Infertility treatments

Synonym: subfertility

The World Health Organization defines infertility as '*a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse*'.[1]

About 84% of couples in the general population (including all ages and people with fertility problems) will conceive naturally within 1 year if they have regular (every 2–3 days) unprotected sexual intercourse. This rises cumulatively to 92% after 2 years and 93% after 3 years.[2]

Around one in seven couples in the UK is affected by infertility and a small proportion of these need treatment with assisted conception.[3] The National Institute for Health and Care Excellence (NICE) guidelines currently do not have a definition for infertility, although previous versions defined it as failure to conceive despite regular unprotected sexual intercourse for two years.

Current guidance recommends offering investigation after one year. Over 80% of couples should conceive within a year if the woman is aged under 40 and they are having regular unprotected sexual intercourse. Of those who do not conceive within a year, half will conceive within the next year (so 90% over two years).

Causes of infertility[3]

Lifestyle and environmental factors, such as smoking and obesity, can adversely affect fertility.[4] Otherwise, the main causes of infertility in the UK are:

- Unexplained infertility (no identified male or female cause) (25%).
- Ovulatory disorders (25%).
- Tubal damage (20%).

- Factors in the male causing infertility (30%).
- Uterine or peritoneal disorders (10%).

In about 40% of cases disorders are found in both the man and the woman. Uterine or endometrial factors, gamete or embryo defects, and pelvic conditions such as endometriosis may also be involved.

For further information, see the separate Infertility - Female article.

Initial investigations[2]

- Start investigations in couples who have not conceived after 1 year of regular (every 2–3 days) unprotected sexual intercourse.
- Offer investigations earlier than 1 year to couples who have been identified as less likely to conceive.
- Earlier investigations may be prompted by the same factors that prompt an early referral (see below).

Investigations for a woman

- Mid-luteal phase progesterone to confirm ovulation. The sample should be taken 7 days before the expected period.
- Screen for chlamydia.

The following additional tests may be needed:

- Serum progesterone (in women with prolonged irregular menstrual cycles). Serum progesterone may need to be measured later (eg day 28 of a 35-day cycle) to confirm ovulation, and repeated weekly until the next menstrual cycle starts.
- Gonadotrophin measurement (in women with irregular menstrual cycles) Gonadotrophin (follicle-stimulating hormone and luteinising hormone) measurements are of value in women with anovulation or oligo-ovulation and can be used to identify ovulation disorders.
- Thyroid function tests (in women with symptoms of thyroid disease).
- Prolactin measurement (in women with symptoms of an ovulatory disorder, eg PCOS, galactorrhoea, or a suspected pituitary tumour.

Investigations for a man

- Semen analysis. Refer men who have two abnormal semen examination results to secondary care for further assessment.
- Screen for chlamydia.

General care[3]

The couple needs support and reassurance. It can be a very difficult time for them, especially if there is pressure from parents or in-laws, that may be more prominent in some cultures but can occur in all. Pregnancy probably will occur even without intervention but they must not feel neglected or that nothing can be done.

Couples often conceive whilst awaiting further investigation, as half of those who have not conceived within a year will do so during the second year. The stress of trying to conceive can adversely affect relationships, further contributing to fertility issues.

Couples who have fertility problems should be informed that they might find it helpful to contact a fertility support group. Counselling may be appropriate for some couples, as fertility problems can cause psychological stress.

General advice

- **Folic acid**: women intending to become pregnant should be informed that dietary supplementation with folic acid (0.4 mg a day) before conception and up to 12 weeks of gestation, reduces the risk of having a baby with neural tube defects. The dose should be 5 mg a day in those women who have previously had an infant with a neural tube defect or in those receiving anti-epileptic medication or who have diabetes.
- **Frequency of sexual intercourse**: couples may be advised that regular intercourse every two to three days optimises the chances of conception occurring.

- **Alcohol**: in men, excessive consumption may affect semen quality but there is no evidence that drinking within recommended safe limits has an adverse effect. Women should be advised that when pregnant, drinking alcohol is not advised due to the potential risk to the developing fetus.
- **Smoking**: advise women that smoking can harm a developing baby; offer those who smoke support and referral to help them quit. Advise men that smoking affects semen quality (although it is not known if this adversely affects fertility) and discuss the benefits of quitting smoking to their general health and discuss risks of passive smoking to partner and potential baby.
- **Weight**: advise women that having a body mass index (BMI) ≥30 may be a cause of taking longer to conceive. Being overweight may reduce fertility in men also. Being underweight with a BMI <19 may also have an adverse effect on fertility.
- **Alternative therapies**: where conventional medicine offers no help, patients are often tempted by alternative therapies. However, what little evidence there is suggests that they are of no benefit and that, as they have not been properly tested, they may even be teratogenic.
- **Timed intercourse**: there are insufficient data to draw conclusions about effectiveness of methods to predict ovulation so that intercourse can be concentrated in the right time of the cycle.[5] Methods used include measuring basal temperature and urinary hormones, monitoring cervical mucus and using ultrasound scans. There may be a slight improvement in pregnancy rates but concerns remain about the side-effects of stress and the detrimental effect on relationships and sexual spontaneity.

