partner or sperm quality).

Univariate analyses also reported statistically significant associations between male age and clinical pregnancy rate, and male age and live birth rate, but the actual rates by male age group were not reported.</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td></td><td>patient characteristics and pregnancy rate or live birth rate.
Multivariate analyses were carried out examining the relationship of selected characteristics with pregnancy rate or live birth rate, allowing for potential confounding factors.</td><td>Association between male age and live birth rate: OR 0.96 (95% CI 0.94–0.98), p<0.001

The actual pregnancy rates and live birth rates by male age were not reported.

Multivariate analysis
Association between female age and pregnancy rate: OR 0.97 (95% CI 0.95-0.99), p=0.031
Association between female age and live birth rate: OR 0.95 (95% CI 0.93–0.98), p<0.001

Outcomes of multivariate analysis by male age were not reported.</td><td>On multivariate analysis, in females there was a statistically significant association between female age and clinical pregnancy rate, and female age and live birth rate. The results of multivariate analysis for male age were not reported (the paper only reported results of multivariate analysis which were statistically significant).

The authors concluded that clinical pregnancy rate and live birth rates after IUI with OS are significantly influenced by female age.
There was no evidence of an association with male age once potential confounders were allowed for.
The age groups compared for both males and females were from ≤35 to >40 years.</td></tr>
<tr><td>Michau et al 2019 [B6]</td><td>1312 couples, 4146 IUI cycles with OS using various types of gonadotrophins.

Women were aged <43 years with at least one patent Fallopian tube.

This was a retrospective cohort study.

Univariate analyses were carried out and CPR in different female age</td><td>Summary of IUI outcomes by age

<table><tr><td colspan="2">Clinical pregnancy rate by age of female (years) *</td></tr><tr><td><30: 13.6%
30-35: 12.8%
35-38: 11.8%
38-40: 8.5%
> 40 8.3%</td><td>The clinical pregnancy rate is lower in older women than in younger women.</td></tr></table>
<table><tr><td colspan="2">Clinical pregnancy rate in women aged >40 years compared with younger age groups *</td></tr><tr><td><30 vs >40 years: p=0.004
30-35 vs >40 years: p=0.03
35-38 vs >40 years: p=0.03
38-40 vs >40 years: p=0.88</td><td>The clinical pregnancy rate is significantly lower in women aged >40 years than in those aged 35-38</td></tr></table></td><td>This study reported retrospectively analysed data from 4146 cycles of IUI with OS. The outcome reported was clinical pregnancy rate by female age groups between <30 and >40 years.

The reported results suggest that pregnancy rate may be higher in younger than older females in these age groups. On multivariate analysis (allowing for potential confounding factors) women aged <38 had a significantly higher chance of clinical pregnancy than those older than this.</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr>
<td></td>
<td>groups was compared using χ^2 tests.
Multivariate analysis included factors which were statistically significant and with no missing data on univariate analysis.</td>
<td>
<table>
<tr><td></td><td>years and younger. It was not significantly different in those aged 38-40 years and >40 years.</td></tr>
</table>
*It was not clear which age bands included the women aged 35 and 38 years.

Multivariate analysis
Women aged <38 had a significantly higher chance of clinical pregnancy (OR 1.5, 95% CI 1.2-2, p<0.001).
</td>
<td>When age groups were compared women aged >40 years (with an upper age limit of <43 years) had a significantly lower chance of pregnancy than those aged 35-38 and younger, but their chance of pregnancy was not significantly different from those aged 38-40. Because of the way the results were reported it was not clear which age bands included the women aged 35 and 38 years.

The authors concluded that age significantly affects pregnancy rate after IUI with OS, with a significantly lower chance of pregnancy after the age of 38 (this appeared to mean those aged 38 and over).</td>
</tr>
<tr>
<td>Tatsumi et al 2018 [B7]</td>
<td>1576 IUI cycles. 59% were natural cycles, the remainder used OS with CC and/or hMG.

Women were aged 40 years or less. The age range of men was not stated but in 6.5% of cycles the man was aged ≥47 years.

This was a retrospective cohort study.

Univariate analyses were carried out examining the relationship between</td>
<td>Univariate analyses
<table>
<tr><td colspan="2">Clinical pregnancy rate by age of female (years)</td></tr>
<tr><td>≤34: 9%
35-37: 9.7%
38-40: 4.7%
p=0.002</td><td>Clinical pregnancy rate was significantly lower in the older age group than in younger age groups.</td></tr>
</table>
<table>
<tr><td colspan="2">Clinical pregnancy rate by age of male (years)</td></tr>
<tr><td>≤34: 9.2%
35-37: 12.9%
38-40: 5.3%
41-43: 4.4%
44-46: 3.8%
≥47: 6.8%
p=0.002</td><td>Clinical pregnancy rate was significantly lower in older age groups than in younger age groups.</td></tr>
</table>
</td>
<td>This study reported retrospectively analysed data from 1576 IUI treatment cycles, 59% natural cycles and the remainder with OS and 799 (26% natural cycles). Outcomes were pregnancy rate and live birth rate by female age groups from ≤34 to 38-40 years, and by male age groups from ≤34 to ≥47 years.

The clinical pregnancy rate, and the odds of a pregnancy cycle on multivariate analysis (allowing for confounders) were significantly lower in women aged 38-40 than in younger age groups. The live birth rate was significantly lower in the older age group of women than in</td>
</tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr>
<td></td>
<td>patient characteristics and pregnancy rate.

Analysis of IUI outcomes was also carried out using generalised estimating equations (GEE) which adjust for confounders and correlations within patients (for example, where some patients have undergone multiple cycles of IUI).</td>
<td>
<table>
<tr><td colspan="2">Live birth rate by age of female (years)</td></tr>
<tr><td>≤34: 7.4%
35-37: 7.4%
38-40: 3.4%
p=0.002</td><td>Live birth rate was significantly lower in the older age group than in younger age groups.</td></tr>
</table>
<table>
<tr><td colspan="2">Live birth rate by age of male (years)</td></tr>
<tr><td>≤34: 7.8%
35-37: 10.1%
38-40: 3.8%
41-43: 3.4%
44-46: 1.5%
≥47: 5.8%
p=0.001</td><td>Live birth rate was significantly lower in older age groups than in younger age groups.</td></tr>
</table>
GEE analysis (all adjusted for male and female age, smoking status, ovulation induction agent and correlations within patients).
<table>
<tr><td colspan="2">Pregnancy cycles by age of female (years)</td></tr>
<tr><td>≤34: Reference
35-37: OR 1.07 (0.64-1.80), p=0.806
38-40: OR 0.60 (0.36-0.98), p=0.041</td><td>The odds of a pregnancy cycle were significantly lower in women aged 38-40 than those aged ≤34.</td></tr>
</table>
<table>
<tr><td colspan="2">Live birth cycles by age of female (years)</td></tr>
<tr><td>≤34: Reference
35-37: OR 1.01 (0.57-1.79), p=0.965
38-40: OR 0.59 (0.34-1.01), p=0.053</td><td>There was no significant difference between women of different ages in the odds of a live birth cycle.</td></tr>
</table>
<table>
<tr><td colspan="2">Pregnancy cycles by age of male (years)</td></tr>
<tr><td>≤34: Reference</td><td>There was no significant difference between men</td></tr>
</table>
</td>
<td>younger age groups, but on multivariate analysis allowing for confounders there was no significant difference between women of different ages in the odds of a live birth cycle.

The clinical pregnancy rate was significantly lower in the older age groups of men than in younger age groups, but on multivariate analysis allowing for confounders there was no significant difference between men of different ages in the odds of a pregnancy cycle. The live birth rate was significantly lower in the older age groups of men than in younger age groups, but on multivariate analysis allowing for confounders there was no significant difference between men of different ages in the odds of a live birth cycle.

The authors concluded that the age of the female partner affected the pregnancy rate (but not the live birth rate), but that advanced paternal age did not adversely affect the clinical pregnancy rate or live birth rate. This study included women aged up to 40 years, and men aged up to ≥47 years (the upper age limit was not stated).</td>
</tr>
</table>

Reference	Study details	Outcomes		Comments
		35-37: OR 1.54 (0.88-2.68), p=0.129 38-40: OR 0.65 (0.36-1.17), p=0.151 41-43: OR 0.56 (0.28-1.12), p=0.100 44-46: OR 0.49 (0.17-1.36), p=0.169 ≥47: OR 0.92 (0.40-2.10), p=0.837	of different ages in the odds of a pregnancy cycle.	
		Live birth cycles by age of male (years)		
		≤34: Reference 35-37: OR 1.43 (0.80-2.55), p=0.228 38-40: OR 0.55 (0.28-1.06), p=0.072 41-43: OR 0.50 (0.23-1.08), p=0.079 44-46: OR 0.22 (0.05-1.04), p=0.056 ≥47: OR 0.93 (0.38-2.29), p=0.881	There was no significant difference between men of different ages in the odds of a live birth cycle.	

Abbreviations
CC: clomiphene citrate; CI: confidence intervals; CPR: clinical pregnancy rate; hMG: human menopausal gonadotrophins; OR: odds ratio; OS: ovarian stimulation; rFSH: recombinant FSH

What are the relative values of antral follicle count (AFC) and follicle-stimulating hormone (FSH) levels in predicting ovarian response to ovarian stimulation and effectiveness of IVF/ICSI and what are the optimum thresholds below which response/effectiveness of IVF/ICSI is significantly lower?

Table C1: Summary of studies: Relative strengths of AFC and FSH in predicting ovarian response to ovarian stimulation and effectiveness of IVF/ICSI

Reference	Study details	Outcomes	Comments
Systematic reviews			
Ribeiro and Sousa 2014 [C3]	Systematic review (search date July 2021). Aim: to assess the effect of age, ovarian reserve and male factor or outcomes of IVF/ICSI. 96 papers included; number reporting results for indicators of ovarian reserve not reported. Review articles, incomplete and inaccessible articles and articles not written in English, Portuguese or French were excluded.	Pregnancy rate (PR) 3 studies reported that low basal FSH (bFSH) levels are associated with higher PR. No further details reported. 1 of the 3 studies reported that in younger women bFSH is not associated with PR whereas in women aged >38 years PR was significantly reduced as bFSH increased. No further details reported. 1 study reported that AFC was not associated with PR. No further details reported. Live birth rate (LBR) 2 studies reported that low bFSH levels are associated with higher LBR. No further details reported. 1 of the 2 studies reported that in younger women bFSH is not associated with LBR whereas in women aged >38 years LBR was significantly reduced as bFSH increased. No further details reported. 1 study reported that AFC was not associated with LBR. No further details reported. Response to ovarian stimulation 5 studies reported a negative association between bFSH and number of oocytes retrieved. No further details reported.	Studies were identified using the following search terms: “IVF”, “ICSI”, “IVF/ICSI” and “predicting factor” and included if they evaluated the effect of age, male factor or ovarian reserve on outcomes. The paper did not state how many of the 96 included papers investigated associations between bFSH or AFC and PR or LBR, or the sizes, countries or characteristics of the studies that reported this. For each statement, the paper cited a number of studies, but it is not clear if these were the only studies reporting that outcome. The paper did not report any numerical results (p values, relative risk, etc.) or threshold values for AFC or bFSH associated with effectiveness of IVF/ICSI. It is not clear whether the results for AFC and bFSH are from the same or different groups of patients.

Reference	Study details	Outcomes	Comments
		AFC has been positively correlated with the number of retrieved oocytes (1 study cited). No further details reported.	
Liu and Case 2017 [C4]	Systematic review and updated Society of Obstetricians and Gynaecologists of Canada (SOGC) clinical practice guideline (search date December 2010). Only systematic reviews, RCTs, controlled trials and observational studies were included.	Only narrative results reported. Pregnancy rate "FSH results have been shown to be predictive for … non-pregnancy only when the levels are extremely elevated." The paper states that "only a small number of women will have abnormal tests at this threshold" and "it has been associated with a false positive rate of 5%." No further details reported. AFC is "not a good predictor of pregnancy". Live birth rate Not reported. Poor ovarian response to ovarian stimulation "Basal FSH levels have been shown to be predictive for poor response to ovarian stimulation." And "AFC and AMH have been shown to be useful for prediction of poor ovarian response with IVF." No further details reported.	Although the search for evidence was systematic, only narrative results were provided with no details regarding the number of included papers that investigated associations between bFSH or AFC and PR or LBR, or the sizes, countries or characteristics of the studies that reported this. The paper did not report any numerical results (p values, RR, etc.) or threshold values for AFC or bFSH associated with effectiveness of IVF/ICSI. It is not clear whether the results for AFC and bFSH are from the same or different groups of patients. The authors suggested that ovarian reserve testing is useful for predicting egg quantity but of little value in predicting egg quality and may be considered in women aged over 35 years for counselling but abnormal tests do not preclude the possibility of pregnancy. The authors suggest that for women aged under 35, ovarian reserve markers are not good predictors of pregnancy rate with IVF/ICSI.
Broer et al 2013 [C5]	Systematic review and meta-analysis (search date December 2009)	Pregnancy rate Ongoing pregnancy defined as visible gestational sac on ultrasound with heartbeat at least 9 weeks gestation.	Meta-analysis was based on individual patient data.

Reference	Study details	Outcomes	Comments
	Aim: to assess the added value of ovarian reserve tests to patient characteristics in prediction of IVF outcomes. Databases from 28 studies (5,705 women) included. Baseline characteristics reported only for full cohort of 5,705 women (mean (5^{th} to 95^{th} percentile)): Female age (years): 34.3 (26.7 to 41.9) FSH (IU/l): 7.8 (3.8 to 14.0) AFC (number): 11.6 (3.0 to 25.0) Duration of subfertility (years): 4.01 (10 to 9.1)	n=420 women FSH and AFC had only a very small or no predictive effect in predicting pregnancy after IVF. FSH: AUC 0.53 (95% confidence interval (CI) 0.43 to 0.62), p=0.348. AFC: AUC 0.50 (95% CI 0.40 to 0.59), p=0.100 Live birth rate Not reported. Poor ovarian response to ovarian stimulation Poor response defined as ≤4 oocytes at follicle aspiration or cancelled cycle due to poor response. (n=617 women) AFC: AUC 0.76 (95% CI 0.70 to 0.82), p<0.001 FSH: AUC 0.68 (95% CI 0.61 to 0.74), p=0.051	Studies were reviewed if they presented data on at least one ovarian reserve test, at least one patient characteristic and IVF outcome. Authors of eligible studies were invited to share their data. The main meta-analysis only included studies which provided data for all of FSH, AFC, anti-Müllerian hormone (AMH) and age. This was to minimise bias from indirect comparisons because studies varied in individual patient populations, stimulation protocols, hormone assays, ultrasound techniques and other features that meta-analysis cannot easily account for. Corresponding results for the total patient cohort were reported separately and have not been reported here for this reason. The paper did not report any threshold values for AFC or bFSH associated with effectiveness of IVF/ICSI. Age was the strongest single predictor of pregnancy after IVF, with moderate accuracy (AUC 0.57 (95% CI 0.47 to 0.66)) and no single or combined ovarian response test significantly added predictive power to age. Adding FSH dosage to models did not affected the predictive capacity for ongoing pregnancy, suggesting that this was not a confounding factor.

