Management of infertility

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Delay in childbearing and the adverse effect of increasing age on women's fertility have increased referrals for fertility investigations and treatment. In the past 25 years the percentage of births to women age 30 and over in England and Wales has doubled (see fig A on bmj.com).[1 2] One in six couples require referral for investigation or treatment for subfertility.[3] Couples are more aware of what can be done from media attention. Unfortunately, this often leads to falsely high expectations of fertility treatments. Natural human fertility is low compared with most other species. Peak human fertility (the chance of pregnancy per menstrual cycle in the most fertile couples) is no higher than 33%, and it is unrealistic to expect a higher chance of pregnancy than this from any fertility treatment. This review of the management of infertility, or more correctly subfertility, focuses on investigations (including over the counter fertility tests) and appropriate actions and treatments in response to test results.

Summary points

- Natural human fertility is low, and most couples have falsely high hopes of fertility treatments
- The major causes of subfertility are sperm dysfunction, ovulation disorder, and fallopian tube damage
- Most investigations to establish a cause of subfertility are simple to undertake
- For most couples, history and examination will not indicate a cause, and full subfertility investigations will be needed
- Couples with sperm dysfunction or likely tubal damage should be referred early for specialist opinion
- Ovulation disorders often respond to simple treatments that can be safely initiated in primary care

Methods

This article is based on 20 years' combined experience of running tertiary infertility clinics, together with the resources and regularly updated literature searches we have used over the past 14 years in preparation for annual postgraduate study days for primary care doctors.

What can a couple expect when trying to conceive?

Within a year of regular intercourse, 90% of fertile couples should become pregnant. After two years, this rises to 95%. Thus, 5-10% of normal fertile couples take more than a year or two to conceive. Some couples therefore present with a delay in conceiving purely by chance, having low normal fertility rather than subfertility. The usual criterion to define subfertility, and initiate investigations, is a delay of more than one year. Investigations should establish a diagnosis promptly and identify couples likely to need referral for specialist treatment.

Causes of subfertility

The main causes of subfertility are sperm dysfunction, ovulation disorder, and fallopian tube damage (table 1). Sperm dysfunction (in motility, normality, survival, or mucus penetration) is likely to impair fertilisation chances. Complete absence of sperm in the man's ejaculate, due to blockage or failure of production, is rare (2% of cases referred to specialist fertility clinics). Women who are not ovulating may have variable cycle lengths, oligomenorrhoea, or amenorrhoea. Polycystic ovary syndrome is present in 90% of women with oligomenorrhoea and 30% of women with amenorrhoea.[4] Fallopian tube blockage or damage (most commonly due to chlamydia infection) and adhesions involving the tubes or ovaries (due to surgery or endometriosis) occur in about 20% of women referred to fertility clinics. Many of the investigations to identify these common causes of subfertility are simple to undertake.

Endometriosis and cervical mucus disorders are infrequent causes of subfertility. Minor endometriosis, without structural damage or adhesions, may not even be a cause of subfertility but simply a development in women who delay conceiving, either voluntarily or involuntarily.

About 15% of couples will have more than one cause for their subfertility.[3 5 6] It is therefore important to make complete investigations from the outset rather than focusing treatment on the first cause identified. In about 25% of couples no definite cause will be found, even after complete investigation. These couples are said to have unexplained subfertility.

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Other factors affecting fertility

Increasing age reduces a woman's fertility and the likelihood of successful treatment.[7 8] Even in younger women, a depleted ovarian reserve will reduce natural fertility and can be predicted by a raised serum concentration of follicle stimulating hormone (table 2). Women with a raised hormone concentration also have a poor prognosis for assisted conception.[9] Extremes of weight loss or obesity reduce female fertility: even moderate obesity (a body mass index of 25-30) reduces the chances of conception with most fertility treatments[10] and increases the risk of miscarriage (see fig B on bmj.com).[11 12] Smoking, particularly by women, reduces fertility,[13] as does a longer duration of subfertility, particularly more than 3 years.[6 14] A previous full term pregnancy is associated with a better chance of conception, either naturally[6 14] or after treatment.[15] These factors can be combined to calculate the likelihood of natural conception without treatment for any couple.

History and examination

Couples with a fertility problem should ideally be seen together from the outset, and a full medical history taken from both partners (see box 1). A family history is particularly helpful from the woman, as it might suggest a genetic predisposition to polycystic ovary syndrome (see box A on bmj.com). Examination of the woman should include measurement of body mass index, assessment for any signs of endocrine disorder, particularly polycystic ovary syndrome (see box B on bmj.com), and a pelvic examination. Examination of the man is not usually necessary unless indicated by his medical history (such as previous orchidopexy, inguinal hernia repair, or testicular torsion) or if his initial semen analysis result is abnormal. In most couples the initial history and examination will give no indication of the cause of their subfertility, and full investigations will be needed.