Referral[2]

Referral criteria for people presenting with infertility may vary between health authorities. Refer to local guidelines.

For woman younger than 36 years of age: consider referral, along with her partner, if history, examination, and investigations are normal in both partners and the couple has not conceived after 1 year.

Consider earlier referral if the following factors are present:

- Women:
    - Age 36 years and older (refer after 6 months).
    - Amenorrhoea or oligomenorrhoea.
    - Previous abdominal or pelvic surgery.
    - Previous pelvic inflammatory disease.
    - Previous sexually transmitted infection (STI).
    - Abnormal pelvic examination.
    - Known reason for infertility (for example prior treatment for cancer).
- Men:
    - Previous genital pathology.
    - Previous urogenital surgery.
    - Previous STI.
    - Varicocele.
    - Significant systemic illness.
    - Abnormal genital examination.
    - Known reason for infertility (eg, prior treatment for cancer).

Ensure that the couple has been offered counselling before, during, and after investigation and treatment. Explain that fertility problems and their investigation and treatment can cause psychological stress. Usually counselling will be arranged by the specialist infertility team.

Treatment options [2]

There are three main types of fertility treatment: medical, surgical, and assisted conception.

- Medical treatment includes the use of drugs to induce ovulation:
    - Clomifene (an anti-oestrogen drug) is an effective treatment for anovulation.
    - Gonadotrophins may be offered to women with clomifene-resistant anovulatory infertility. They are also effective in improving fertility in men with hypogonadotropic hypogonadism.
    - Pulsatile gonadotrophin-releasing hormone and dopamine agonists are other treatments that induce ovulation. Dopamine agonists can be considered for women with ovulatory disorders secondary to hyperprolactinaemia.
- Surgical treatment of infertility includes:
    - Tubal microsurgery in women with mild tubal disease — tubal catheterisation or cannulation improves the chance of pregnancy in women with proximal tubal obstruction.
    - Surgical ablation, or resection of endometriosis plus laparoscopic adhesiolysis in women with endometriosis.
    - Surgical correction of epididymal blockage in men with obstructive azoospermia.

Editor's note

Dr Krishna Vakharia, 16th October 2023
Removal, preservation and reimplantation of ovarian tissue for restoring fertility after gonadotoxic treatment [6]
NICE has recommended the removal, preservation and reimplantation of ovarian tissue for restoring fertility after gonadotoxic treatment if arrangements are in place for clinical governance, consent and audit.
It is advised that clinicians enter details about everyone having removal, preservation and reimplantation of ovarian tissue for restoring fertility after gonadotoxic treatment onto a suitable register, such as the UKSTORE register.
This surgical option is important for those that may have not reached puberty when this reimplantation of ovarian tissue could offer a chance of becoming pregnant in the future.
Evidence suggests that this is a safe procedure and that people who have had the procedure can become pregnant and have successful live births.

- Assisted conception treatments include:
    - Intrauterine insemination (IUI): timed to coincide with ovulation, sperm is placed in the woman's uterus using a fine plastic tube.
    - In vitro fertilisation (IVF): retrieval of one or more eggs, which are mixed with sperm and incubated for 2–3 days, with the resultant embryo injected into the uterus via the cervix.
    - Intracytoplasmic sperm injection (ICSI): injecting an individual sperm directly into the egg to bypass natural barriers that prevent fertilisation. The embryo is then transferred into the uterus.
    - Donor insemination: insemination of sperm, from a donor, into a woman via her vagina into the cervical canal or into the uterus itself.
    - Oocyte donation: stimulation of the donor's ovaries and collection of eggs. The donated eggs are then fertilised by the recipient's partner's sperm. After 2–3 days, the embryos are transferred to the uterus of the recipient via the cervix, after hormonal preparation of the endometrium.
    - Embryo donation: couples who have had successful IVF or ICSI may decide to donate their spare embryos to help other infertile couples.
    - Gamete intrafallopian transfer: retrieving eggs, mixing them with prepared sperm, and injecting the eggs (maximum of three) with the sperm into the fallopian tube.

Treatments for disorders of the male genital tract and spermatogenesis[3]

Management of abnormal sperm counts

- Whilst a low sperm count is a poor prognostic feature, and the lower the count the worse the prognosis, it is not totally incompatible with fertility.