Reference	Study details	Outcomes	Comments
			Results were also reported for prediction of excessive ovarian response and for combinations of different ovarian reserve tests and age. These are not presented here as they were not listed as outcomes of interest in the PICO framework for this review question and are not likely to be useful for developing commissioning policy.
Other studies			
Brodin et al 2015 [C6]	Retrospective cohort study in a private infertility centre, Sweden. Aim: To compare the ability of 4 different ovarian reserve tests to predict live births and poor and excessive ovarian response during IVF. n=892 consecutive women regardless of cause or duration of infertility or expected response to ovarian stimulation. Maximum female age of 42 years.; 1,230 IVF/ICSI cycles. Stepwise multivariable analyses were also carried out in a subgroup with complete data on 4	Pregnancy rate Not reported Live birth rate Defined as live births per started stimulation (including cancelled cycles). FSH / LH groups: (FSH was assessed in combination with LH levels and three combinations were defined by cut-offs of 6.7 U/l for FSH and 4.9 U/l for LH (Group 1 low FSH / high LH; group 2 low FSH / low LH or high FSH / high LH; group 3 high FSH / low LH). n=942 Odds ratio (OR) of live birth (95% CI): 0.86 (0.64 to 1.16), p=0.33 (c statistic not applicable) Log AFC: n=830	AFC was defined as the sum of all follicles of 2 to 10 mm before treatment. AFC was analysed as a continuous variable with skewed distribution and log AFC was used. FSH was reported in combination with LH levels. Results were not reported for FSH alone. Generalised estimating equation models were used to account for possible dependence between treatments where more than one IVF/ICSI cycle was included for a couple. The paper did not report any threshold values for AFC associated with effectiveness of IVF/ICSI. The univariate c statistic for age for prediction of live birth was 0.61.

Reference	Study details	Outcomes	Comments
	ovarian response tests: n=443 women; 620 cycles. Baseline characteristics (mean (standard deviation) (range)): AFC (number, n=595): 17.8 (10.9) (3 to 70) FSH (IU/l, n=740): 7.3 (3.1) (1.0 to 28.0) Mean cycle length (days, n=829): 28.2 (2.3) (21 to 38)	OR for live birth (95% CI): 1.64 (1.22 to 2.12), p value not reported, c statistic[53] 0.58 Poor ovarian response to ovarian stimulation The threshold for poor ovarian response was defined using the ovarian stimulation index (OSI), the amount of oocytes retrieved (times 1000) divided by the given dose (IU) of FSH or human menopause gonadotropin at ovarian stimulation. The threshold level for poor response was mean logOSI (x 1000) - 1 SD (= 1.697/IU) FSH / LH groups: n=942 c statistic for poor response: 0.60, p<0.0001. Log AFC: n=830 c statistic for poor response: 0.85, p<0.0001	Results were also reported for prediction of excessive ovarian response and for combinations of different ovarian reserve tests and age. These are not presented here as they were not listed as outcomes of interest in the PICO framework for this review question and are not likely to be useful for developing commissioning policy.
Dai et al 2014 [C7]	Retrospective cohort study, China. Aim: To identify efficient predictors of clinical outcomes of IVF. Exclusion criteria not specified. Inclusion criteria: regular spontaneous menstrual cycle (25 to 35 days),	Pregnancy rate Clinical pregnancy was defined as the identification of a gestational sac via ultrasound 3 weeks after embryo transfer. bFSH: Correlated with clinical pregnancy rate in <35 year olds (p<0.05, correlation coefficient -0.115, AUC 0.509) but not in women aged ≥35 years (p>0.05, correlation coefficient -0.036, AUC 0.521).	Serum FSH was measured on day 2 or 3 of cycle within 3 months of IVF. AFC was the number of follicles in both ovaries of 2 to 5 mm on either day 2 or mid-luteal phase morning within the stimulation cycle. The paper did not report any threshold values for AFC or bFSH associated with effectiveness of IVF/ICSI.

[53] The c statistic is a measure of the discriminative capacity of the test to predict live birth. It is interpreted relative to 0.5 which is the equivalent of pure guessing. The univariate c statistic for age for prediction of live birth was 0.61.

Reference	Study details	Outcomes	Comments
	both ovaries and no previous ovarian surgery, no evidence of endocrine disorder, and no cytotoxic drugs, pelvic radiation or hormonal therapy in previous 6 months. n=201 women undergoing their first IVF cycle (August 2009 to July 2010). Baseline characteristics (mean +/- SD): Age (years): 35.5 +/- 8.3 (range 24 to 43). 155 aged <35 years, 46 aged ≥35 years. AFC (number): 11.0 +/- 6/2 and 65. +/- 3.2 in women <35 years and ≥35 years respectively. bFSH (IU/l): 7.6 +/- 2.1 and 8.9 +/- 3.8 in women <35 years and ≥35 years respectively. Clinical pregnancy rate: 44.5% (69/155) and 28.3% (13/46) in women <35 years and ≥35 years respectively.	AFC: Correlated with clinical pregnancy rate in women aged ≥35 years ($p<0.05$, correlation coefficient 0.404, AUC 0.729) but not in <35 year olds ($p>0.05$, correlation coefficient -0.035, AUC 0.520). Live birth rate Not reported. Poor ovarian response to ovarian stimulation Defined as ≤4 oocytes retrieved. bFSH: Correlated with poor ovarian response rate in <35 year olds ($p<0.001$, correlation coefficient -0.279, AUC 0.752) but not in women aged ≥35 years ($p>0.05$, correlation coefficient -0.199, AUC 0.619). AFC: Correlated with poor ovarian response rate in women aged <35 years ($p<0.05$, correlation coefficient 0.179, AUC 0.661) but not in women aged ≥35 years ($p>0.05$, correlation coefficient -0.126, AUC 0.574).	Results were also reported for prediction of excessive ovarian response and for combinations of different ovarian reserve tests and age. These are not presented here as they were not listed as outcomes of interest in the PICO framework for this review question and are not likely to be useful for developing commissioning policy.

Reference	Study details	Outcomes	Comments
Other indirectly relevant studies			
Wang et al 2021 [C8] (does not report pregnancy or live birth rates, the two outcomes of interest)	Retrospective cohort study. 5 centres in China, January 2013 to December 2019. Aim: to explore the value of ovarian reserve tests for predicting poor ovarian response. Inclusion criteria: regular menstruation and bilateral ovaries. Exclusion criteria: evidence of polycystic ovary syndrome, ovarian surgery, chemotherapy, pelvic radiotherapy, oral contraceptives within 2 months, natural cycle or mild stimulation IVF, cancelled oocyte collection not due to poor ovarian response. n=89,002 women with infertility undergoing their first ovarian stimulation for IVF. Baseline characteristics: Mean (SD) Age (years): 32.0 (5.1)	Pregnancy rate Not reported. Live birth rate Not reported. Poor ovarian response to ovarian stimulation bFSH: n=85,052 OR per IU/l: 1.258 (95% CI 1.250 to 1.266), p<0.0001 AUC 0.689 (95% CI 0.683 to 0.695) Cut-off: ≤9.8 mIU/ml (90.0% specificity, 38.4% sensitivity) Cut-off including age group stratification: <35 years: ≤9.62 (specificity 90.0%, sensitivity 35.4%) 35-38 years: ≤10.18 (specificity 90.0%, sensitivity 35.1%) 38-40 years: ≤10.49 (specificity 90.0%, sensitivity 36.2%) >40 years: ≤11.51 (specificity 90.0%, sensitivity 32.0%) AFC: Defined as the number of 2-10mm follicles in 2 ovaries. n=84,884 OR per extra follicle: 0.707 (95% CI 0.702 to 0.711), p<0.0001 AUC 0.842 (95% CI 0.838 to 0.846) Cut-off: ≤5 (90.8% specificity, 55.9% sensitivity) Cut-off including age group stratification: <35 years: ≤6 (specificity 89.5%, sensitivity 53.8%) 35-38 years: ≤4 (specificity 92.5%, sensitivity 37.7%) 38-40 years: ≤3 (specificity 93.3%, sensitivity 31.9%) >40 years: ≤3 (specificity 87.5%, sensitivity 46.5%)	This study was included because although it did not report either of the outcomes of interest listed in the PICO framework for this review question (pregnancy rate or live birth rate), it was by far the largest study reporting predictors of ovarian response. The authors stated that the ideal screening test should have high specificity to minimise false positive determination of diminished ovarian reserve, even if it means reduced sensitivity. The paper also reported results for age, AMH and combinations of different tests. These are not reported here as they are not listed as outcomes of interest in the PICO framework for this review. Most of the 89,002 patients had both AFC and bFSH levels recorded. Hence the sample size was large and these two tests were compared in the same population, reducing the potential for bias due to differences in baseline characteristics, stimulation protocols, etc. However, all patients were from China and it is not known whether there are differences between the Chinese population or IVF protocols and those of the UK

Reference	Study details	Outcomes	Comments
	Infertility duration: 4.0 (10.3) bFSH: 7.7 (3.3) AFC: 11.1 (5.5)		which may affect the generalisability of these results.
Abbreviations: AFC – antral follicle count; AMH – anti-Müllerian hormone; AUC – area under curve (for graph of test sensitivity against 100-specificty); bFSH – basal FSH; CI – confidence interval; FSH – follicle-stimulating hormone; ICSI – intracytoplasmic sperm injection; IVF – in vitro fertilisation; LBR – live birth rate; LH – luteinising hormone; OR – odds ratio; PICO – population, indication, comparator, outcomes framework for evidence review; PR – pregnancy rate; RR – relative risk; SD – standard deviation.			

Obesity / BMI

What is the effectiveness of IVF/ICSI where the woman has a BMI ≥30 compared to a BMI <30?

Table D1: Summary of studies: Female BMI ≥30, IVF/ICSI

Reference	Study details	Outcomes	Comments
Systematic Reviews			
Ribeiro et al 2022 [D2]	Systematic review and meta-analysis, evaluating BMI and IVF/ICSI outcomes, from oocytes retrieved to live birth. The final search was carried out in March 2019. The search excluded review articles, those that did not use WHO BMI criteria, papers that clustered overweight and obesity into one group, only included a cost evaluation and studies	**Effectiveness** The studies represent 1,445,406 cycles of assisted reproduction, primarily combined IVF/ICSI (71.7%) *Pregnancy rate* Obese (BMI ≥30) vs normal weight (BMI 18.5 – 24.9) • RR = 1.09, 95% CI 1.03 to 1.16 • I^2 = 29.8% • GRADE low certainty of evidence *Livebirth rate* Obese (BMI ≥30) vs normal weight (BMI 18.5 – 24.9) • RR = 1.08, 95% CI 1.00 to 1.16 • I^2 = 23.9% • GRADE: low certainty of evidence	The systematic review was registered on PROSPERO and conducted using PRISMA guidelines. Study quality was assessed using the Newcastle-Ottawa scale; the GRADE system was used to evaluate the certainty of the evidence. Eleven of the studies were deemed to be of high methodological quality and the remaining 42 were of moderate methodological quality. No studies were found to be of low or very low quality. The BMI of women were categorised using WHO classifications: normal weight (BMI 18.5 – 24.9), overweight

Reference	Study details	Outcomes	Comments
	that included oocyte donation. A total of 53 cohort studies were included in the review; 12 prospective, 21 retrospective.	**Safety** *Miscarriage rate* Obese (BMI ≥30) vs normal weight (BMI 18.5 – 24.9) • RR = 1.21, 95% CI 1.02 to 1.44 • I^2 = 4.7% • GRADE: low certainty of evidence	(BMI 25 – 29.9) and obese (BMI ≥30). Those of normal weight were compared to those that were obese or overweight. The primary outcomes of interest were clinical pregnancy, miscarriage, livebirth, duration and dose of gonadotropin administration and number of retrieved and mature oocytes. No information was available regarding the women's fertility or age. The data presented showed low certainty evidence of decreasing pregnancy and livebirth rates in women with a BMI ≥30, when compared to women with a BMI <25, and increased rates of miscarriages in the same cohort. Clinical pregnancy rates and miscarriage rates were statistically significant.
Supramaniam et al 2018 [D3]	Systematic review and meta-analysis, evaluating the impact of raised BMI on assisted reproduction treatments (ART), specifically IVF/ICSI. The final search was carried out in March 2019. The search excluded papers published before	**Effectiveness** *Pregnancy rate* Overweight/Obese (BMI ≥25) vs normal weight (BMI <25), 37 studies included • OR = 0.82, 95% CI 0.77 to 0.88 • p < 0.001 • I^2 = 58% Obese (BMI ≥30) vs normal weight (BMI 18.5 – 24.9), 18 studies included	The BMI of women were categorised using WHO classifications: normal weight (BMI 18.5 – 24.9), overweight (BMI 25 – 29.9) and obese (BMI ≥30). Those of normal weight were compared to those that were obese or overweight. The primary outcomes of interest were livebirth rate, clinical pregnancy rate and miscarriage rate.

Reference	Study details	Outcomes	Comments
	1966, those that did not use WHO BMI criteria, reported donor cycles, conception by natural cycles, waist hip ratios and papers that reported the effects of paternal BMI. A total of 49 observational studies were included.	• OR = 0.80, 95% CI 0.74 to 0.87 • p < 0.001 • I^2 = 32% *Livebirth rate per IVF/ICSI cycle* Overweight/Obese (BMI ≥25) vs normal weight (BMI <25), 14 studies included • OR = 0.81, 95% CI 0.74 to 0.89 • p < 0.001 • I^2 = 65% Obese (BMI ≥30) vs normal weight (BMI 18.5 – 24.9), 10 studies included • OR = 0.81, 95% CI 0.79 to 0.82 • p < 0.001 • I^2 = 0% **Safety** *Miscarriage rate* Overweight/Obese (BMI ≥25) vs normal weight (BMI <25), 26 studies were included • OR = 1.30, 95% CI 1.15 to 1.48 • p < 0.001 • I^2 = 53% Obese (BMI ≥30) vs normal weight (BMI 18.5 – 24.9), 17 studies included • OR = 1.52, 95% CI 1.28 to 1.81 • p < 0.001 • I^2 = 46%	No information was available regarding the women's fertility or age. The authors note that few of the included studies adjusted for confounding due to age, smoking and duration of fertility. The data presented showed women with a BMI ≥25 have a lower odds of pregnancy and livebirth per IVF/ICSI cycle and increased odds of miscarriage when compared to women with a BMI <25. Women who are obese have a higher odds of miscarriage than those that are overweight, when both groups are compared to women of a normal BMI. All results reached statistical significance.
Tang et al 2021 [D4]	Systematic review and meta-analysis, evaluating the dose response of BMI and IVF/ICSI outcomes. The final	**Effectiveness** The studies represent 975,889 cycles of IVF. *Pregnancy rate*	The systematic review was conducted using PRISMA guidelines. Egger's tests and Begg's tests were used to identify publication bias and the I^2 index was calculated to assess heterogeneity.

