

CLINICAL FOCUS

Your guide to key clinical issues in primary care

Subfertility part 1

Overall key points

- Approximately one in seven couples in the UK is affected by infertility.
- Causes can be categorised as problems of the oocytes, Fallopian tubes or sperm.
- A history from both partners will inform what investigations should be done and their priority.
- Apart from rubella testing in women, semen analysis is usually the first investigation to be done.
- Fallopian tube patency can be determined by ultrasound, X-ray or laparoscopy.

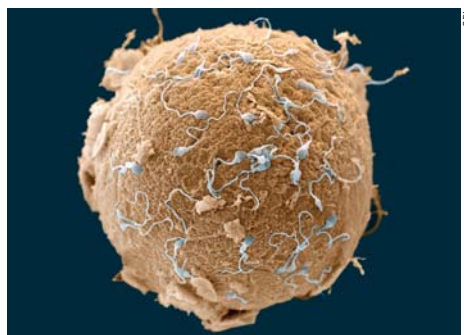
Part 1 What is subfertility?

At its most fundamental level, conception and successful pregnancy only requires four things: a good quality egg (oocyte), good quality sperm, the ability for them to meet, and a suitable environment for the embryo to implant and grow to maturity.

There is no clear-cut definition of 'subfertility' but it is generally taken as being a lack of conception after one to two years of frequent, unprotected sexual intercourse. Hence, subfertility can be due to problems of the egg, sperm, the Fallopian tubes, the endometrium or a combination of these.

Approximately one in seven couples in the UK is affected by infertility, which may be primary (couples who have never conceived before) or secondary (couples who have previously conceived). It is estimated that the proportion of affected couples is likely to increase.

NHS funding for investigation is generally



Conception needs good quality egg and sperm

available, but there is widespread variation and often limited access to funding for treatment such as IVF. In the UK, fertility treatment that involves the handling of embryos or donated gametes is regulated by the Human Fertilisation and Embryology Authority.

Couples will generally have been trying to

Conception

- Successful conception requires:
 - A good quality egg.
 - Good quality sperm.
 - The ability for sperm and egg to meet.
 - A suitable environment for the embryo to implant and grow to maturity.
- Subfertility can be due to problems of the egg, sperm, Fallopian tubes, endometrium or a combination of these.

conceive for at least 12 to 18 months before they approach their clinician. It is difficult to be prescriptive about when to refer, but we believe that because female fertility declines appreciably as a woman ages, after 35 years old they should be referred as soon as they have raised the issue.

Part 2 Causes of subfertility

Causes of subfertility can be categorised as oocyte problems (quality of oocytes or frequency of ovulation), sperm problems (oligospermia/azoospermia) and tubal causes. Treatment can then be directed depending on the identified cause.

Tubal disease will reduce the chance of an egg and sperm meeting and will also increase the risk of the embryo implanting in the Fallopian tube, resulting in ectopic pregnancy. Obesity, smoking, alcohol, drugs and occupation may also impact on a couple's fertility.

The main reasons why the prevalence of fertility problems is rising in the UK are that increasingly, women are attempting to start a family in their mid- to late-30s, and sperm quality is possibly declining.

More and more women are delaying starting a family in order to develop their careers but unfortunately there is a biological price to pay, because female fertility declines with age.



Tubal disease raises risk of ectopic pregnancy

Oocyte quality is reduced (so that eggs do not fertilise as readily), embryo quality is poorer (so that implantation is less likely to occur), and the incidence of chromosomal abnormalities is increased (resulting in an increase in miscarriage rates).¹

Additionally, in the developed world, sperm quality is also possibly declining

Common causes

- Lifestyle: including alcohol and smoking.
- Ovulatory: PCOS; obesity; severe underweight; physical/psychological stress.
- Fallopian tube: past infection; previous pelvic surgery; Fallopian tube adhesions.
- Endometriosis: may affect sperm function, oocyte quality or Fallopian tube function.
- Sperm problems: see part 4.
- Psychosexual.

because of environmental pollutants, but this remains an area of heated debate.²

Subfertility may also be due to psychosexual problems, where a couple is unable to complete successful coitus. In some cases, the subfertility may remain unexplained, with no obvious cause being identified after thorough investigation.

Part 3 Investigating subfertility in women

A history taken from both partners will help inform what investigations should be undertaken and their priority. It provides an opportunity to advise on a healthy lifestyle, which improves the chances of conception.

Advice should include a reduction in alcohol consumption and smoking, and taking folic acid (400µg daily) to reduce the risk of spina bifida.³ If the woman is due a cervical smear then this can be taken as well. Rubella immunity status should be determined in all women, so that the non-immune can receive the vaccine before any fertility treatment is commenced.

