

# Female infertility

## What is female infertility?

The term 'subfertility' may be preferable to infertility, as many of the bars to conception are relative rather than absolute and in about 25% of cases no cause is found.

People who are concerned about their fertility should be informed that over 80% of couples in the general population will conceive within one year if:

- The woman is aged under 40 years; and
- They do not use contraception; and
- They have regular sexual intercourse (every two to three days).

Of those who do not conceive in the first year, about half will do so in the second year (cumulative pregnancy rate over 90%).<sup>[1]</sup>

Infertility may be due to problems with one or both partners. Natural female fertility declines with age and increasing maternal age is also associated with increased obstetric risks and risk of miscarriage. This should be noted by women who choose to delay their family.

## Causes of female infertility

### Disorders of ovulation

They may occur at the level of pituitary or hypothalamus as well as at the level of the ovary. If there is amenorrhoea it should be investigated as such and oligomenorrhoea along similar lines.

The World Health Organization (WHO) classifies ovulation disorders into three groups:

- **Group I:** hypothalamic pituitary failure (hypothalamic amenorrhoea or hypogonadotropic hypogonadism).
- **Group II:** hypothalamic-pituitary-ovarian dysfunction, predominately a result of [polycystic ovary syndrome \(PCOS\)](#). This is the cause of the vast majority of ovulation disorder.
- **Group III:** ovarian failure.

As above, PCOS is responsible for the majority of ovulation disorders. Others include:

- [Pituitary tumours](#) can displace or destroy normal tissue and the production of follicle-stimulating hormone (FSH) and luteinising hormone (LH) is often the first to be affected. Panhypopituitarism is also called Simmonds' disease.
- [Sheehan's disease](#) is pituitary infarction following postpartum haemorrhagic shock.
- [Hyperprolactinaemia](#) may present with galactorrhoea or amenorrhoea. The control of prolactin (PRL) is unlike the other releasing factors, in that it is controlled by an inhibiting rather than a releasing factor from the hypothalamus into the hypothalamic-pituitary portal circulation. It is also released in response to thyrotropin-releasing factor, as is thyroid-stimulating hormone (TSH), and so it is elevated if thyroxine is low.
- The pituitary gland may be responsible for other disorders such as [Cushing's syndrome](#).

- A number of chromosomal disorders result in inadequate ovarian function and usually primary [amenorrhoea](#):
    - [Turner syndrome](#) - there is a loss or abnormality of the second X chromosome in at least one cell line in a phenotypic female. The ovaries are usually just streaks. This condition may be a mosaic.
    - In testicular feminisation there is primary amenorrhoea. The karyotype is XY but there is androgen insensitivity.
    - XXY, or [Klinefelter's syndrome](#), appears as a male.
    - The XXX karyotype - this is the most common female chromosomal abnormality, occurring in approximately 1 in 1,000 female births. While fertility in women with trisomy X is generally considered normal, there is an increased risk for premature ovarian failure.
  - Premature ovarian failure or premature menopause (menopause that occurs <40 years, although many gynaecologists use <45 years) causes [secondary amenorrhoea](#). [Premature ovarian failure](#) occurs in about 1% of women.
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## **Problems of tubes, uterus or cervix**

- The Fallopian tubes are delicate structures whose cilia waft the ovum, or even early embryo, to its destination for implantation - more correctly called nidation:
  - Damage to the tubes may occur as a result of infection:
    - A history of [pelvic inflammatory disease \(PID\)](#) is highly suggestive of damage to tubes.
    - Severe pelvic infection following illegal abortion is rarely seen in this country but still occurs in places where termination of pregnancy is illegal or difficult to secure.
    - Even a legal [termination](#) or [miscarriage](#) can lead to infection of retained products of conception.
    - Postpartum infection can also affect fertility.
  - [Sexually transmitted infections](#) may cause female infertility, largely through associated PID. [Chlamydia](#) and [gonorrhoea](#) are the most important.
  - Infection may be less direct, and spread from [appendicitis](#) is possible, even without overt peritonitis.
  - [Female sterilisation](#) operations involve disruption of the tube and results of attempted reversal are poor. Laparoscopic proof of patency of the tubes is not necessarily evidence that they function normally.
  - Infection can also damage the uterus. Adhesions in the uterus and cervix are called Asherman's syndrome. <sup>[2]</sup>
  - Deformity of the uterus, such as a septum or [bicornuate uterus](#), may be more likely to cause recurrent abortion than failure to conceive.
  - Significant distortion of the uterine cavity by [fibroids](#) can prevent implantation and hence fertility, although the impact on fertility remains a subject for debate.
  - The cervix may have been shortened and damaged by a cone biopsy.