Reference	Study details	Outcomes	Comments
	search was carried out in March 2020. The search excluded papers published before 1988, case reports, non-human studies, editorials and review articles. A total of 18 cohort studies were included in the review; 2 prospective, 16 retrospective.	16 studies, representing 586,630 cycles of IVF were used in the BMI dose response calculations. Rate per 5-unit increase in BMI • RR = 0.95, 95% CI 0.94 to 0.97 • p < 0.001 • I^2 = 14.1% • no evidence of publication bias *Livebirth rate* 13 studies, representing 740,839 cycles of IVF were used in the BMI dose response calculations. Rate per 5-unit increase in BMI • RR = 0.93, 95% CI 0.92 to 0.95 • p < 0.001 • I^2 = 26.4% • the dose response was non-linear, suggesting a more rapidly decreasing live birth rate in women with a BMI ≥30 • no evidence of publication bias **Safety** *Miscarriage rate* 13 studies, representing 235,167 cycles of IVF were used in the BMI dose response calculations. Rate per 5-unit increase in BMI • RR = 1.09, 95% CI 1.05 to 1.12 • p < 0.001 • I^2 = 24.4% • the dose response for miscarriage risk was j-shaped, with the lowest risk in women with a BMI of 22-25 and increased risk for women who are underweight as well as overweight • no evidence of publication bias	The primary outcomes of interest were clinical pregnancy, miscarriage, live birth. No information was available regarding the women's fertility or age. Data on women's ethnicity was limited and did not allow for subgroup analyses. The data presented showed that for each five-unit increase in a woman's BMI, pregnancy rate following IVF was statistically significantly decreased by 5% and livebirths following IVF were statistically significantly decreased by 7%. The risk of miscarriage following IVF procedures was shown to increase 9% per five-unit increase in BMI; this finding was statistically significant. The results are non-linear for livebirth and miscarriage, with the highest risks in women with a BMI ≥ 35.

Treated status	Age category (years)	BMI (kg/m^2) category	Predicted mean cost (95% CI), £	Predicted probability of live birth (95% CI)
Not treated	≤30	<18.50	308.53 (273.48–351.15)	0.664 (0.489–0.810)
		18.5–24.99	352.39 (327.22–383.70)	0.710 (0.646–0.772)
		25.00–29.99	370.77 (335.65–414.08)	0.702 (0.627–0.771)
		30.00–34.99	349.21 (312.80–394.98)	0.641 (0.535–0.741)
		≥35.00	337.99 (306.97–377.77)	0.524 (0.389–0.656)
	31–35	<18.50	307.78 (266.15–354.97)	0.577 (0.390–0.747)
		18.5–24.99	351.64 (316.90–387.39)	0.628 (0.554–0.698)
		25.00–29.99	370.01 (329.99–416.81)	0.619 (0.527–0.700)
		30.00–34.99	348.46 (305.74–396.56)	0.551 (0.434–0.661)
		≥35.00	337.24 (299.90–380.57)	0.431 (0.296–0.562)
	36–40	<18.50	317.54 (271.19–369.54)	0.421 (0.249–0.611)
		18.5–24.99	361.40 (318.61–406.21)	0.474 (0.384–0.562)
		25.00–29.99	379.78 (327.99–433.94)	0.464 (0.367–0.558)
		30.00–34.99	358.22 (303.83–412.41)	0.396 (0.284–0.515)
		≥35.00	347.00 (297.66–400.80)	0.288 (0.179–0.416)
	>40	<18.50	274.45 (230.82–324.85)	0.139 (0.051–0.287)
		18.5–24.99	318.31 (283.60–359.98)	0.167 (0.080–0.266)
		25.00–29.99	336.68 (299.00–383.13)	0.162 (0.074–0.267)
		30.00–34.99	315.13 (272.10–365.31)	0.128 (0.054–0.228)
		≥35.00	303.91 (266.64–350.21)	0.083 (0.030–0.162)
Treated	≤30	<18.50	3672.59 (2617.80–4634.72)	0.755 (0.599–0.871)
		18.5–24.99	2776.35 (2530.87–3038.52)	0.792 (0.744–0.841)
		25.00–29.99	2586.97 (2305.49–2875.25)	0.786 (0.726–0.841)
		30.00–34.99	1888.88 (1513.24–2328.74)	0.736 (0.638–0.820)
		≥35.00	1535.62 (1056.63–2038.42)	0.632 (0.494–0.751)
	31–35	<18.50	4193.66 (3092.31–5199.34)	0.680 (0.499–0.822)
		18.5–24.99	3297.42 (3032.16–3568.84)	0.724 (0.661–0.781)
		25.00–29.99	3108.04 (2770.92–3446.59)	0.716 (0.638–0.783)
		30.00–34.99	2409.95 (2030.39–2820.31)	0.657 (0.546–0.755)
		≥35.00	2056.69 (1521.13–2571.47)	0.541 (0.400–0.671)
	36–40	<18.50	3912.79 (2823.51–4968.66)	0.531 (0.342–0.711)
		18.5–24.99	3016.55 (2683.98–3343.65)	0.583 (0.495–0.669)
		25.00–29.99	2827.17 (2458.57–3194.83)	0.574 (0.479–0.666)
		30.00–34.99	2129.07 (1708.32–2580.57)	0.505 (0.384–0.629)
		≥35.00	1775.82 (1181.19–2333.30)	0.387 (0.255–0.535)
	>40	<18.50	3540.47 (2352.16–4710.29)	0.201 (0.079–0.391)
		18.5–24.99	2644.23 (2024.99–3265.32)	0.238 (0.115–0.364)
		25.00–29.99	2454.86 (1825.68–3100.13)	0.231 (0.109–0.363)
		30.00–34.99	1756.76 (1076.39–2504.75)	0.185 (0.079–0.312)
		≥35.00	1403.50 (599.76–2018.79)	0.123 (0.046–0.232)

Note: All other model predictors were set at the reference category or mean/median, i.e. primary infertility, median registration year = 2003, mean duration of infertility = 23 months. CI: confidence interval.

Figure D1: Predicted probability of livebirth and predicted treatment and investigation costs, with 95% CIs for different combinations of treated status, BMI category and age category in women with unexplained infertility [5]

Age category (years)	BMI (kg/m^2) category	Difference in cost (£)	Difference in probability	Ratio of increased cost to increased probability of live birth (95% CI), £
≤30	<18.50	3364.06	0.091	37081.74 (20645.47–89503.71)
	18.5–24.99	2423.96	0.082	29483.48 (18690.03–63541.02)
	25.00–29.99	2216.21	0.084	26447.88 (16469.91–57655.39)
	30.00–34.99	1539.67	0.095	16292.44 (9590.42–35989.49)
	≥35.00	1197.63	0.108	11130.90 (5678.06–25449.27)
31–35	<18.50	3885.88	0.103	37728.77 (21919.48–84776.37)
	18.5–24.99	2945.78	0.097	30519.91 (19342.95–64990.26)
	25.00–29.99	2738.03	0.098	27995.33 (17588.19–59294.53)
	30.00–34.99	2061.49	0.105	19544.29 (12270.90–41220.00)
	≥35.00	1719.46	0.110	15599.19 (8791.87–34528.85)
36–40	<18.50	3595.24	0.110	32668.68 (18973.95–74556.90)
	18.5–24.99	2655.14	0.110	24149.10 (15534.82–52289.09)
	25.00–29.99	2447.39	0.110	22218.88 (14319.69–47647.60)
	30.00–34.99	1770.85	0.109	16212.82 (10015.85–35143.74)
	≥35.00	1428.82	0.099	14505.39 (7301.39–33657.72)
>40	<18.50	3266.02	0.062	52634.34 (23141.87–176258.29)
	18.5–24.99	2325.92	0.071	32785.52 (11140.60–91488.45)
	25.00–29.99	2118.17	0.069	30555.66 (15826.81–86152.58)
	30.00–34.99	1441.63	0.058	24894.42 (10863.82–81624.38)
	≥35.00	1099.60	0.040	27196.41 (6565.91–100785.59)

Figure D2: Predicted increased costs and increased probability of livebirth with exposure to treatment in couples with unexplained fertility [5]

What is the effectiveness of IVF/ICSI where the woman has a BMI of ≤19 compared to BMI >19?

Table D2: Summary of studies: Female BMI ≤19, IVF/ICSI

Reference	Study details	Outcomes	Comments
Systematic Reviews			
Tang et al 2021 [D4]	Systematic review and meta-analysis, evaluating the dose response of BMI and IVF/ICSI outcomes. The final search was carried out in March 2020. The search excluded papers published before 1988, case reports, non-human studies, editorials and review articles. A total of 18 cohort studies were included in the review; 2 prospective, 16 retrospective.	**Effectiveness** No effectiveness outcomes were reported **Safety** *Miscarriage rate* 13 studies, representing 235,167 cycles of IVF were used in the BMI dose response calculations. Rate per 5-unit increase in BMI • RR = 1.09, 95% CI 1.05 to 1.12 • p < 0.001 • I^2 = 24.4% • the dose response for miscarriage risk was j-shaped, with the lowest risk in women with a BMI of 22-25 and increased risk for women who are underweight as well as overweight (p=0.006) • no evidence of publication bias	The systematic review was conducted using PRISMA guidelines. Egger's tests and Begg's tests were used to identify publication bias and the I^2 index was calculated to assess heterogeneity. The primary outcomes of interest were clinical pregnancy, miscarriage, live birth. No information was available regarding the women's fertility or age. Data on women's ethnicity was limited and did not allow for subgroup analyses. The lowest risk of miscarriage was for women with a BMI of 22-25. The data suggested that women with a BMI <22 and ≥25 had an increased risk of miscarriage; this was statistically significant.
Xiong et al 2021 [D6]	Systematic review and meta-analysis, evaluating the dose response of BMI and IVF/ICSI outcomes. The final search was carried out in September 2018. The search excluded papers had fewer than	**Effectiveness** *Pregnancy rate* Underweight (BMI <18.5) vs normal weight (BMI 18.5 – 24.99) • individual level, 20 studies: OR = 0.84, 95% CI 0.75 to 0.95, I^2 = 0%, • cycle level, 9 studies: OR = 0.95, 95% CI 0.92 to 1.03, p = 0.11, I^2 = 12.4%	The systematic review was registered on PROSPERO and conducted using PRISMA guidelines. Study quality was assessed using the Newcastle-Ottawa scale for observational studies. Heterogeneity was assessed with the I^2 statistic and publication bias was examined with funnel plots and the Egger test.

Reference	Study details	Outcomes	Comments
	ten participants in the underweight group, studies that included oocyte donation, review articles, editorials, conference abstracts, opinions or case reports. A total of 38 cohort studies were included in the review; 9 prospective, 29 retrospective.	*Livebirth rate* Underweight (BMI <18.5) vs normal weight (BMI 18.5 – 24.99) • individual level, 12 studies: OR = 0.97, 95% CI 0.87 to 1.09, I^2 = 0% • cycle level, 8 studies: OR = 0.96, 95% CI 0.93 to 0.99, I^2 = 0% **Safety** *Miscarriage rate* Underweight (BMI <18.5) vs normal weight (BMI 18.5 – 24.99) • per-pregnancy level, 17 studies: OR = 1.00, 95% CI 0.93 to 1.07, I^2 = 0%	Most of the studies were deemed to be of low risk of bias (37/38); one study was deemed to be of moderate risk of bias. No obvious publication bias was present across all outcomes. The WHO definition of underweight was used (BMI <18.5) and normal weight was identified as BMI 18.5 – 24.99. A deviation of 1.5 kg/m^2 was allowed for both definitions to allow for regional variation. The primary outcomes of interest were clinical pregnancy, miscarriage, live birth. No information was available regarding the women's fertility or age. When compared to women of normal BMI, women who are underweight at the time of IVF have a statistically significantly lower odds of pregnancy. Low maternal BMI was not shown to affect live birth rate or miscarriage rate.

What is the clinical effectiveness of IVF/ICSI where the male partner has a BMI ≥30 compared to <30?

Table D3: Summary of studies: Male partner BMI ≥30, IVF/ICSI

Reference	Study details	Outcomes	Comments
Systematic Reviews			
Zhang et al 2022 [D7]	Systematic review and meta-analysis, evaluating BMI and IVF/ICSI outcomes, from oocytes retrieved to live birth. The final search was carried out in December 2021. The search excluded case reports and review articles. A total of 19 observational studies were included in the review; 6 prospective, 13 retrospective.	**Effectiveness** *Pregnancy rate* Overweight/Obese (BMI ≥25) vs normal weight (BMI <25), 4 studies included • OR = 0.69, 95% CI 0.54 to 0.88 • p-value not presented • I^2 = 0% • GRADE very low to low certainty evidence • no indication of publication bias (p=0.19) Obese (BMI ≥30) vs normal weight (BMI 18.5 – 24.9), 5 studies included • OR = 1.09, 95% CI 0.87 to 1.36 • p-value not presented • I^2 = 0% • GRADE very low to low certainty evidence • no indication of publication bias (p=0.76) Per unit increase in BMI, 1 study included • OR = 1.04, 95% CI 0.92 to 1.17 • p-value not presented • I^2 = 0% *Livebirth rate per IVF/ICSI cycle* Overweight/Obese (BMI ≥25) vs normal weight (BMI <25), 1 study included • OR = 0.76, 95% CI 0.69 to 0.83 • p-value not presented • I^2 = 0% • GRADE very low to low certainty evidence	The systematic review was registered on PROSPERO and conducted using PRISMA guidelines. The GRADE system was used to evaluate the certainty of the evidence. The BMI of the male partner were categorised using WHO classifications: normal weight (BMI 18.5 – 24.9), overweight (BMI 25 – 29.9) and obese (BMI ≥30). Those of normal weight were compared to those that were obese or overweight. The primary outcomes of interest were clinical pregnancy and live birth. No information was available regarding the men's or female partner's fertility or age. The data presented showed low to very low certainty evidence of decreasing pregnancy and live birth rates when the male partner is of high weight compared to normal weight; these results are statistically significant. When male partners with a BMI >30 and those with a BMI of 18.5 – 24.9, there is no statistically significant difference in IVF/ICSI outcomes.

Reference	Study details	Outcomes	Comments
		Obese (BMI ≥30) vs normal weight (BMI 18.5 – 24.9), 7 studies included • OR = 0.94, 95% CI 0.81 to 1.09 • p-value not presented • I^2 = 40.0% • GRADE very low to low certainty evidence Per unit increase in BMI, 3 studies included • OR = 1.00, 95% CI 0.98 to 1.02 • p-value not presented **Safety** No safety outcomes were reported	

What is the clinical effectiveness of IVF/ICSI where the male partner has a BMI ≤19 compared to >19?