Investigations

These can be divided into general investigations (justifiable for any couple desiring a pregnancy) and specific investigations to establish a particular cause (table 2). It is generally advisable to undertake full initial investigations for all couples because 15% are likely to have more than one abnormality.

Sperm dysfunction

Seminal analysis is the primary investigation for men despite it being a poor predictor of sperm function and male fertility. One poor analysis result is insufficient for making a diagnosis of sperm disorder. If the first result shows a low sperm count or complete absence of sperm, it should be repeated, preferably two to three months later because of the long development cycle for sperm, which can be influenced by various factors (such as a fever). Table 2 shows the latest World Health Organization criteria for normal semen analysis.[16] The use of the postcoital test is controversial: although some clinicians believe it is of little diagnostic value, sperm behaviour at postcoital testing is closely related to the likelihood of natural conception in couples with subfertility of under three years' duration[17] and the chance of fertilisation with in vitro fertilisation.[18]

Table 1 The causes of infertility and their approximate frequency (adapted from Hull et al 1985[3])

Cause	Frequency (%)
Sperm defects or dysfunction	30
Ovulation failure (amenorrhoea or oligomenorrhoea)	25
Tubal infective damage	20
Unexplained infertility	25
Endometriosis (causing damage)	5
Coital failure or infrequency	5
Cervical mucus defects or dysfunction	3
Uterine abnormalities (such as fibroids or abnormalities of shape)	(<1)

Total exceeds 100% as 15% of couples have more than one cause of subfertility.

Ovulation disorder

Most of the initial investigations for ovulatory disorder must be undertaken at specific stages of the menstrual cycle. For women with irregular length cycles, their luteal phase progesterone concentration may be best measured at five day intervals from seven days before the earliest expected date of menstruation until the time they begin their next period. This ensures that a valid assessment of ovulation is obtained promptly by retrospective review of the appropriate sample (5-10 days before menstruation). Levels of follicle stimulating hormone and luteinising hormone should be measured between days two and five in women who have periods, or at random if cycles are infrequent or absent.

Measurement of thyroid stimulating hormone is important although it is rarely abnormal, especially in women with regular cycles. However, frank or compensated hypothyroidism is readily treated and, if missed, is associated with an increased risk of miscarriage and

Box 1: Medical history of a subfertile couple

Woman

- Previous contraception and any problems (such as "lost" intrauterine contraceptive device)
- Previous pregnancies and outcome
- Medical history (such as pelvic infection, Crohn's disease)
- Surgical history (such as ovarian cyst, appendicectomy)
- Gynaecological history (such as cone biopsy, cervical smear history)
- Current medical illness
- Drug treatments; prescribed and "recreational"
- Diet
- Smoking, alcohol consumption, excessive caffeine intake
- Galactorrhoea
- Hirsutism (may be disguised)
- Menstrual regularity and menorrhagia
- Dysmenorrhoea
- Intermenstrual or postcoital bleeding
- Preovulatory cervical mucus recognition
- Coital frequency and timing

Man

- Occupation (exposure to excessive heat or toxin, such as cellulose thinners)
- Medical history (such as mumps, venereal infections)
- Surgical history (such as orchidopexy, inguinal hernia repair)
- Current medical illness
- Prescribed drug treatments (such as sulfasalazine)
- Drug misuse (such as anabolic steroids)
- Smoking, alcohol consumption, excessive caffeine intake
- Erectile or ejaculatory difficulty