- There may be problems of cervical mucus, including hostility to sperm.
- **Endometriosis** may cause such inflammation, adhesion and distortion in the pelvis that it causes tubal infertility. Even when it is much less severe than that, it is commonly associated with subfertility.<sup>[3]</sup> There is evidence for improvement in conception rates following surgery but not medical treatment of endometriosis.<sup>[4]</sup>

## History<sup>[1]</sup>

### General health

Even in the absence of systemic illness, poor general health will impair fertility. Enquire about general lifestyle, including smoking, alcohol and recreational drug use, in addition to exercise and dietary intake.

- Aim for an ideal BMI:
  - Women with a BMI of <19 and who have irregular menstruation or are not menstruating should be advised that increasing body weight is likely to improve their fertility.
  - Women with a BMI of ≥30 should be informed that they are likely to take longer to conceive and those who are not ovulating should be informed that losing weight is likely to increase their chance of conception.
  - Participating in a group programme involving exercise and dietary advice, rather than receiving weight loss advice alone, leads to more pregnancies.
- Smoking cigarettes impairs fertility and smoking in pregnancy increases the risk of miscarriage, obstetric complications, intrauterine growth restriction<sup>[5]</sup> and sudden unexpected death in infancy.<sup>[6]</sup>
- Women who are trying to become pregnant should be informed that drinking no more than one or two units of alcohol once or twice per week and avoiding episodes of intoxication reduce the risk of harming a developing fetus. Excessive alcohol consumption impairs sperm quality in men and may affect fertility in women.<sup>[7]</sup> <sup>[8]</sup>

- There is growing evidence of an association between excessive caffeine consumption and poor pregnancy outcomes, including miscarriage, stillbirth, low birth weight and/or small for gestational age.<sup>[9]</sup>
- Illicit drugs should be avoided. Some have adverse effects on fertility or the fetus or both and, for most, the question of teratogenicity has not been adequately addressed.<sup>[10]</sup> Cannabis can impair ovulation and cocaine can cause tubal infertility. There is also reason to be concerned about the effect these drugs may have in pregnancy.

## Sexual history

- Enquire about frequency of coitus (ideally two to three times a week) and any prolonged or recurrent absences of one of the partners.
- Ask about potential physical problems such as inadequate penetration or dyspareunia.

## Past medical history

Previous treatment for malignancy (chemotherapeutic agents, such as those used in childhood leukaemia) may result in subsequent sterility. Surgery and radiotherapy may be relevant if they involved the pelvic region.

Systemic disease may impair fertility, probably by interference with the hypothalamic–pituitary axis:

- This may include autoimmune disease such as rheumatoid disease or [systemic lupus erythematosus \(SLE\)](#), although the latter - eg, [antiphospholipid syndrome](#) - may be associated with recurrent miscarriage.<sup>[11]</sup>
- [Chronic kidney disease](#) can impair fertility.
- Poorly controlled [diabetes mellitus](#) should be improved.
- [Anorexia nervosa](#) can cause anovulation and amenorrhoea.

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## Medication and drug history

A thorough review of all medication is required with a view to both fertility and possible adverse effects on pregnancy, including teratogenicity. A number of recreational drugs may have an adverse effect on fertility, as above. Some prescribed medication may also cause problems:

- Phenothiazines and the older typical antipsychotics as well as metoclopramide can increase levels of PRL.
- Non-steroidal anti-inflammatory drug (NSAID) use is associated with luteinised unruptured follicles.<sup>[12]</sup>
- Immunosuppressants, used in autoimmune disease or post-transplant, may also affect fertility.