Table D4: Summary of studies: Female BMI ≥30, IUI

Reference	Study details	Outcomes	Comments
No Systematic Reviews Identified			
Other Studies			
Thijssen et al 2017 [D8]	Prospective cohort study of IUI patients at one centre in Belgium between 2015 and 2020. IUI cycles with use of frozen semen or escape IUI cycles, i.e. couples allocated to IVF/ICSI	**Effectiveness** Of the 556 couples undergoing IUI, 132 reported successful pregnancy during the study period (132/1401 IUI cycles). Average BMI of the women in the study was 23.9 ± 4.5 (range 16.3 to 43.4). *Pregnancy rate*[54]	This study was conducted in Belgium. Questionnaire data were collected by a midwife during the mandatory bed rest following IUI; sperm quality was assessed from an initial sample using specified methodology; pregnancy was defined as presence of a foetal heartbeat at 7-8 weeks post IUI.

[54] univariate analysis

Reference	Study details	Outcomes	Comments
	treatment who received escape IUI treatment because of low response to ovarian stimulation, were excluded from the study. Outcomes available for 556 couples, who received 1401 IUI cycles.	BMI, pregnant/total, pregnancy rate ± SE • BMI <20: 16/245, 0.065 ± 0.016 • BMI 20-24.99: 58/728, 0.080 ± 0.010 • BMI 25-29.99: 43/264, 0.163 ± 0.023 • BMI ≥30: 14/149, 0.094 ± 0.024 • p=0.0319 **Safety** No safety outcomes were reported.	Maternal BMI was found to be of influence during the univariate analyses (presented here) but were not significant during the multivariate analyses and was not included in the model. Multivariate analyses corrected for age (patient and partner), smoking (patient and partner), IUI procedure characteristics and sperm characteristics. The authors note these results are similar to other studies as when ovarian stimulation is adjusted for the patient's weight, clinical pregnancy rates are comparable across BMIs.
Zheng et al 2022 [D9]	Retrospective cohort study of IUI patients at one centre in China between 2015 and 2020. Women with bilateral tubal pathology or endocrine disorders were excluded. Patients receiving more than four cycles were also excluded. Women with a BMI ≥30 were asked to lose weight before being offered IUI.	**Effectiveness** Of the 6,407 couples undergoing IUI, 1,661 (25.92%) reported successful pregnancy and 1,383 (21.59%) reported a live birth during the study period. A total of 990 women were categorised as underweight (BMI <18.2); 4,563 as normal weight (BMI 18.5 – 24.9) and 854 as overweight (BMI 25.0 – 29.9) **Subgroup: Overweight (BMI 25 – 29.99)** *Pregnancy rate* BMI, pregnant/total • BMI 18.5 – 24.9: 1183/4563 • BMI 25 – 29.99: 273/854 • p reported as not significant	This study was conducted in China. All data were collected from patient notes. The primary outcomes of interest were clinical pregnancy and live birth. The BMI of women were categorised using WHO classifications: underweight (BMI ≤18.5), normal weight (BMI 18.5 – 24.9) and overweight (BMI 25 – 29.9). Patients in the overweight subgroup were more likely to be older and have a PCOS (polycystic ovarian syndrome) diagnosis. Women that

Reference	Study details	Outcomes	Comments
	Outcomes available for 6,407 patients who received 13,745 cycles of IUI.	BMI, HR (95% CI)[55] • BMI 18.5 – 24.9: reference group • BMI 25 – 29.99: 1.19 (1.04 to 1.36) • p value not reported *Live birth rate* BMI, live births/total, live birth rate (95% CI) • BMI 18.5 – 24.9: 986/4563, 21.61% (20.4% to 22.8%) • BMI 25 – 29.99: 227/854, 26.58% (23.7% to 29.6%) • p < 0.001 BMI, HR (95% CI)[56] • BMI 18.5 – 24.9: reference group • BMI 25 – 29.99: 1.19 (1.02 to 1.38) • p value not reported **Safety** No safety outcomes were presented.	were overweight had a statistically significant longer infertility duration when compared to women that were underweight. The data show a statistically significantly increased cumulative pregnancy and live birth rates in multivariate analysis for women that were in the overweight subgroup.

[55] adjusted for age, basal follicle stimulating hormone, basal luteinizing hormone, basal antral follicle count, diagnosis of polycystic ovarian syndrome, diagnosis of endometriosis, unilateral tubal obstruction, parity, duration of infertility (years), post wash total motile sperm count (10^6)

[56] adjusted for age, basal follicle stimulating hormone, basal luteinizing hormone, basal antral follicle count, diagnosis of polycystic ovarian syndrome, diagnosis of endometriosis, unilateral tubal obstruction, parity, duration of infertility (years), post wash total motile sperm count (10^6)

What is the effectiveness of IUI where the woman has a BMI ≤19 compared to a BMI >19?

Table D5: Summary of studies: Female BMI ≤19, IUI

Reference	Study details	Outcomes	Comments
No Systematic Reviews Identified			
Other Studies			
Zheng et al 2022 [D9]	Retrospective cohort study of IUI patients at one centre in China between 2015 and 2020. Women with bilateral tubal pathology or endocrine disorders were excluded. Patients receiving more than four cycles were also excluded. Women with a BMI ≥30 were asked to lose weight before being offered IUI. Outcomes available for 6,407 patients who received 13,745 cycles of IUI.	**Effectiveness** Of the 6,407 couples undergoing IUI, 1,661 (25.92%) reported successful pregnancy and 1,383 (21.59%) reported a live birth during the study period. A total of 990 women were categorised as underweight (BMI <18.2); 4,563 as normal weight (BMI 18.5 – 24.9) and 854 as overweight (BMI 25.0 – 29.9) *Pregnancy rate* BMI, pregnant/total • BMI <18.5: 205/990 • BMI 18.5 – 24.9: 1183/4563 • p reported as not significant BMI, HR (95% CI)[57] • BMI <18.5: 0.85 (0.73 to 0.98) • BMI 18.5 – 24.9: reference group • p value not reported *Live birth rate* BMI, live births/total, live birth rate (95% CI) • BMI <18.5: 170/990, 17.17% (14.9% to 19.5%) • BMI 18.5 – 24.9: 986/4563, 21.61% (20.4% to 22.8%) • p < 0.001	This study was conducted in China. All data were collected from patient notes. The primary outcomes of interest were clinical pregnancy and live birth. The BMI of women were categorised using WHO classifications: underweight (BMI ≤18.5), normal weight (BMI 18.5 – 24.9) and overweight (BMI 25 – 29.9). Compared with normal weight patients, underweight patients were more likely to be younger and have endometriosis. Parity was slightly higher in those that were underweight and they had a significantly lower duration of infertility when compared to women that were overweight. The data show a statistically significantly decreased cumulative live birth rate in women that were underweight compared to those that

[57] adjusted for age, basal follicle stimulating hormone, basal luteinizing hormone, basal antral follicle count, diagnosis of polycystic ovarian syndrome, diagnosis of endometriosis, unilateral tubal obstruction, parity, duration of infertility (years), post wash total motile sperm count (10^6)

Reference	Study details	Outcomes	Comments
		BMI, HR (95% CI)[58] • BMI <18.5: 0.80 (0.67 to 0.95) • BMI 18.5 – 24.9: reference group • p value not reported **Safety** No safety outcomes were presented.	were normal weight or overweight. In multivariate analysis, being underweight was associated with both lower cumulative pregnancy and live birth rates; these results were statistically significant.

What is the clinical effectiveness of IUI where the male partner has a BMI ≥30 compared to <30?

Table D6: Summary of studies: Male BMI ≥30, IUI

Reference	Study details	Outcomes	Comments
No Systematic Reviews Identified			
Other Studies			
Thijssen et al 2017 [D8]	Prospective cohort study of IUI patients at one centre in Belgium between 2015 and 2020. IUI cycles with use of frozen semen or escape IUI cycles, i.e. couples allocated to IVF/ICSI treatment who received escape IUI treatment because of low response to ovarian stimulation,	**Effectiveness** Of the 556 couples undergoing IUI, 132 reported successful pregnancy during the study period (132/1401 IUI cycles). Average BMI of the male partners in the study was 25.8 ± 3.5 (range 16.7 to 46.1). *Pregnancy rate* BMI, pregnant/total, pregnancy rate ± SE • BMI <20: 3/30, 0.100 ± 0.056 • BMI 20-24.99: 55/595, 0.092 ± 0.012 • BMI 25-29.99: 55/606, 0.091 ± 0.012	This study was conducted in Belgium. Questionnaire data were collected by a midwife during the mandatory bed rest following IUI; sperm quality was assessed from an initial sample using specified methodology; pregnancy was defined as presence of a foetal heartbeat at 7-8 weeks post IUI. Paternal BMI was not found to be significant at univariate or multivariate analyses (univariate analyses presented here and

[58] adjusted for age, basal follicle stimulating hormone, basal luteinizing hormone, basal antral follicle count, diagnosis of polycystic ovarian syndrome, diagnosis of endometriosis, unilateral tubal obstruction, parity, duration of infertility (years), post wash total motile sperm count (10^6)

Reference	Study details	Outcomes	Comments
	were excluded from the study. Outcomes available for 556 couples, who received 1401 IUI cycles.	• BMI ≥30: 19/154, 0.123 ± 0.027 • p reported as not significant **Safety** No safety outcomes were reported.	paternal BMI was not included in the final multivariate model). Multivariate analyses corrected for age (patient and partner), smoking (patient and partner), IUI procedure characteristics and sperm characteristics.

Chewing tobacco and use of betel nut

The only relevant studies identified were of tobacco chewing in relation to IVF.

Table E1: Summary of studies: Chewing tobacco and IVF

Reference	Study details	Outcomes	Comments
No Systematic Reviews Identified			
Other studies			
Kumari et al [E2]	Retrospective cohort study from one centre in Patna, Bihar, India from 2019 to 2022 Outcomes are available for 105 women undergoing IVF, aged 21 to 40 years, and their partners	Effectiveness None of the women reported a history of chewing tobacco. 16/105 of the male partners reported using chewing tobacco. Day three and day five embryo quality were found to be negatively associated with chewing tobacco; these associations were statistically significant. Day three embryo quality, n (% of sperm quality category) • Good: 4 (7) • Moderate: 6 (35.3) • Poor: 6 (19.4) • p = 0.01	This study was conducted in India. All data was collected retrospectively from patient records using a predesigned spreadsheet. The main study aim was to look at multiple lifestyle factors and their potential impact on embryo quality at day 3 and day 5. No information was provided on live birth rates, complications of pregnancy, neonatal complications or safety. Two-thirds of the women had primary infertility (66.7%). The mean age of

Reference	Study details	Outcomes	Comments
		Day five embryo quality, n (% of sperm quality category) • Good: 3 (7.5) • Moderate: 8 (25.0) • Poor: 5 (15.2) • p = 0.12 Safety No safety outcomes reported	the women was 31.06 ± 4.19 years; the male partners was 36.54 ± 5.75. No women reported chewing tobacco use and 15% of their partners reported tobacco use.
Parn et al [E3]	Prospective cohort study from one clinic in Uppsala, Sweden from 2011 to 2014 Outcomes are available for 62 men	Effectiveness 16/62 of the men (28.3%) reported using chewing tobacco/snuff. Snuff use was statistically significantly negatively correlated with sperm concentration, sperm numbers, motile concentration, total motile sperm and total sperm motility. The effect on sperm volume was not statistically significant. Snuff use, r (p-value) • sperm volume: -0.048 (p > 0.05) • sperm concentration: -0.314 (0.015) • sperm number: -0.299 (0.020) • motile concentration: -0.375 (0.003) • total motile sperm: -0.349 (0.006) • total motility: -0.299 (0.020) Day five embryo quality, n (% of sperm quality category) • Good: 3 (7.5) • Moderate: 8 (25.0) • Poor: 5 (15.2) • p = 0.12 Safety No safety outcomes reported	This study was conducted in Sweden. Data on semen were analysed by standard WHO measures on a single sample provided to the fertility clinic; lifestyle factors were collected by questionnaire at baseline. The main study aim was to evaluate a physical activity intervention for men experiencing infertility. Female partner infertility was not explored. The mean age of the men was 35.2 ± 5.7 years. The average BMI was 25.8 ± 4.0.

Indications for IUI

Table F1: Summary of studies: Unexplained infertility

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td>Systematic Reviews</td><td></td><td></td><td></td></tr>
<tr><td>Pandian et al 2015 [F3]</td><td>Cochrane systematic review (search to May 2015)

Subjects in the studies were couples with unexplained infertility, which may have included couples with minimal endometriosis or mild male factor subfertility, who had been trying to conceive for one year or longer.

Included RCTs addressing relevant questions, and no. of cycles compared in each:
IVF vs unstimulated IUI: 2 RCTs:
Goverde 2000: 6 cycles IVF + cryocycles vs 6 cycles IUI.
Elzeiny 2014: 1 cycle IVF vs 1 cycle IUI.
IVF vs IUI+OS with injectable gonadotropins (Gt): 5 RCTs.
Goverde 2000: not stated
Reindollar 2010: unclear
Goldman 2014: unclear</td><td>Summary of outcomes comparing IVF with IUI (review authors' assessment of certainty of evidence in brackets)

<table>
<tr><td colspan="2">Live birth rate per woman</td></tr>
<tr><td>IVF: 320 per 1000
Unstimulated IUI: 160 per 1000
OR 2.47 (95% CI 1.19 to 5.12)</td><td>IVF may result in more births than unstimulated IUI (LOW)</td></tr>
<tr><td>IVF: 308 per 1000
IUI+OS with Gt: 273 per 1000
OR 1.27 (95% CI 0.94 to 1.73)</td><td>No conclusive evidence of a difference in live birth rates between IVF and stimulated IUI using Gt (MODERATE)</td></tr>
<tr><td>IVF: 314 per 1000
IUI+OS with CC: 154 per 1000
OR 2.51 (95% CI 0.96 to 6.55)</td><td>No conclusive evidence of a difference in live birth rates between IVF and stimulated IUI using Clomiphene (LOW)</td></tr>
</table>

<table>
<tr><td colspan="2">Pregnancy rate</td></tr>
<tr><td>IVF: 400 per 1000
Unstimulated IUI: 121 per 1000
OR 4.83 (95% CI 0.94 to 24.95)</td><td>No conclusive evidence of a difference in pregnancy rates between IVF and unstimulated IUI (VERY LOW)</td></tr>
</table>

OS: ovarian stimulation
OR: odds ratio
Gt: gonadotrophins
CC: clomiphene citrate</td><td>Systematic review following Cochrane methodology including RCTs comparing IVF with other interventions including IUI+/-ovarian stimulation. The results for the comparisons reported here are based on between two and five RCTs.
The number of included cycles being compared varied between studies or was not stated in the review. The reviewers reported that two studies included IVF-SET and cryocycles; the IVF regime in the remaining studies was not stated.
They reported that there was no evidence of a difference in multiple birth rates between IVF and stimulated IUI, and insufficient evidence to say whether there was a difference in multiple birth rates between IVF and unstimulated IUI.

Reported results indicate that IVF is likely to result in more live births, and may result in more pregnancies, than IUI without ovarian stimulation.