- Men should be informed that there is an association between elevated scrotal temperature and reduced semen quality but that it is uncertain whether wearing loose-fitting underwear actually improves fertility.
- Where appropriate expertise is available, men with obstructive azoospermia should be offered surgical correction of epididymal blockage because it is likely to restore patency of the duct and improve fertility.
- Persistent azoospermia is incompatible with fertility. The couple may wish to consider donor sperm.
- Treatments not recommended:
    - Men should not be offered surgery for varicoceles as a form of fertility treatment because it does not improve pregnancy rates.
    - Men with idiopathic semen abnormalities should not be offered anti-oestrogens, gonadotrophins, androgens, bromocriptine or kinin-enhancing drugs because they have not been shown to be effective.
    - Men should be informed that the significance of antisperm antibodies is unclear and the effectiveness of systemic corticosteroids is uncertain.
    - Men with leukocytes in their semen should not be offered antibiotic treatment unless there is an identified infection, as there is no evidence that this improves pregnancy rates.

Management of disorders of the male genital tract

- Men with hypogonadotrophic hypogonadism should be offered gonadotrophins as these have been shown to improve fertility.
- In men with cryptorchidism and azoospermia, orchidopexy may result in spermatozoa being present in the ejaculate. It is uncertain to what extent age at orchidopexy affects future fertility.[7]
- Obstructive lesions of the seminal tract should be suspected in azoospermic or severely oligo-azoospermic patients with normal-sized testes and normal endocrine results. Results of reconstructive microsurgery depend on the cause and location of the obstruction and the expertise of the surgeon.

- There are many causes of non-obstructive azoospermia. In some cases testicular biopsy and testicular sperm extraction may be indicated.

Ovulation disorder treatment[3]

World Health Organization (WHO) Group I ovulation disorder

This is due to hypothalamic pituitary failure (hypothalamic amenorrhoea or hypogonadotrophic hypogonadism). These women should be advised that they can improve their chance of regular ovulation, conception and an uncomplicated pregnancy by increasing their body weight (for those with a BMI of <19) and/or moderating their exercise levels (if they undertake high levels of exercise). These women should be offered pulsatile administration of gonadotrophin-releasing hormone or gonadotrophins with luteinising hormone activity to induce ovulation.

WHO Group II ovulation disorder

This is due to hypothalamic-pituitary-ovarian dysfunction, predominately due to polycystic ovary syndrome (PCOS). Clomifene citrate (CC) - an anti-oestrogen - is an initial treatment for the majority of these. Metformin (or a combination of clomifene and metformin) can be also considered. However, those women with a BMI of >30 should be advised to lose weight before starting treatment. Women using CC treatment should be monitored by ultrasound and should not have treatment for more than six months.

Women who are known to be resistant to CC should consider one of the following second-line treatments, depending on clinical circumstances and the woman's preference:

- Laparoscopic ovarian drilling (by laser or by diathermy). Laparoscopic ovarian drilling with and without medical ovulation induction may decrease the live birth rate in women with anovulatory PCOS and clomiphene citrate resistance compared with medical ovulation induction alone.[8]
- Combined treatment with CC and metformin.
- Gonadotrophins.

WHO Group III ovulation disorder

This is due to ovarian failure or hypergonadotrophic hypogonadism.

Women with ovulatory disorders due to hyperprolactinaemia should be offered treatment with dopamine agonists such as bromocriptine.

Treatments for other female factors in infertility

A number of other treatments may be appropriate in certain cases. These include:

- Tubal and uterine surgery: for women with blockages or adhesions.
- Medical or surgical treatment of endometriosis. See the separate Endometriosis article for more detail.
- Ovarian hyperstimulation. Agents used are CC, anastrozole and letrozole. This is not advised in women with unexplained infertility.

Assisted conception[3]

Assisted conception broadly refers to procedures whereby treated or manipulated sperm are brought into proximity with oocytes. As listed above, assisted conception options include:

- Intrauterine insemination (IUI) with partner or donor sperm (in natural or stimulated cycles).
- Gamete intrafallopian transfer (GIFT).
- In vitro fertilisation and embryo transfer (IVF-ET, widely known as IVF).
- Intracytoplasmic sperm injection (ICSI).

In certain cases donor sperm or eggs may be required for these procedures.

Success depends upon numerous factors, including the woman's age, BMI, previous pregnancy history and lifestyle factors, as well as differences between clinic treatment populations, etc.

Intrauterine insemination (IUI)

IUI involves the introduction of prepared sperm into the uterine cavity around the time of ovulation (spontaneous or induced).

NICE guidelines advise that unstimulated IUI can be considered as a treatment option in the following groups:

- 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.

People with unexplained infertility, mild endometriosis or 'mild male factor infertility', who are having regular unprotected sexual intercourse should no longer routinely be offered IUI, either with or without ovarian stimulation. They should be considered for IVF if they have not conceived after trying for two years.

Gamete intrafallopian transfer (GIFT)

NICE guidelines state there is insufficient evidence to recommend the use of GIFT or zygote intrafallopian transfer in preference to IVF in couples with unexplained fertility problems or male factor fertility problems.

