

For the Primer, visit doi:10.1038/s41572-018-0058-8

➔ **Subfertility (also known as infertility) is common and affects 1 in 6 couples. The World Health Organization definition of female subfertility is the failure to achieve a clinical pregnancy after 12 months of unprotected regular sexual intercourse, or due to impairment of a woman's capacity to reproduce.**

MANAGEMENT



The chance of achieving pregnancy in women with unexplained subfertility can be estimated using prognostic models. Women with a good prognosis should undergo expectant management as many couples will achieve pregnancy without active treatment. The optimal time frame to stop expectant management and commence active treatment (such as in vitro fertilization (IVF) or intrauterine insemination) is unknown. Women with ovulatory disorders should be offered lifestyle management initially and, if unsuccessful, ovulation induction therapy. IVF is a third-line treatment. Women with tubal or uterine diseases (such as those with adhesions, fibroids and endometriosis) are often treated using surgery, with IVF as a second-line therapy. Women with premature ovarian failure require IVF using an oocyte donor.

MECHANISMS

! Pregnancy requires normal follicular development, oocyte fertilization, successful uterine implantation and development; disorders that affect any of these processes can cause subfertility

Ovarian dysfunction includes altered frequency or duration of the menstrual cycle, and can be caused by genetic conditions (such as Turner syndrome), polycystic ovary syndrome or other endocrine disorders

Infectious diseases (such as gonorrhoea, chlamydia and HIV) and endometriosis can lead to tubal abnormalities

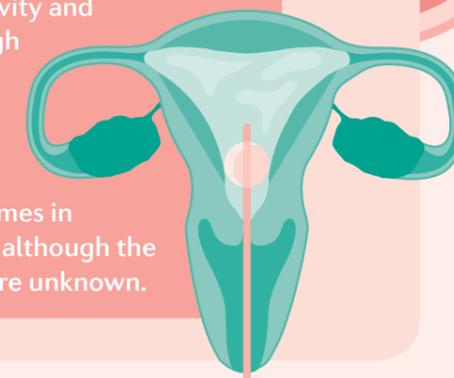
Uterine abnormalities such as fibroids, polyps or adenomyosis reduce the chance of ongoing pregnancy, but whether they affect conception is unclear

In some women, early menopause (premature ovarian failure) can cause subfertility

DIAGNOSIS

Couples are usually investigated for causes of subfertility after >12 months of unprotected intercourse and failure to conceive. Typically, diagnosis starts with a comprehensive assessment of fertility, including medical history, clinical examination and, if indicated, specific diagnostic tests. The latter can include the following: hysterosalpingography (HSG), hysterosalpingo contrast sonography (HyCoSy) and laparoscopy to assess the fallopian tubes; transvaginal ultrasonography to assess the uterine cavity and ovaries; measurement of mid-luteal progesterone to assess ovulation; and measurement of anti-Müllerian hormone, follicle-stimulating hormone and/or the antral follicle count to assess ovarian reserve.

! HSG involves the insertion of a radio-opaque dye into the uterine cavity and X-ray. Although used for diagnosis, HSG can improve fertility outcomes in some women, although the mechanisms are unknown.



QUALITY OF LIFE

Subfertility is associated with emotional distress and reductions in quality of life compared with population norms and women with other gynaecological conditions. In addition, disorders causing subfertility and subfertility treatments can be painful, associated with stigma and emotionally demanding.



OUTLOOK

Priorities for future research include addressing the preventable causes of subfertility, providing support and alternatives for

individuals with subfertility and encouraging new initiatives to increase the global accessibility, affordability and acceptability of

assisted reproductive technology, along with efforts to improve established assisted reproductive technology techniques.

EPIDEMIOLOGY

Between 48.5 and 72.4 million couples have subfertility globally. Of these, ~10 million are in sub-Saharan Africa and ~14 million in south Asia. Risk factors for female subfertility include older age, smoking and excess alcohol consumption and caffeine use, overweight, unprotected sexual intercourse with multiple partners, stress and exposure to some pesticides.