There is no conclusive evidence of a difference in live birth rates between IVF and IUI with ovarian stimulation either using gonadotrophins or clomiphene citrate.</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td></td><td>Van Rumste 2014; 1 cycle IVF-SET + cryocycle vs 3 cycles IUI
Bensdorp 2015: 3 cycles IVF-SET + cryocycles vs 6 cycles IUI.
IVF vs IUI+OS with Clomiphene Citrate (CC): 1 RCT (Goldman 2014): unclear</td><td></td><td></td></tr>
<tr><td>Wang et al 2019 [F4]</td><td>Cochrane systematic review (search to September 2018)

Included couples had been trying to conceive for at least one year, women having at least one patent fallopian tube and an ovulatory cycle, and men having a pre-wash total motile sperm count >3x10^6. Women with mild endometriosis were included.

Included 3 RCTs addressing relevant questions (no. of cycles not stated):
Custers 2011: IVF-SET + cryocycle vs IUI+OS
Nandi 2017: IVF with up to 2 embryos transferred, no cryocycle
Bensdorp 2015: IVF-SET + cryocycle vs IUI+OS</td><td>Summary of outcomes comparing IVF with IUI (review authors' assessment of certainty of evidence in brackets)

<table><tr><th colspan="2">Live birth rate</th></tr><tr><td>IVF-ICSI: 319 per 1000
IUI+OS: 354 per 1000
OR 1.17 (95% CI 0.64 to 2.12)</td><td>No conclusive evidence of a difference in live birth rates between IVF and stimulated IUI (LOW)</td></tr></table>
<table><tr><th colspan="2">Clinical pregnancy rate</th></tr><tr><td>IVF-ICSI: 437 per 1000
IUI+OS: 344 per 1000
OR 1.30 (95% CI 0.68 to 2.50)</td><td>No conclusive evidence of a difference in clinical pregnancy rates between IVF and stimulated IUI (LOW)</td></tr></table>
OR: odds ratio
OS: ovarian stimulation</td><td>Systematic review following Cochrane methodology including RCTs comparing a range of different clinical management options for couples with unexplained infertility. The results for the comparisons reported here are based on three RCTs.
The number of included cycles of IVF or IUI being compared in the studies was not stated in the review. Two studies used SET only and reported cryocycles, the thirds transferred up to two embryos and did not report cryocycles.

The authors also reported that there was no evidence of a difference in multiple birth rates between IVF-ICSI and IUI+OS

There is no conclusive evidence of a difference in live birth rates or clinical pregnancy rates between IVF and IUI with ovarian stimulation.</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Nandi et al 2022 [F5]</td><td>Systematic review (search to November 2019).

Females were aged <43 years, with or without minimal or mild endometriosis, the male partner having normal semen parameters.

Included studies addressing relevant questions:
ESHRE trial 1991
Goverde 2000
Reindollar 2010
Custers 2011 *
Elzeiny 2014
Goldman 2014
Bensdorp 2015 *
Nandi 2017 *
*these studies offered between 3 and 6 cycles of IUI+COH vs 1–3 cycles of IVF, the remainder offered equal numbers of cycles of IUI+COH or IVF.</td><td>Summary of outcomes comparing IVF with IUI-COH (review authors' assessment of certainty of evidence in brackets)

<table><tr><td colspan="2">Live birth rate (7 studies)</td></tr><tr><td>IUI-COH: 318 per 1000
IVF: 487 per 1000 (95% CI 321–738)
RR 1.53 (95% CI 1.01–2.32)</td><td>IVF may result in more live births than IUI-COH (LOW)</td></tr></table>
<table><tr><td colspan="2">Clinical pregnancy rate (7 studies)</td></tr><tr><td>IUI-COH: 374 per 1000
IVF: 620 per 1000 (95% CI 381–1000)
RR 1.66 (95% CI 1.02–2.70)</td><td>IVF may result in more clinical pregnancies than IUI-COH (LOW)</td></tr></table>
RR: Risk Ratio
COH: controlled ovarian hyperstimulation
CI: confidence intervals</td><td>This appears to have been a well-conducted systematic review. It included RCTs comparing IUI+COH (using either clomiphene citrate/letrozole or injectable gonadotropins or both) with IVF for couples with unexplained infertility. IVF included studies allowing multiple embryo transfer but only 2 of the studies included frozen as well as fresh embryos. Five of the studies compared equal numbers of cycles of IUI-COH and IVF.

Authors considered all the studies to be at low risk of bias, apart from blinding of participants and physicians, which was considered not to be practically possible. They reported that there was considerable clinical and methodological heterogeneity across the studies.

The pooled results of 6 trials showed no significant difference in the multiple pregnancy rate between the two groups (RR 0.83, 95% CI 0.50–1.38, P = 0.56).

The study found that IVF may result in more live births and more clinical pregnancies than IUI-COH; however in both analyses the 95% Confidence Intervals only just reached statistical significance.</td></tr>
<tr><td>Other studies</td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr>
<td>Van Rumste et al 2014 [F7]

(findings on pregnancy outcomes from this study were included in Pandian et al 2015, Wang et al 2019, Nandi et al 2021 and Cissen et al 2016)</td>
<td>Multicentre RCT conducted between 2006-2009 in Holland. 116 couples with unexplained or mild male subfertility were randomised. Female age 18-38 years, 12-month prognosis of <30% for natural conception. Groups were similar at baseline.

Randomly allocated to 1 cycle of IVF–SET followed by one cryocycle or to 3 cycles of IUI–OS. Costs used prices set at November 2010 by the Dutch Health Care Authority and included hospital, medication and laboratory costs. Cost-effectiveness was defined as the ratio of the sum of the total costs per randomized group divided by the number of couples with an ongoing pregnancy.</td>
<td>Summary of outcomes comparing IVF with IUI
<table>
<tr><td colspan="2">Ongoing pregnancies confirmed by ultrasound at 12 weeks' gestation: number (%)</td></tr>
<tr><td>IVF: 14/58 (24%)
IUI-OS: 12/58 (21%)</td><td>Numbers of ongoing pregnancies are similar for IVF and IUI but no statistical significance measures were reported.</td></tr>
</table>
<table>
<tr><td colspan="2">Costs</td></tr>
<tr><td>Total costs
IVF: €161,327
IUI-OS: €108,808</td><td>Total costs of IUI are about two-thirds those of IVF</td></tr>
<tr><td>Mean cost per couple
IVF: € 2781 (95% CI €2293–3270)
IUI-OS: €1876 (95% CI €1462–2270)
P<0.01</td><td>Mean cost per couple of IUI is significantly less than that of IVF</td></tr>
<tr><td>Mean cost per cycle
IVF: €2933
IUI-OS: €761</td><td>Mean cost per cycle for IUI is about one quarter that of IVF</td></tr>
<tr><td>Mean cost per ongoing pregnancy
IVF: €11,523
IUI-OS: €9067
Difference in mean cost €2456 higher for IVF (95% CI €898–4014)</td><td>Mean cost per ongoing pregnancy for IUI is significantly lower than that for IVF.</td></tr>
</table>
OS: ovarian stimulation
CI: confidence intervals</td>
<td>This RCT appeared to be reasonably well-conducted, but had a relatively small sample size and follow-up was short-term (ongoing pregnancies at 12 weeks).
The economic analysis was performed from the perspective of the healthcare institution and did not include costs incurred by couples themselves. It also excluded healthcare costs due to multiple pregnancies. Statistical significance analyses were only reported for some of the findings.

The IVF success rate was lower than is generally reported but this may be due to random variation due to the small sample size.

Costs were calculated using Dutch healthcare costs in 2010 so may have limited generalisability to the UK setting; however findings using the relative costs of IVF and IUI may be more generalisable.

The study found that the mean cost per couple of treatment and the mean cost per ongoing pregnancy was significantly lower for IUI-OS than for IVF-SET. However the short follow-up and limited cost analysis limit the usefulness of this study.</td>
</tr>
<tr>
<td>Tjon-Kon-Fat et al 2015 [F8]</td>
<td>Multicentre RCT conducted between January 2009 and</td>
<td>Summary of outcomes comparing IVF with IUI
<table>
<tr><td>Live births</td></tr>
</table></td>
<td>This RCT appeared to be well-conducted, with a robust randomisation process and 12-month follow-up.</td>
</tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr>
<td></td>
<td>February 2012 in Holland.

602 couples with unexplained or mild male factor subfertility were randomised. Female age 18-38 years, 12-month prognosis of < 30% for natural conception.

Couples were randomised to 3 cycles of IVF-SET plus subsequent frozen embryo transfers (201 couples), 6 cycles of IVF-MNC (modified natural cycle) (194 couples) or 6 cycles of IUI-COH (207 couples). Groups were comparable at baseline. A cost-effectiveness analysis was performed from a health care perspective, focusing on direct medical costs (in Holland) of all interventions up to 12 months after randomisation. Costs were expressed in 2013 Euros.</td>
<td>
<table>
<tr><td>IVF-SET: 118/201 (59%)
IVF-MNC: 99/194 (51%)
IUI-COH: 116/207 (56%)
RR IVF-SET vs IUI-COH: 1.05 (95% CI 0.89–1.24)
RR IVF-MNC vs IUI-COH: 0.91 (95% CI 0.76–1.09)</td><td>No conclusive evidence of a difference in live birth rates between IVF-SET and IUI-COH or between IVF-MNC and IUI-COH.</td></tr>
</table>
<table>
<tr><td colspan="2">Birth of a healthy child*</td></tr>
<tr><td>IVF-SET: 104/201 (52%)
IVF-MNC: 83/194 (43%)
IUI-COH: 97/207 (47%)
RR, IVF-SET vs IUI-COH: 1.10 (95% CI 0.91–1.34)
RR, IVF-MNC vs IUI-COH: 0.91 (95% CI 0.73–1.14)</td><td>No conclusive evidence of a difference in rates of birth of a healthy child between IVF-SET and IUI-COH or between IVF-MNC and IUI-COH.</td></tr>
</table>
*defined as a healthy child resulting from a singleton pregnancy conceived within 12 months after randomization, born at term (gestational age between 37-42 weeks), birthweight above the 5th percentile, without congenital anomalies, and developing normally up to 6 weeks after birth
<table>
<tr><td colspan="2">Ongoing pregnancies</td></tr>
<tr><td>IVF-SET: 121/201 (60%)
IVF-MNC: 102/194 (53%)
IUI-COH: 119/207 (57%)
RR, IVF-SET vs IUI-COH: 1.05 (95% CI 0.89–1.23)
RR, IVF-MNC vs IUI-COH: 0.91 (95% CI 0.77–1.09)</td><td>No conclusive evidence of a difference in ongoing pregnancy rates between IVF-SET and IUI-COH or between IVF-MNC and IUI-COH.</td></tr>
</table>
<table>
<tr><td>Costs</td></tr>
</table>
</td>
<td>The economic analysis was performed from the perspective of the healthcare institution and did not include costs incurred by couples themselves.
Costs were calculated using Dutch healthcare costs in 2013 but the authors also reported an estimate using UK hospital costs inputted into the same model. This produced estimated costs of IVF-SET of €10,100 and IUI-COH of €6174, with an ICER for IVF-SET vs IUI-COH of €80,429.

The authors reported that multiple pregnancy rates (as a proportion of ongoing pregnancies) were similar for all three groups: 7 (6%) for IVF-SET, 5 (5%) for IVF-MNC, and 8 (7%) for IUI-COH.

The study found no conclusive evidence of a difference in live birth rates, rates of birth of a healthy child or ongoing pregnancies between IUI-COH and either method of IVF.
The study reported that the mean cost per couple was significantly lower for IUI-COH than for either method of IVF. IUI-COH was reported to be more cost-effective than IVF-SET with an estimated ICER of €43,375. Compared with IVF-MNC, IUI-COH was the dominant strategy being both more effective and less costly.</td>
</tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Mean cost per couple 12 months after randomisation
IVF-SET: €7187
IVF-MNC: €8206
IUI-COH: €5070</td><td>Mean cost per couple was lowest for IUI-COH and highest for IVF-MNC</td></tr>
<tr><td>Mean cost difference per couple
Between IVF-SET and IUI-COH: €2117 (95% CI: €1544–€2657)
Between IVF-MNC and IUI-COH: €3136 (95% CI: €2519–€3754)</td><td>Mean cost per couple was significantly higher for IVF-MNC and IVF-SET than for IUI-COH.
The mean cost difference per couple was greater between IVF-MNC and IUI-COH than between IVF-SET and IUI-COH.</td></tr>
</table>
<table>
<tr><td colspan="2">Cost-effectiveness</td></tr>
<tr><td>ICER for IVF-SET vs IUI-COH: €43,375</td><td>Achieving one additional healthy child would cost an estimated €43,375 more using IVF-SET than with IUI-COH.</td></tr>
<tr><td>ICER for IVF-MNC vs IUI-COH: €76,925)</td><td>Achieving one additional healthy child would cost an estimated €76,925 more using IVF-MNC than with IUI-COH. IUI-COH was the dominant strategy (i.e. more effective at lower cost)</td></tr>
</table>
RR: Relative Risk
COH: controlled ovarian hyperstimulation
MNC: modified natural cycle
ICER: incremental cost-effectiveness ratio
</td><td></td></tr>
</table>

Table F2: Summary of studies: Male factor infertility

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td>Systematic Reviews</td><td></td><td></td><td></td></tr>
<tr><td>Cissen et al 2016 [F6]</td><td>Cochrane systematic review (search to April 2015)

Subjects included couples with male subfertility who had been trying to conceive for at least one year (including oligo-, terato-, asthenospermia, or a combination of these).

Included studies and no. of cycles compared in each:
IVF vs IUI in natural cycles: 1 RCT:
Goverde 2000: maximum 6 cycles IVF (max 2 embryos transferred) + cryocycles vs maximum 6 cycles IUI.
IVF vs IUI in stimulated cycles: 2 RCTs.
Goverde 2000: maximum 6 cycles IVF (max 2 embryos transferred) + cryocycles vs maximum 6 cycles IUI
Bensdorp 2015: 3 cycles IVF-SET + cryocycles vs 6 cycles IUI.</td><td>Summary of outcomes comparing IVF with IUI (review authors' assessment of certainty of evidence in brackets)

<table><tr><td colspan="2">Live birth rate per couple</td></tr><tr><td>IVF: 346 per 1000
IUI in natural cycles: 407 per 1000
OR 0.77 (95% CI 0.25 to 2.35)</td><td>No conclusive evidence of a difference in live birth rates between IVF and IUI in natural cycles (LOW)</td></tr><tr><td>IVF: 460 per 1000
IUI in stimulated cycles: 452 per 1000
OR 1.03 (95% CI 0.43 to 2.45)</td><td>No conclusive evidence of a difference in live birth rates between IVF and IUI in stimulated cycles (VERY LOW)</td></tr></table>
<table><tr><td colspan="2">Pregnancy rate per couple</td></tr><tr><td>IVF: 666 per 1000
IUI in stimulated cycles: 611 per 1000
OR 1.27 (95% CI 0.33 to 4.97)</td><td>No conclusive evidence of a difference in pregnancy rates between IVF and IUI in stimulated cycles (VERY LOW)</td></tr></table>
OR: Odds Ratio</td><td>Systematic review following Cochrane methodology including RCTs comparing a range of treatment options for male factor subfertility. The results for the comparisons reported here are based on two RCTs. Both of these included a larger number of couples with subfertility, a minority of whom had male factor subfertility: the results reported in the review are for the couples with male factor subfertility only.
The two RCTs used different approaches to IVF and compared different numbers of cycles.
Multiple pregnancy rates were not reported.