A mid-luteal phase progesterone level (commonly day 21 of a 28 day menstrual cycle) is taken to determine evidence of ovulation (considered to have occurred if serum progesterone concentration is >20nmol/l).

Basal body temperature charts do not reliably predict ovulation and are therefore not recommended; serum prolactin, gonadotrophins and thyroid function tests should only be determined in women with relevant features such as an irregular menstrual cycle.

Fallopian tube patency can be determined by ultrasound, X-ray or laparoscopy. For the majority of couples, the woman will have no



Adhesions can be seen with laparoscopy

history suggesting pelvic disease, but tubal patency needs to be confirmed as part of the investigations. In these cases, Echovist hystero-contrast-salpingography (HyCoSy) can be performed (see box).

Laparoscopy and hydrotubation should be employed in women with a history of past pelvic infection or surgery as it allows direct inspection of pelvic organs. Under laparoscopic vision, a coloured dye is instilled through the cervix; tubal patency is confirmed by seeing the dye fill and spill from the fimbrial ends of the Fallopian tubes.

It allows diagnoses such as endometriosis

Ultrasound investigation

- Echovist HyCoSy involves an echo-reflective solution (Echovist) being instilled through the cervix.
- If Fallopian tubes are patent, the fluid is seen to flow along the tubes and spill into the peritoneal cavity.
- Echovist allows visualisation of ovaries (including ovarian cysts and endometriomata) without anaesthesia or irradiation.

and pelvic adhesions to be made; in some instances they can be treated simultaneously. However, laparoscopy involves general anaesthesia and can also, rarely, result in trauma to intra-abdominal organs, which can lead to peritonitis.

Alternatively, a hysterosalpingogram can be undertaken whereby radio-opaque contrast is injected through the cervix without the need for anaesthesia. The dye outlines the uterine cavity and is seen to spill from the Fallopian tubes. However, the technique irradiates the pelvis and ovaries cannot be visualised and so it has largely fallen out of use.

Part 4 Subfertility in men

Subfertility in men may be due to a variety of factors, including lifestyle (see box). Apart from rubella testing in females, semen analysis is usually the first investigation to be organised.

The WHO has drawn up reference values for semen analysis.⁴ According to these, the ejaculate should have a pH above 7.2 and a volume greater than 2ml. Sperm concentration should be more than 20 million/ml and the total sperm count above 40 million.

If the sperm count is markedly abnormal, this might prompt further investigation of the male partner, by determining his chromosomes and cystic fibrosis (CF) status as possible causes for the sperm abnormality. One in 20 people in the UK are carriers for an abnormal recessive gene for CF, the commonest genetic disease in the UK.

Azoospermia (no sperm in the ejaculate) can be due to testicular failure, vas deferens obstruction secondary to past infection or congenital absence of the vas deferens. This is most commonly due to occult CF and as such, it is important to screen these men for CF and

Male factors

Potential causes of male subfertility are:

- Lifestyle factors: including smoking; alcohol; obesity; stress.
- Idiopathic oligospermia.
- Vas deferens obstruction.
- Cystic fibrosis.
- Past testicular infection.
- Previous vasectomy
- Y-chromosome gene microdeletions.

offer genetic counselling as appropriate.

The WHO reference values state that more than three quarters of sperm in a sample should be alive, with more than 30 per cent having a normal morphology. They also grade sperm motility as 'A', rapid progressive motility; or 'B', slow or sluggish progressive motility. More than half of grade A and B sperm combined, or more than 25 per cent of grade A sperm alone in a sample should be motile within 60 minutes of ejaculation.⁴

Resources

- NICE. *Fertility: assessment and treatment for people with fertility problems*. London: NICE; 2004. Available from: www.nice.org.uk/pdf/CG011niceguideline.pdf
- Prodigy guidance on infertility: www.prodigy.nhs.uk/infertility
- British Fertility Society: www.britishfertilitysociety.org.uk
- Infertility Network UK: www.infertilitynetworkuk.com
- Women's Health Information: www.womens-health.co.uk/infertility.asp

References

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2. Waddell WJ. Epidemiological studies and effects of environmental estrogens. *Int J Toxicol* 1998;17(2):173-91.
3. Detrait ER, et al. Human neural tube defects: developmental biology, epidemiology, and genetics. *Neurotoxicol Teratol* 2005;27(3):515-24.
4. WHO. *Laboratory manual for the examination of human semen and semen-cervical mucus interaction*. Cambridge: Cambridge University Press; 1992.

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