In vitro fertilisation (IVF) [9]

The chances of success reduce with increasing age of the woman. There is a trend of increasing demand for IVF in same-sex female couples. Ovarian stimulation is advised prior to IVF with ultrasound monitoring of the ovarian response. Progesterone is used after embryo transfer for luteal phase support.

When IVF is used and a top-quality blastocyst is available, a single embryo transfer is now recommended. This is to minimise the numbers and associated risks of a multiple pregnancy. HFEA has produced criteria for single/multiple embryo transfers and a strategy to reduce the numbers of multiple births.

The Human Fertilisation and Embryology Authority (HFEA) records show that: [10]

- In 2019, birth rates for patients under 35 were 32% per embryo transferred, compared to below 5% for patients aged 43+ when using their own eggs.
- Patients aged 35-37 and 38-39 had a live birth rate per embryo transferred of 6% in 1991, this increased to 25% and 19% respectively in 2019.
- In 2019 the multiple birth rate reached 6%, falling from 28% in the 1990s.
- Single embryo transfer has become common practice and in 2019, one embryo was put back in 75% of IVF cycles, compared to just 13% in 1991.
- The growth in IVF cycles has stabilised since 2017, but frozen embryo transfers continue to increase year on year, increasing 86% from 2014-2019.
- Most IVF treatments involve the use of patient eggs and partner sperm (86% of IVF cycles in 2019), but the use of donor eggs and sperm has increased.
- The use of donor eggs considerably increases the chance of a live birth to over 30% for all age groups. Despite this, only 17% of patients aged 40+ used donor eggs in 2019.
- The proportion of IVF cycles undertaken by patients aged 40 and over has more than doubled from 10% (689 cycles) in 1991 to 21% (14,761 cycles) in 2019.
- There have also been changes in partner type, with donor insemination cycles in 2019 more likely to involve a female partner than a male partner.

Intracytoplasmic sperm injection (ICSI)

In ICSI, a single sperm is injected directly into an oocyte. It should be considered for those with severe deficits in semen quality, obstructive azoospermia or those with non-obstructive azoospermia. In addition, treatment by ICSI should be considered for couples in whom a previous IVF treatment cycle has resulted in failed or very poor fertilisation.

Where the indication for ICSI is a severe deficit of semen quality or non-obstructive azoospermia, the man's karyotype should be established (after genetic counselling).

Donor insemination

Conditions where donor insemination may be considered include:

- Azoospermia (obstructive or non-obstructive not amenable to treatment).
- Severe deficits in semen quality in couples who do not wish to undergo ICSI.
- 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.

Oocyte donation

Conditions where oocyte donation may sometimes be appropriate include:

- Premature ovarian failure.
- Gonadal dysgenesis (eg, Turner syndrome).
- Bilateral oophorectomy.
- Ovarian failure following chemotherapy or radiotherapy.
- Some cases of IVF treatment failure.
- Some cases where there is a high risk of transmitting a genetic disorder to the offspring.

Guidelines exist for the screening of sperm and egg (and embryo) donations. [11]

Complications of assisted conception[3] [4]

Many of the complications are related to multiple pregnancies. Elective single embryo transfer has been shown to be associated with reduced risks of preterm birth and low birth weight compared with double embryo transfer but higher risks of preterm birth compared with spontaneously conceived singletons.[12]

The most serious complication is ovarian hyperstimulation syndrome (OHSS) which may occur when ovarian stimulation techniques are used.[13] It usually presents with lower abdominal discomfort, nausea, vomiting, diarrhoea and abdominal distension. Signs of severe disease, indicating a need for hospital management, include:

- Presence of ascites.
- Rapid weight gain.
- Tachycardia.
- Hypotension.
- Oliguria.
- U&E/other metabolic abnormalities.

Its incidence may be reduced by careful tailoring of the pharmacological agents and embryo implantation techniques used. New strategies are being introduced to try to prevent OHSS from developing.[14] Cochrane systematic reviews found the use of cabergoline may be of benefit but found no convincing evidence for "coasting" (the term used for stopping the gonadotrophin stimulation and continuing the agonist suppression until oestrogen levels decline to acceptable values before proceeding to egg collection).[15] [16]

NICE recommends that women who are offered ovulation induction should be informed that:

- No direct association has been found between these treatments and invasive cancer.

- No association has been found in the short- to medium-term between these treatments and adverse outcomes (including cancer) in children born from ovulation induction.
- Information about long-term health outcomes in women and children is still awaited.

The use of ovulation induction or ovarian stimulation agents is kept at the lowest effective dose and duration of use.

Although the absolute risks of long-term adverse outcomes of IVF treatment, with or without ICSI, are low, a small increased risk of borderline ovarian tumours cannot be excluded.

Further reading

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