There is no conclusive evidence of a difference in live birth rates between IVF and IUI with or without ovarian stimulation.
There is no conclusive evidence of a difference in pregnancy rates between IVF and IUI with ovarian stimulation.</td></tr>
</table>

Table F3: Summary of studies: All causes of infertility

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td>Other studies</td><td></td><td></td><td></td></tr>
<tr><td>Bahadur et al 2020 [F9]</td><td>Retrospective analysis using the HFEA database of 319,105 IVF/ICSI and 30,669 IUI cycles performed between 2012 and 2016 in the UK.
The database reported number of cycles rather than number of patients, and lacked details including cause of subfertility, age of patient, and details of procedures.
In 2012–2016 overall causes of infertility for IVF/ICSI only were male infertility 37%, unexplained 32%, ovulatory disorder 13%, tubal disease 12% and endometriosis 6%.
Costs were estimated using a previously developed cost of multiple births model, adjusted for inflation. A cost-effectiveness analysis was modelled on the 2016 national mean IVF and IUI success rates, with allowance for clinics with variable success rates. Mean 2016 IVF tariffs</td><td>Summary of outcomes comparing IVF with IUI

<table><tr><td colspan="3">Live births, % of treatment cycles</td></tr><tr><td></td><td>IVF</td><td></td></tr><tr><td>2012-2016*</td><td>IVF: 26.96%
IUI: 11.49%</td><td>Live birth rate per cycle for IVF is more than double that for IUI</td></tr></table>
*authors reported that between 2012 and 2016 there was a small but statistically significant increase in the % of live births for IVF but not for IUI.

<table><tr><td colspan="3">Estimated maternal and neonatal costs ** and number of cycles</td></tr><tr><td>Estimated maternal and neonatal costs for one baby 2012-2016</td><td>IVF: £6,186.54
IUI: £6,000.41</td><td>Maternal and neonatal costs for one baby are higher for IVF than IUI (statistical significance not reported)</td></tr><tr><td>Estimated total maternal and neonatal costs, 2016</td><td>IVF: £115,082,017
IUI: £2,940,196</td><td>There was a 39.1-fold difference between IVF and IUI in 2016 total maternal and neonatal costs</td></tr><tr><td>No. cycles, 2016</td><td>IVF: 68,099
IUI: 4,051</td><td>There was a 16.8-fold*** difference between IVF and</td></tr></table></td><td>This study used a very large UK dataset but many details were not available meaning that cause of subfertility and other couple characteristics and specific procedures could not be linked to outcomes. Live birth rates were reported for single cycles of IVF and IUI.
The authors reported a significantly higher rate of multiple pregnancies with IVF than with IUI (IVF: 13.88% (95% CI 13.65–14.11); IUI: 9.59% (95% CI 8.62–10.56)).

The study reported a live birth rate per cycle for IVF more than double that for IUI. The authors reported that the overall maternal and neonatal cost of one baby over the period 2012-2016 was higher for IVF than IUI (statistical significance not reported).
The authors reported that IVF activity in 2016 was approximately 17 times that of IUI activity, while the maternal and neonatal costs resulting from IVF were approximately 39 times those resulting from IUI. This was largely due to the higher rates of multiple pregnancies resulting from IVF.
The authors reported that IUI was more cost-effective than IVF in terms of cost for one live birth using varying estimates for success rates of IVF and IUI and varying estimates for IVF</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study details</th><th>Outcomes</th><th>Comments</th></tr>
<tr>
<td></td>
<td>and common tariffs for IUI treatment cycles were used.</td>
<td>
<table>
<tr><td></td><td></td><td>IUI in 2016 number of cycles</td></tr>
</table>
** taking into account risk and associated costs of multiple pregnancies
*** the paper included an error in calculating this figure, the correct figure is reported here
<table>
<tr><td colspan="3">ICER to deliver one live birth</td></tr>
<tr><td>At cheapest IVF tariff</td><td>£13,633</td><td>IUI more cost-effective</td></tr>
<tr><td>At mean IVF tariff</td><td>£42,558</td><td>IUI more cost-effective</td></tr>
</table>
HFEA: Human Fertilisation and Embryology Authority
ICER: incremental cost-effectiveness ratio
</td>
<td>and IUI tariffs. These results were reported graphically, the graphs showing IUI to be more cost-effective than IVF for all success rates and tariffs modelled. Two examples cited using different tariffs for IVF have been reported here.

However, the limited details available about the patients and procedures included limit the usefulness of this study for a direct comparison of IVF vs IUI.</td>
</tr>
</table>

Abbreviations

CC: clomiphene citrate; CI: confidence intervals; COH: controlled ovarian hyperstimulation; DET: double embryo transfer; Gt: gonadotrophins; HFEA: Human Fertilisation and Embryology Authority; ICER: incremental cost-effectiveness ratio; ICSI: intracytoplasmic sperm injection; IUI: intra-uterine insemination; IVF: in vitro fertilisation; MNC: modified natural cycle; OR: odds ratio; OS: ovarian stimulation; RCT: randomised controlled trial; RR: relative risk; SET: single embryo transfer;

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

Sterilisation and reversal

What is the effectiveness of a cycle of IVF/IUI when the woman undergoing IVF/IUI has had a successful reversal of a sterilisation procedure versus in a woman who has never had a sterilisation procedure?

Table G1: Summary of studies: Sterilisation and reversal for women

Reference	Study details	Outcomes	Comments
Systematic Reviews			
van Seeters et al 2017 [G3]	Systematic review (search date July 2016) Women had received sterilisation with reversal or sterilisation with IVF (no reversal) Included 37 studies on sterilisation reversal with 10,689 women. Studies were retrospective cohort studies (n=16), prospective cohort studies (n=1), case series (n=10) and case-control studies (n=10) Included 3 retrospective cohort studies comparing sterilisation and reversal to sterilisation and IVF	Effectiveness Outcomes after sterilisation reversal Pooled pregnancy rate by type of surgery • Laparotomic macro-surgery (4 studies): 42% (95%CI 23 to 77) • Laparotomic micro-surgery (21 studies): 68% (95%CI 58 to 71) • Laparoscopic surgery (15 studies): 65% (95%CI 61 to 74) • Robotic laparoscopic surgery (4 studies): 65% (95%CI 59 to 72) There was no statistically significant difference in pregnancy rate between the different surgical techniques The authors reported that the only prognostic factor affecting the chance of conception was female age Outcomes after sterilisation and IVF Outcomes were reported for the individual included studies, without pooling In one study: • Delivery rates were higher after sterilisation reversal (72%) than IVF (52%) for women aged <37 years	The countries of the included studies was not stated The aim of the systematic review was to evaluate fertility outcomes for different surgical methods of reversal of female sterilisation, compare these to IVF results and assess prognostic factors for success Prognostic factors considered were age, body mass index, postoperative tubal length, method of sterilisation, time from sterilisation to reversal and type of anastomosis The comparison between reversal surgery types reported pregnancy rates but not live birth rate. The descriptive data available outcomes after sterilisation and reversal and sterilisation and IVF favoured sterilisation reversal with the possibility of better outcomes with IVF, rather than reversal for older women. However, these outcomes are based on limited information

Reference	Study details	Outcomes	Comments
		• Delivery rates were higher after IVF (51%) than sterilisation reversal (37%) for women aged ≥37 years These differences were not statistically significant. Number of IVF cycles not reported In one study (all women were aged <40): • Pregnancy rates were higher after sterilisation reversal (78%) than IVF (47%) • Live birth rates were higher after sterilisation reversal (67%) than IVF (35%) No statistical analysis was reported. Number of IVF cycles not reported In one study: • Pregnancy rates after sterilisation reversal: 73% • Live birth rates after sterilisation reversal: 51% (median women's age 35.4 years) • Live birth rates per IVF cycle: • Women <35: 39% • Women aged 35-38: 31% • Women aged 38-40: 21% No statistical analysis reported Safety Outcomes after sterilisation reversal Pooled ectopic pregnancy rate by type of surgery • Laparotomy macro-surgery (4 studies): 8.4% (95%CI 4 to 29) • Laparotomy micro-surgery (21 studies): 10.4% (95%CI 4 to 9) • Laparoscopic surgery (15 studies): 5.6% (95%CI 3 to 9) • Robotic laparoscopic surgery: 2 studies reported rates of 11% and 22% respectively	

Reference	Study details	Outcomes	Comments
		Outcomes after sterilisation and IVF Outcomes were reported for the individual included studies, without pooling In one study ectopic pregnancy rates were 33% after reversal surgery and 2% after IVF. No statistical analysis was reported. Number of IVF cycles not reported	
Other studies			
Chua et al 2020 [G4]	Retrospective cohort study of outcomes after female sterilisation at one centre in Singapore between 2011 and 2016 Outcomes were available for 12 women who had sterilisation and surgical reversal and 31 women who had sterilisation and IVF, without reversal All women were <40 years old. Patients were followed up for 2 years	Effectiveness The authors reported statistically significantly higher pregnancy and live birth rates in women who had reversal compared to one cycle of IVF ($p<0.05$) Outcomes for women who had sterilisation and reversal (n=12) Pregnancy rate: 9/12 (75%) Live birth rate: 7/12 (58.3%) Mean (SD) time from surgery to conception: 3.9 (4.8) months Outcomes for women who had sterilisation and IVF (n=31, 39 cycles) Pregnancy rate: 11/31 (35.5%) Live birth rate: 8/31 (25.8%) (1 set of twins) Safety Outcomes for women who had sterilisation and reversal (n=12) Miscarriage rate: 1/9 (11.1%) Ectopic pregnancy: 1/9 (11.1%) Clinically important ovarian hyperstimulation syndrome: 0/12 (0%)	This study was conducted in Singapore The main study aim was to compare outcomes between laparoscopic reversal surgery and IVF in women who had previously been sterilised Women with other sub-fertility factors were excluded Women receiving IVF had one stimulated cycle and all embryos generated were transferred within 10 months, either fresh or frozen. 31 fresh and 8 frozen-thaw IVF cycles were performed Mean (SD) female age (years): • At IVF: 35 (4) • At reversal: 34 (4) There were no significant differences between groups in age, body mass index, parity or anti-mullerian hormone level The authors concluded that surgical reversal may be a better

Reference	Study details	Outcomes	Comments
		Outcomes for women who had sterilisation and IVF (n=31) Miscarriage rate: 3/11 (27.3%) Ectopic pregnancy: 0/31 (0%) Clinically important ovarian hyperstimulation syndrome: 2/31 (6.5%)	option than IVF for women <40 years old with no other subfertility factors
Libby et al 2021 [G5]	Retrospective cohort study of women receiving IVF/ICSI after prior sterilisation in an analysis of a US database between 2004 and 2013 Outcomes were available for 8,478 women receiving IVF/ICSI after prior sterilisation. These were compared to outcomes for 371,488 women receiving IVF for another infertility diagnosis No women were reported to have had a reversal of sterilisation	Effectiveness The authors reported no differences in clinical pregnancy rate in singleton pregnancies between sterilised or infertile women after adjusting for age, parity and cycle type For single gestations, the authors reported no clinically significant differences between groups in live births after adjustment for age, body mass index and parity Outcomes for women who had sterilisation and IVF/ICSI (n=8,478, 10,674 cycles) Clinical pregnancy: 44.3% Deliveries: 3,663 (1,198 multiple births) Live birth: 35.6% Live births (adjusted): 65.3% Outcomes for women who had infertility and IVF/ICSI (n=371,488, 555,124 cycles) Clinical pregnancy: 45.2% Deliveries: 176,098 (53,101 multiple births) Live birth: 36.9% Live births (adjusted): 64.4% Safety For single gestations, the authors reported no clinically significant differences in miscarriage, neonatal deaths, or length of gestation between groups after adjustment for age, body mass index and parity	This study was conducted in the US The main study aim was to compare outcomes from IVF/ICSI in couples with a history of female sterilisation compared to couples with other infertility diagnoses Prior sterilisation was the only indication for IVF/ICSI in couples with a history of female sterilisation Mean female age at IVF/ICSI (years): • After sterilisation: 35.3 • For infertility: 34.6 Sterilised women were significantly older and had significantly higher body mass index than infertile women ($p<0.05$) Most (86%) sterilised women had ≥2 or more previous births. Most (60%) infertile women had ≤1 previous births The authors concluded that fertile couples with a history or sterilisation did not have significantly different perinatal

Reference	Study details	Outcomes	Comments
		Pre-term births were higher in sterilised women but the authors suggested that this difference may not have clinical significance. Birth weight for single gestations was lower for sterilised women Miscarriage (adjusted): • Sterilised women: 18.0% • Infertile women: 17.7% There was 1 neonatal death in each group Mean length of gestation (days): • Sterilised women: 247 • Infertile women: 249 Preterm births (<37 weeks): • Sterilised women: 14.4% • Infertile women: 12.5% Mean birth weight (single gestations): • Sterilised women: 3,189g • Infertile women: 3,240g	outcomes compared to infertile couples
Cost effectiveness			
Messinger et al 2015 [G6]	Cost effectiveness analysis of fertility options for women who had undergone prior sterilisation Options modelled were sterilisation reversal followed by natural conception and IVF without reversal	Cost effectiveness The 2 options considered were: 1. Sterilisation reversal followed by natural conception 2. IVF without reversal Cost per pregnancy were reported by female age groups The authors reported that sterilisation reversal was more cost effective than IVF for women aged <35 years old and aged 35 to 40 years. However, IVF was the most cost-effective option for women aged >40 years old Cost per ongoing pregnancy after sterilisation reversal: • <35 years: $16,315	This study was conducted in the US The main study aim was to compare the cost and efficacy of sterilisation reversal to IVF in women with prior sterilisation The authors used a decision tree model using US data and costs Sensitivity analysis considered a range of probabilities for each procedures success and also considered a range of costs. This

Reference	Study details	Outcomes	Comments
		• 35-40 years: $23,914 • >40 years: $218,742 Cost per ongoing pregnancy after IVF, without reversal: • <35 years: $32,814 • 35-40 years: $45,839 • >40 years: $111,45	did not change the most and least cost effective strategies The IVF without reversal strategy allowed for a single fresh cycle of IVF and subsequent single frozen-thaw transfer if required

What is the effectiveness of a cycle of IVF/IUI when the male partner in the couple has had a reversal of a vasectomy versus when the male partner in the couple has never had a vasectomy?