## Examination in female infertility

- Look for signs of [hirsutism](#):
  - Facial hair may be more profuse than normal, although this should be interpreted in the light of racial norms.
  - Acne may also indicate high androgen levels.
  - There may be a hint of male pattern alopecia with slight bitemporal recession.
  - The pubic hairline may extend up towards the umbilicus in a typical male pattern.
- Abdominal examination should be performed and it must precede bimanual pelvic examination or it is very easy to miss a large mass such as a big ovarian cyst.
- Gynaecological examination, especially vaginal examination, may indicate undisclosed sexual difficulties – eg, vaginismus.
- Bimanual examination: may detect an adnexal mass from an ovary of tubo-ovarian mass or tenderness suggesting PID or endometriosis, or the presence of uterine fibroids.

# Investigations<sup>[1]</sup>

The search for the cause of female infertility or subfertility should be systematic and led by clinical features, not a blind screening process for everything.

- Mid-luteal progesterone level to assess ovulation:
  - If low, it may need repeating, as ovulation does not occur every month.
  - The blood test is taken seven days before the anticipated period, ie on day 21 of a 28-day cycle. However, this day will need to be adjusted for different lengths of cycle
- FSH and LH should be measured if there is menstrual irregularity:
  - High levels may suggest poor ovarian function.
  - A comparatively high LH level relative to FSH level can occur in PCOS.
- Women who are concerned about their fertility should be offered testing for their rubella status. Those women who are susceptible to rubella should be offered vaccination and advised not to become pregnant for at least one month following vaccination.
- Basal body temperature charts are not recommended to predict ovulation, as they are unreliable.
- Other tests are not recommended in primary care.

## Secondary care investigations<sup>[1]</sup>

Each clinic may well have its own protocol for the investigation of couples in whom no problem has been identified, and even after extensive investigation no problem is found in 25%.

An earlier referral for specialist consultation for female infertility should be offered when:

- The woman is aged  $\geq 36$  years.



- There is a known cause of infertility.
- There is a history of predisposing factors for female infertility.
- Investigations show there is apparently no chance of pregnancy with expectant management.

### **Tubal patency**

Tubal damage is estimated to account for 20% of infertility in women.

- A **hysterosalpingogram (HSG)** or a hysterosalpingo-contrast ultrasound is recommended by the National Institute for Health and Care Excellence (NICE) for women who are not known to have comorbidities (such as PID, ectopic pregnancy or endometriosis).
  - A **laparoscopy and dye test** is recommended for those women who are thought to have comorbidities
  - Prior to undergoing uterine instrumentation, women should be offered screening for *Chlamydia trachomatis* and be treated appropriately if the result is positive.
  - Prophylactic antibiotics should be considered before uterine instrumentation if screening has not been undertaken.
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### **Ovarian reserve testing**

The woman's age should be used as an initial predictor of her overall chance of success through natural conception.

One of the following measures should be used (measured around Day 3 of the menstrual cycle) to predict the likely ovarian response to gonadotrophin stimulation in IVF:

- Total antral follicle count of  $\leq 4$  for a low response and  $>16$  for a high response.
- Anti-Müllerian hormone of  $\leq 5.4$  pmol/L for a low response and  $\geq 25.0$  pmol/L for a high response.
- FSH  $>8.9$  IU/L for a low response and  $<4$  IU/L for a high response.

A high response results in more mature follicles developing, leading to higher-than-average pregnancy rates.

The following tests should not be used individually to predict any outcome of fertility treatment:

- Ovarian volume
- Ovarian blood flow
- Inhibin B
- Estradiol (E2)

People undergoing IVF treatment should be offered testing for HIV, hepatitis B and hepatitis C. Those people found to test positive for one or more of HIV, hepatitis B or hepatitis C should be offered specialist advice and counselling and appropriate clinical management.

## Female infertility treatment and management

See the separate [Infertility Treatments](#) article.

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### Further reading

- [Balasch J, Gratacos E](#); Delayed childbearing: effects on fertility and the outcome of pregnancy. *Curr Opin Obstet Gynecol.* 2012 Jun;24(3):187–93. doi: 10.1097/GCO.0b013e3283517908.
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12. [Micu MC, Micu R, Ostensen M](#); Luteinized unruptured follicle syndrome increased by inactive disease and selective cyclooxygenase 2 inhibitors in women with inflammatory arthropathies. *Arthritis Care Res (Hoboken)*. 2011 Sep;63(9):1334-8. doi: 10.1002/acr.20510.

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