Table G2: Summary of studies: Sterilisation and reversal for men

Reference	Study details	Outcomes	Comments
No systematic reviews identified			
Other studies			
Lopes et al 2020 [G7]	Retrospective cohort study of men who received a first cycle of IVF/ICSI between 2008 and 2015 at 2 centres in Brazil. All men had had obstructive azoospermia, either due to a past vasectomy or congenital obstruction Outcomes were available for 621 men receiving a first cycle of IVF/ICSI. 576 after a vasectomy and 45 with congenital obstruction Men with vasectomy were either unwilling to	Effectiveness The authors reported no statistically significant differences between men who had a vasectomy and men with congenital obstruction fertilisation, pregnancy or live birth rates (p>0.05). The differences remained non-significant after adjustment for men and women's age Outcomes for men who had vasectomy (n=576) The sample size decreases for pregnancy and birth rates due to missing information in patient records Sperm cell retrieval: 100% Fertilisation rate: 66.9% Clinical pregnancy rate: 216/521 (41.5%) Live birth rate: 75/424 (17.7%) Outcomes for men who had congenital obstruction (n=45)	This study was conducted in Brazil The main study aim was to investigate potential differences in outcomes of ICF/ICSI between groups with different obstruction aetiologies Only outcomes from the first cycle of IVF/ICSI were reported Mean male age at IVF/ICSI (years): • After vasectomy: 48.03 • Congenital obstruction: 37.88 Mean female age at IVF/ICSI (years): • After vasectomy: 36.21

Reference	Study details	Outcomes	Comments
	undergo surgical reversal or had a history of failed reversal	The sample size decreases for pregnancy and birth rates due to missing information in patient records Sperm cell retrieval: 100% Fertilisation rate: 70% Clinical pregnancy rate: 17/40 (42.5%) Live birth rate: 11/37 (29.7%) Safety No safety outcomes reported	• Congenital obstruction: 33.75
Uvin et al 2018 [G8]	Retrospective cohort study of men at one centre in Belgium who had received a past vasectomy and were seeking treatment between 2006 and 2011 Outcomes were available for 163 men who either received a vasectomy reversal (n=99) or underwent immediate surgical sperm retrieval and IVF/ICSI treatment (n=64) All patients were followed up for a minimum of 57 months	Effectiveness Outcomes for men who had vasectomy reversal (n=99) Sperm found in ejaculate: 79.3% Outcomes were reported for: • Men who had a reversal and attempted natural pregnancy ('reversal only') (n=45) • Men who had a reversal and then switched to IUI/IVF/ICSI ('switchers') (n=54) • 50 men had a reversal and later switched to IVF/ICSI • 4 men had a reversal and then switched to IUI with or without later IVF/ICSI. In 'switchers', 41% of sperm were obtained by ejaculation Clinical pregnancy • Reversal only: 21/45 (46.7%) • Switchers: 41/54 (75.9%) Crude cumulative delivery rate: • Reversal only: 40.0% • Switchers: 57.4% (mean number of cycles 2.5 ± 2.1) Outcomes for men who had immediate surgical sperm retrieval and IVF/ICSI (n=64)	This study was conducted in Belgium The main study aim was to consider the effectiveness of vasectomy reversal or IVF/ICSI after a vasectomy Mean male age at vasectomy: 35.5 years Mean male age at vasectomy reversal: 344.4 years Mean obstructive interval: 9.5 years (range 1 to 27) Mean female age ranged 20 to 45 years. The study authors reported no significant differences in female characteristics such as age or parity between groups 51% of the 99 men who had vasectomy reversal and attempted natural pregnancy later switched to IUI/IVF/ICSI

Reference	Study details	Outcomes	Comments
		Clinical pregnancy: 45/64 (67.2%) Crude cumulative delivery rate: 43.8% (mean number of cycles 2.4 ± 1.6) Comparative analysis The authors reported no statistically significant differences in cumulative delivery rate between patients who had immediate surgical sperm retrieval and IVF/ICSI and patients who had reversal and then switched to IUI/IVF/ICSI Safety Outcomes for men who had vasectomy reversal (n=99) Miscarriage: • Reversal only: 3/45 (6.7%) • Switchers: 10/54 (18.5%) Outcomes for men who had immediate surgical sperm retrieval and IVF/ICSI (n=64) Miscarriage: 15/64 (23.4%)	Outcomes were available for men who had a vasectomy reversal and then IVF/ICSI. Outcomes were also available for men who had a vasectomy and then moved straight to IVF/ICSI without reversal. Outcomes are not compared to men who had never had a vasectomy.
Kapadia et al 2018 [G9]	Retrospective cohort study using data from a prospectively collected database of vasectomy reversals conducted by two surgeons at one US centre between 2006 and 2014 Outcomes were available for 136 men who had vasectomy reversal	Effectiveness Outcomes for men who had vasectomy reversal Patency rate: 90% Pregnancy rate: 47/136 (34.6%) • Natural pregnancies: 42/47 • IUI pregnancies: 5/47 Live birth rate: 41/136 (30.1%) Pregnancy rates by female partner age: • 35-37 years (n=73): 37.3% • 38-40 years (n=50): 32.0% • >40 years (n=13): 23.1%	This study was conducted in the US The main study aim was to explore outcomes from vasectomy reversals in men with female partners aged ≥35 years and compare these to national IVF results Median male patient age: 41 years Median female partner age: 37 years Median obstructive interval: 9 years

Reference	Study details	Outcomes	Comments
	National data (2015) on IVF outcomes were also obtained for all-cause and male factor infertility using fresh and frozen non-donor eggs	Live birth rates by female partner age: • 35-37 years (n=73): 35.6% • 38-40 years (n=50): 26.0% • >40 years (n=13): 15.4% 74% of natural pregnancies were achieved within 1 year of reversal National ART data was reported according to women's age Pregnancy rates for all-cause infertility using fresh non-donor eggs: • 35-37 years: 32% • 38-40 years: 23.1% • >40 years: 10.4% Pregnancy rates for all-cause infertility using frozen non-donor eggs: • 35-37 years: 51.2% • 38-40 years: 47.5% • >40 years: 38.3% Pregnancy rates for male factor infertility using fresh non-donor eggs: • 35-37 years: 34.2% • 38-40 years: 29.1% • >40 years: 14.2% Pregnancy rates for male factor infertility using frozen non-donor eggs: • 35-37 years: 51.7% • 38-40 years: 49.7% • >40 years: 38.4% Live birth rates for all-cause infertility using fresh non-donor eggs: • 35-37 years: 26.1%	Most of the pregnancies achieved following vasectomy reversal were natural pregnancies and therefore the comparison to national IVF rates is more about the success of the vasectomy reversal than the effectiveness of a cycle of IUI. The number of pregnancies resulting from IUI was reported. However, it is not clear how many couples received IUI. It is not possible to draw any conclusions about the effectiveness of a cycle of IUI when the male partner in the couple has had a reversal of a vasectomy versus when the male partner in the couple has never had a vasectomy

Reference	Study details	Outcomes	Comments
		• 38-40 years: 16.9% • >40 years: 5.8% Live birth rates for all-cause infertility using frozen non-donor eggs: • 35-37 years: 41.5% • 38-40 years: 37.2% • >40 years: 27.8% Live birth rates for male factor infertility using fresh non-donor eggs: • 35-37 years: 28% • 38-40 years: 18.7% • >40 years: 6.5% Live birth rates for all-cause infertility using frozen non-donor eggs: • 35-37 years: 42% • 38-40 years: 38.8% • >40 years: 27.4% Safety No safety outcomes reported	
Cost effectiveness			
Cheng et al 2021 [G10]	Cost utility analysis of fertility options for men who had undergone vasectomy and had a female partner of advanced maternal age (<35) Options modelled were vasectomy reversal, sperm retrieval with IVF and a combination of	Cost effectiveness The four options considered were: 3. Vasectomy reversal followed by natural conception attempt over 1 year (VR & NC) 4. Sperm retrieval with IVF/ICSI for up to 4 cycles (SR & IVF) 5. Vasectomy reversal and sperm retrieval followed by failed attempt at natural conception for 6 months and then up to 2 cycles of IVF/ICSI (VR & NC & IVF) 6. Vasectomy reversal and sperm retrieval followed by 2 failed IVF/ICSI attempts and then natural conception for 6 months (VR & IVF & NC)	This study was conducted in the US The main study aim was to determine the cost effectiveness of different fertility options in men who have undergone vasectomy in couples where the female is of advanced maternal age The authors used a Markov model using US data and costs

Reference	Study details	Outcomes	Comments
	vasectomy reversal with sperm retrieval and IVF	Cost per QALYs were reported by female age groups The most cost effective strategy was option 1 (VR & NC). Cost per QALY: • 35-37 years: $7,150 • 38-40 years: $7,203 • >40 years: $7,367 The second most cost-effective strategy was option 4 (VR & IVF & NC). Cost per QALY: • 35-37 years: $31,289 • 38-40 years: $33,226 • >40 years: $35,700 The third most cost-effective strategy was option 3 (VR & NC & IVF). Cost per QALY: • 35-37 years: $34,142 • 38-40 years: $35,404 • >40 years: $37,061 The least cost-effective strategy was option 2 (SR & IVF). Cost per QALY: • 35-37 years: $40,821 • 38-40 years: $46,247 • >40 years: $54,599	Sensitivity analysis adjusted for live birth rates per IVF cycle. This did not change the most and least cost effective strategies Outcomes were reported as cost per QALY, defined as cost for one QALY gained by each fertility treatment pathway to have a healthy child The authors concluded that for couples with a history of vasectomy and where the female is over >35 years old, the most cost effective option is vasectomy reversal. If couples opt for surgical retrieval for IVF it is more cost effective to undergo a concomitant vasectomy reversal than do surgical retrieval alone

Cryopreservation of gametes and embryos

How is the quality of sperm stored for future use in IVF affected by the duration of cryopreservation?

Table H1: Summary of studies: Storage of sperm

Reference	Study details	Outcomes	Comments
No Systematic Reviews Identified			
Other studies			
Muller et al 2016 [H3]	Retrospective cohort study of cancer patients who cryopreserved sperm at one centre in The Netherlands between 1983 and 2013 Outcomes available for 78 patients who used their cryopreserved sperm at the centre	Effectiveness Mean storage time for patients who used their cryopreserved sperm (n=78): 4.8 years (range 0.5 to 13.3) Cryopreserved sperm were used for IUI (108 cycles), IVF (79 cycles) and/or ICSI (101 cycles) Fertilisation rates • IVF: 49% • ICSI: 51% Clinical pregnancies • IUI: 15 • IVF: 33 • ICSI: 47 Live births • IUI: 14 • IVF: 27 (22 single births & 5 twins) • ICSI: 40 (32 single births & 8 twins) 60 of the 78 patients (77%) fathered at least one child The authors reported no difference in mean storage time between couples who did and did not conceive (59 and 57 months respectively)	This study was conducted in the Netherlands. All samples were stored using the same cryopreservation procedure The main study aim was to report usage rates for cryopreserved sperm in cancer patients and the effectiveness of assisted reproductive technology with the cryopreserved sperm. Limited details were provided about the duration of storage No information was available regarding the women's fertility. The mean age of the female partner was 31.2 years (range 21 to 43) The shortest storage time was six months and the longest 13.3 years. The authors did not report outcomes separately for different storage durations, but did include a statement that there was no significant difference between time since cryopreservation and fertilisation or live birth rate

Reference	Study details	Outcomes	Comments
		The authors reported no significant difference between time since cryopreservation and fertilisation or live birth rate, but did not provide these figures Safety No safety outcomes reported	

How is the quality of oocytes stored for future use in IVF affected by the duration of cryopreservation?

Table H2: Summary of studies: Storage of oocytes

Reference	Study details	Outcomes	Comments
No Systematic Reviews Identified			
Other studies			
Porcu et al 2022 [H4]	Prospective cohort study of cancer patients who cryopreserved oocytes at one centre in Italy between 1996 and 2021 Outcomes available for 44 cancer patients who used their cryopreserved oocytes at the centre Outcomes were also reported for 870 non-oncological infertile patients who had cryopreserved and then used supernumerary oocytes in the same time period	Effectiveness Mean storage time for cancer patients who used their cryopreserved oocytes (n=44): 5.0 years (range 2 to 15) Mean storage time for non-oncological patients who used their cryopreserved oocytes (n=870): 4.8 years (range 2 to 15) Outcomes are reported for cancer patients Survival of thawed/warmed oocytes: 157/194 (80%) Fertilisation rates: 101/138 (73.2%) Pregnancy rate per transfer: 18/57 (31.5%) Pregnancy rate per patient: 18/44 (41%) Live births: 13 (15 newborns) Births per cycle: 13/64 (20.3%) Births per patient: 13/44 (29.9%) The length of storage was reported for each of the 13 live births was reported. These were: • 2 years: n=2	This study was conducted in Italy. Two cryopreservation procedures were used: slow freezing/ rapid thawing from 1996 to 2006 (69 cycles) and vitrification/warming from 2006 to 2021 (439 cycles) The main study aim was to demonstrate that oocyte cryopreservation is a feasible and efficient options for fertility preservation in cancer patients, through comparison of outcomes with non-cancer patients Detailed information about the duration of storage was only provided for oocytes that resulted in a live birth No information was available regarding male fertility

Reference	Study details	Outcomes	Comments
		• 3 years: n=4 • 4 years: n=3 • 5 years: n=2 • 6 years: n=1 • 7 years: n=1 The authors did not comment on the outcomes by different storage periods No statistically significant differences were seen in outcomes for cancer and non-oncological patients Safety Miscarriages: 4/44 (22%) Children born showed normal growth and development with a median follow up of 4 years 1 month (range one month to 13.5 years) One minor malformation (labiopalatoschisis) was detected in a child born from an oocyte stored for 5 years	Mean ± standard deviation age at the time of cryopreservation (years) • Cancer patients: 29.4 ± 4.0 • Non-oncological patients: 30.0 ± 6.8 Mean ± standard deviation age at the time of cryopreserved oocyte use (years) • Cancer patients: 36.0 ± 5.1 • Non-oncological patients: 37.1 ± 4.2 The shortest storage time for cryopreserved oocytes used was 2 years and the longest 15 years. The authors did not report outcomes separately for different storage durations. However, the longest storage duration that resulted in a live birth was 7 years
Mayeur et al 2021 [H5]	Retrospective cohort study of female cancer patients who cryopreserved oocytes or embryos at one centre in France between 2009 and 2017 Outcomes available for 40 patients who used their cryopreserved oocytes or embryos at the centre in 49 thaw cycles	Effectiveness The authors compared results according to the process used to collect oocytes for cryopreservation (controlled ovarian stimulation (COS) or in vitro maturation (IVM)). Some comparisons were also made by the cryopreservation technique (slow freezing and vitrification) Median (interquartile range) storage time (years) for cancer patients (n=21) who used their cryopreserved oocytes: • After COS: 3.0 (2.7 to 4.0) • After IVM: 5.0 (5.0 to 6.0) Outcomes for cryopreserved oocytes are reported below	This study was conducted in France. Two cryopreservation procedures were used: slow freezing from 2009 to 2012 and vitrification from 2013 to 2017 The main study aim was to evaluate the outcomes of frozen oocytes or embryos cryopreserved for female cancer patients prior to gonadotoxic therapy No information was available regarding male fertility

Reference	Study details	Outcomes	Comments
	Outcomes for 21 patients who cryopreserved oocytes are reported here. Outcomes for 19 patients who cryopreserved embryos are reported in relation to the question regarding the storage of embryos	Survival rate • Cryopreserved by slow freezing: 54.3% • Cryopreserved by vitrification: 54.5% Fertilisation rate • After COS: 68.8% • After IVM: 49.1% Implantation rate • After COS: 1/9 (11.1%) • After IVM: 2/11 (18.2%) Live birth rate per patient • After COS: 1/6 (16.7%) • After IVM: 2/15 (13.3%) Live birth rate per thaw cycle • After COS: 1/7 (14.3%) • After IVM: 2/18 (11.1%) Length of storage was reported for each of the 3 live births: • 47 months: n=1 • 65 months: n=1 • 73 months: n=1 The authors did not comment on the outcomes by different storage periods Safety No safety outcomes were reported	Age at the time of cryopreservation ranged from 28.7 to 39.5 years Age at the time of cryopreserved oocyte use ranged from 33 to 42 years The lower end of the interquartile range for storage time for cryopreserved oocyte used was 2.7 years and the upper end 6 years. The authors did not report outcomes separately for different storage durations. However, the longest storage duration that resulted in a live birth was 73 months

How is the quality of embryos stored for future use in IVF affected by the duration of cryopreservation?

Table H3: Summary of studies: Storage of embryos

Reference	Study details	Outcomes	Comments
Systematic Reviews			
Ma et al 2021 [H6]	Systematic review and meta-analysis (search date June 2020) Included 7 retrospective cohort studies	Effectiveness There was no significant association between storage time and the outcomes assessed for any cryopreservation technique or in sub-group analysis by technique. The effectiveness outcomes assessed were survival rate, implantation rate, clinical pregnancy rate and live birth rate Survival rate: • Any cryopreservation technique: OR 0.74 (95%CI 0.44 to 1.23), I^2 = 76% (4 studies) • Vitrification: OR 0.67 (95%CI 0.33 to 1.37), I^2 = 68% (3 studies) • Slow-freezing: OR 0.92 (95%CI 0.72 to 1.18), I^2 = N/a (1 study) Implantation rate: • Any cryopreservation technique: OR 1.05 (95%CI 0.78 to 1.42), I^2 = 36% (5 studies) • Vitrification: OR 0.84 (95%CI 0.57 to 1.24), I^2 = 11% (3 studies) • Slow-freezing: OR 1.24 (95%CI 0.90 to 1.72), I^2 = 18% (2 studies) Clinical pregnancy rate: • Any cryopreservation technique: OR 0.94 (95%CI 0.83 to 1.07), I^2 = 1% (6 studies) • Vitrification: OR 0.91 (95%CI 0.80 to 1.03), I^2 = 0% (4 studies) • Slow-freezing: OR 1.22 (95%CI 0.85 to 1.75), I^2 = 0% (2 studies)	The included studies were conducted in Japan, China (2 studies), Austria, Iran (2 studies) and the USA. Four studies reported using vitrification and 3 studies slow-freezing No information was provided on the reason for embryo cryopreservation. It is not known if any of the patients cryopreserved embryos prior to treatment that is likely to cause infertility. Donor embryos were excluded. The study compared the highest versus the lowest category of storage time The lowest storage time categories started at 0 to 12 months in the different studies. The highest storage time category was presented as a fixed time period in 3 studies (60, 72 and 97 months respectively). In the remaining studies the higher storage time category was >180 days, >1,095 days (2 studies) and >48 months respectively The studies did not find an association between storage time and pregnancy outcomes

Reference	Study details	Outcomes	Comments
		Live birth rate: • Any cryopreservation technique: OR 0.99 (95%CI 0.78 to 1.25), I^2 = 29% (5 studies) • Vitrification: OR 0.90 (95%CI 0.79 to 1.03), I^2 = 0% (3 studies) • Slow-freezing: OR 1.37 (95%CI 0.76 to 2.46), I^2 = 54% (2 studies) Safety There was no significant association between storage time and the outcomes assessed for any cryopreservation technique or in sub-group analysis by technique. The safety outcomes assessed were miscarriage rate and congenital malformation rate. Miscarriage rate: • Any cryopreservation technique: OR 1.05 (95%CI 0.85 to 1.29), I^2 = 0% (4 studies) • Vitrification: OR 1.20 (95%CI 0.74 to 1.96), I^2 = 22% (3 studies) • Slow-freezing: OR 1.11 (95%CI 0.38 to 3.26), I^2 = N/a (1 study) Congenital malformation rate: • Vitrification: Risk Difference -0.00 (95%CI -0.02 to 0.01), I^2 = 0% (3 studies) No studies reported this outcome for slow-freezing	
Other studies			
Shi et al 2022 [H7]	Retrospective cohort study of women who underwent frozen embryo transfer at one centre in China between 2013 and 2017	Effectiveness Outcomes were reported for 5 storage durations: • 6-12 months: 770 cycles • 13–36 months: 359 cycles • 37-60 months: 220 cycles • 61-84 months: 177 cycles • >84 months: 98 cycles	This study was conducted in China. Only embryos cryopreserved using slow freezing were included because these embryos had been stored for longer durations The main study aim was to evaluate the effect of cryopreservation

Reference	Study details	Outcomes	Comments
	Outcomes were available for 1,624 thaw cycles with 4,630 cryopreserved and thawed embryos	There were no statistically significant differences between storage duration groups for survival rates, implantation rates, clinical pregnancy, live birth, term birth or birth weight outcomes (p>0.05) Survival rate: • 6-12 months: 77.65% • 13–36 months: 77.69% • 37-60 months: 77.18% • 61-84 months: 73.66% • >84 months: 75.69% Implantation rate: • 6-12 months: 23.14% • 13–36 months: 22.09% • 37-60 months: 25.63% • 61-84 months: 20.44% • >84 months: 19.75% Clinical pregnancy rate: • 6-12 months: 40.64% • 13–36 months: 37.65% • 37-60 months: 46.26% • 61-84 months: 42.35% • >84 months: 37.50% Live birth rate: • 6-12 months: 34.08% • 13–36 months: 30.59% • 37-60 months: 30.83% • 61-84 months: 34.71% • >84 months: 30.21% Term birth rate (37 to 42 week gestation): • 6-12 months: 91.11% • 13–36 months: 89.16%	duration on the clinical and neonatal outcomes of slow-frozen embryos No information was provided on the reason for embryo cryopreservation. It is not known if any of the patients cryopreserved embryos prior to treatment that is likely to cause infertility No information was available regarding male fertility Mean age at the time of cryopreservation ranged from 28.84 to 30.53 years in the 5 groups Mean age at the time of cryopreserved embryo use ranged from 31.22 to 37.83 years in the 5 groups The group with the shortest storage duration for cryopreserved embryos used was 6-12 months and the longest storage duration group was >84 months (7 years). The authors also separately reported descriptive outcomes for a subgroup of embryos that had been cryopreserved for more than 10 years. The authors did not conduct comparative analysis for this subgroup and concluded that the sample size was too small to draw solid conclusions

Reference	Study details	Outcomes	Comments
		• 37-60 months: 98.18% • 61-84 months: 90.74% • >84 months: 86.96% Normal birth weight (2,500 to 4,500g): • 6-12 months: 90.56% • 13–36 months: 89.16% • 37-60 months: 98.18% • 61-84 months: 85.19% • >84 months: 100% Logistic regression analysis adjusted for maternal age and body mass index at freezing, maternal age at embryo transfer, number of embryos transferred and endometrial preparation found no correlation between storage duration and clinical pregnancy or live birth rate Linear regression analysis adjusted for body mass index, maternal age at embryo transfer, number of embryos transferred newborn sex, gestational age and endometrial preparation found no correlation between storage duration and singleton birth weight The study authors also separately reported descriptive outcomes for 65 embryos (18 thaw cycles) that had been cryopreserved for >120 months. Due to the small sample size, this storage duration was not analysed as a separate group For embryos cryopreserved for >120 months: • Survival rate: 67.69% • Implantation rate: 12.50% • Clinical pregnancy rate: 27.78% • Live birth rate: 27.78% • Mean gestational age: 37.8 weeks • Mean birth weight: 3,406g Safety	

Reference	Study details	Outcomes	Comments
		There were no statistically significant differences between storage duration groups for malformation rates (p=0.803) Malformations in babies born: • 6-12 months: 5/308 (1.62%) • 13–36 months: 2/125 (1.60%) • 37-60 months: 2/77 (2.60%) • 61-84 months: 2/64 (3.12%) • >84 months: 0/35 (0%) Malformations recorded included hearing abnormalities, atrial septal defects, cleft lip and palate, ear deformities, cryptorchidism, echogenic intracardiac focus, thoracic haemangioma, neonatal ovarian cysts, syndactyly and hydrocephalus	
Mayeur et al 2021 [H5]	Retrospective cohort study of female cancer patients who cryopreserved oocytes or embryos at one centre in France between 2009 and 2017 Outcomes available for 40 patients who used their cryopreserved oocytes or embryos at the centre in 49 thaw cycles Outcomes for 19 patients who cryopreserved embryos are reported here. Outcomes for 21 patients who cryopreserved oocytes	Effectiveness The authors compared results according to the process used to collect embryos for cryopreservation (controlled ovarian stimulation (COS) or in vitro maturation (IVM)). Some comparisons were also made by the cryopreservation technique (slow freezing and vitrification) Median (interquartile range) storage time (years) for cancer patients who used their cryopreserved embryos (n=19): • After COS: 3.0 (1.7 to 5.0) • After IVM: 5.0 (3.0 to 5.0) Outcomes for cryopreserved embryos are reported below Survival rate • Cryopreserved by slow freezing: 69.2% • Cryopreserved by vitrification: 76.2% Implantation rate • After COS: 4/22 (18.2%)	This study was conducted in France. Two cryopreservation procedures were used: slow freezing from 2009 to 2012 and vitrification from 2013 to 2017 The main study aim was to evaluate the outcomes of frozen oocytes or embryos cryopreserved for female cancer patients prior to gonadotoxic therapy No information was available regarding male fertility Age at the time of cryopreservation ranged from 28.7 to 39.5 years Age at the time of cryopreserved embryo use ranged from 34.8 to 42 years

Reference	Study details	Outcomes	Comments
	are reported in relation to the question regarding the storage of oocytes	• After IVM: 1/12 (8.3%) Live birth rate per patient • After COS: 4/9 (44.4%) • After IVM: 1/10 (10.0%) Live birth rate per thaw cycle • After COS: 4/14 (28.6%) • After IVM: 1/10 (10.0%) The length of storage was reported for each of the 5 live births was reported. These were: • 12 months: n=1 • 14 months: n=1 • 33 months: n=1 • 64 months: n=1 • 77 months: n=1 The authors did not comment on the outcomes by different storage periods Safety No safety outcomes were reported	The lower end of the interquartile range for storage time for cryopreserved embryos used was 1.7 years and the upper end 5 years. The authors did not report outcomes separately for different storage durations. However, the longest storage duration that resulted in a live birth was 77 months
Barcroft et al 2013 [H8]	Retrospective cohort study of female cancer patients who cryopreserved embryos at one UK centre between 1996 and 2011 Outcomes available for 5 cancer patients who used their cryopreserved embryos at the centre in 9 frozen-thaw cycles	Effectiveness Mean storage time for cancer patients who used their cryopreserved embryos (n=5): 4.2 years (range 2.4 to 7.9) Clinical pregnancy rate per patient: 3/5 (60%) Clinical pregnancy rate per thaw cycle: 3/9 (33%) Clinical pregnancy rate per thawed embryo: 3/21 (14%) Live births: 2 (3 newborns) Live birth rate per patient: 2/5 (40%) Live birth rate per thaw cycle: 2/9 (22%) Live birth rate per thawed embryo: 2/21 (9.5%)	This study was conducted in the UK. Embryos were cryopreserved using slow freezing The main study aim was to explore the long-term outcomes of IVF in patients with cancer Limited details were provided about the duration of storage

Reference	Study details	Outcomes	Comments
		The authors did not comment on the outcomes by different storage periods Safety Miscarriage rate per thaw cycle: 1/9 (11.1%)	No information was available regarding male fertility Mean ± standard deviation age at the time of cryopreservation: 31.9 ± 3.9 years (range 25 to 41) Age at the time of cryopreserved embryo use not reported The shortest storage time for cryopreserved embryos used was 2.4 years and the longest 7.9 years. The authors did not report outcomes separately for different storage durations. The longest storage duration that resulted in a live birth is not clear

Appendix 5: Summary of key ICB ethical / decision-making principles

Key ethical principles	Definition from NICE Glossary	Examples of quotes from ICB decision-making frameworks relevant to ethical principle
Effectiveness & safety	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.	"committees will seek best available **evidence of clinical effectiveness**, and choose appropriate clinically and patient defined outcomes, where possible QOL should be considered."[1,2]
Cost-effectiveness	Value for money: how well a technology works in relation to how much it costs.	"committees will seek best available evidence of cost effectiveness […] where possible cost utility analysis should be considered"[1,2]
Allocation of resources according to need and/or capacity to benefit from the treatment	Health need and capacity to benefit are not explicitly defined in the NICE glossary.	"Health care should be allocated justly and fairly according to need and capacity to benefit, such that the health of the population is maximised within the resources available."[2]
Avoiding discrimination except where this is relevant to capacity to benefit from the treatment	Discrimination is not explicitly defined in the NICE glossary.	"The ICB considers all lives of all patients to be of equal value and in making decisions about funding treatments will seek not to discriminate on the grounds of age, gender, race, religion, lifestyle, occupation, family and caring responsibilities, social position, financial status, family status (including responsibility for dependents), intellectual/cognitive functioning or physical functioning save where a difference in the treatment options made available to patients is directly related to the patient's clinical condition or is related to the anticipated clinical benefits for this individual to be derived from a proposed form of treatment."[3,4]
Absolute costs, affordability in relation to the overall ICB resources for healthcare	Affordability is not explicitly defined in the NICE glossary.	"What are the absolute costs involved in funding this treatment, in relation to the overall resources of the ICB for health care"[3] "ICB will balance the needs of each individual against the benefit which could be gained by alternative investment possibilities to meet the needs of the community"[3,4]

The decision-making frameworks available for review at the time of this report were:

- Northamptonshire ICB Prior Approval Scheme Policy and Individual Funding Requests Policy
- Nottingham and Nottinghamshire ICB Ethical Decision-Making Framework
- Leicester City, Leicestershire County and Rutland ICB East Midlands Commissioning Policy for Individual Funding Requests (IFR) (2011) and East Midlands Commissioning Policy for Individual Funding Requests (IFR), updated version (2023, approval pending)
- Lincolnshire Integrated Care Board Individual Funding Requests (IFR) Commissioning Policy
- Derby and Derbyshire ICB Ethical Framework for Decision Making

References:

1. Nottingham and Nottinghamshire ICB Ethical Decision-Making Framework
2. NHS Derby and Derbyshire Integrated Care Board Ethical Framework for Decision Making
3. East Midlands Commissioning Policy for Individual Funding Requests (IFR) (2011), used by Leicester City, Leicestershire County and Rutland ICB
4. Lincolnshire Integrated Care Board (ICB) Individual Funding Requests (IFR) Commissioning Policy