Table 2 Investigations for subfertility in primary or secondary care

Investigation	Purpose	Appropriate action if abnormal
General infertility investigations		
Rubella serology	Ensures rubella immunity (risk to fetus if mother not immune)	Rubella vaccination if not immune and recheck immunity after 1 month
Full blood count, possibly plus ferritin	Ensures adequate reserve for pregnancy and exclude anaemia	Investigate unless clearly related to menorrhagia. Give iron if deficient
Hepatitis B and C and HIV serology	Checks for patient welfare, and that of unborn child (a stipulation of HFEA for couples undergoing assisted conception)	Refer to gastroenterologist if seropositive for hepatitis and to virologist if HIV positive (many fertility clinics will not treat couples if either partner positive for hepatitis or HIV)
For sperm dysfunction		
Semen analysis	Checks sperm production Normal values: volume >2.5 ml, sperm count >20 million/ml, >50% motile, >15% normal Calculate result as motile normal sperm concentration (count× (% motile)×(% normal)/ml): normal value >1 million/ml	Low volume: check sample complete or possible retrograde ejaculation Azoospermia: repeat sample; testicular examination for reduced size, consistency, and presence of vas deferens; check FSH and karyotype and (if possible absence of vas) test for cystic fibrosis Oligospermia (<10 million/ml): check karyotype; early specialist referral if repeat sample abnormal
Postcoital test (generally not feasible in primary care)	Checks sperm, cervical mucus, and coital function Normal value: >1 motile progressing sperm per high power (×400) microscope field 8-18 hours after coitus	Negative test indicates likely sperm dysfunction only if clear, copious (>0.3 ml), and ductile (>10 cm) cervical mucus with pH>6.5 Non-motile sperm only: request test for sperm antibodies in seminal plasma or cervical mucus Early specialist referral if repeat test abnormal
For ovulatory disorder		
FSH (days 2-5 of menstrual cycle)	Assesses ovarian reserve If raised indicates (incipient) ovarian failure	Early specialist referral if raised (>10 IU/l) May still respond to exogenous gonadotrophin or IVF
LH (days 2-5 of cycle)	If raised (with normal FSH) suggests PCOS	PCOS is complex syndrome: clomifene for anovulation, metformin if impaired oocyte quality suspected; specialist referral if no response or after 6 months
Testosterone	Moderately raised level suggests PCOS	
Progesterone (5-10 days before menstruation)	Assesses ovulation. Low mid-luteal level (generally <30 nmol/l) suggests anovulation or ovulatory dysfunction	Specific treatment if identified cause (eg hyperprolactinaemia). For idiopathic anovulation, clomifene as first line treatment
SHBG	Low level suggests PCOS	Low SHBG often secondary to hyperinsulinaemia in PCOS Metformin treatment if irregular cycle
TSH	If raised suggests hypothyroidism	Check thyroid autoantibodies Referral to (reproductive) endocrinologist
Prolactin	Checks for hyperprolactinaemia: if marginally raised with regular cycle may suggest PCOS; if raised with amenorrhoea suggests prolactinoma	Exclude drug induced causes Referral to (reproductive) endocrinologist
For fallopian tube damage		
Chlamydia serology	Screens for tubal infective damage: normal ⩽1:128	If titre ⩾1:256 treat both partners with appropriate antibiotics (see text) Early referral to specialist clinic if raised
Ultrasound contrast salpingography	Assesses tubal patency	Appropriate antibiotic cover for procedures if positive chlamydia serology or chlamydia antigen
Hysterosalpingogram	Assesses uterine cavity, tubal patency, and tubal mucosal pattern	Early referral to specialist clinic
Laparoscopy and dye	Assesses tubal patency and ovarian morphology and mobility	Assessment of likelihood of pregnancy by tubal surgery or IVF

HFEA=Human Fertilisation and Embryology Authority, FSH=follicle stimulating hormone, LH=luteinising hormone, PCOS=polycystic ovary syndrome, SHBG=sex hormone binding globulin, TSH=thyroid stimulating hormone, IVF=in vitro fertilisation.

possible long term health consequences for any child.[19] Hyperprolactinaemia is rare in the absence of amenorrhoea. However, a moderately raised prolactin level is found in 8-10% of women with polycystic ovary syndrome and can be useful if there is uncertainty about this diagnosis. Sex hormone binding globulin would not routinely be investigated, but if there is uncertainty about a diagnosis of polycystic ovary syndrome, a low globulin concentration provides supportive evidence.

Fallopian tube damage

Chlamydia serology is the best initial screen for tubal disorder. A raised chlamydia antibody titre (>1:256) is associated with a high likelihood of tubal damage.[20] High antibody titres may indicate current or previous tubal infection, and both partners should be treated with an appropriate antibiotic (such as oxytetracycline, erythromycin, azithromycin, or ofloxacin). Treatment does not correct tubal damage but prevents reactivation if laparoscopy or other pelvic surgery is indicated.

New over the counter diagnostic techniques

Fertility tests that are available over the counter have aroused much interest recently. In addition, contraceptive kits such as Persona (Unipath, Bedford) predict mid-cycle fertility and can also be used to optimise the chance of conception. Med-Direct (www.Med-Direct.com) sells products that can predict ovulation, store temperature chart data from cycle to cycle, or test a sperm sample against a given sperm density. Not yet available is Fertell (Genosis, London), which combines a test for men (of sperm function) and for women (of ovarian reserve).

The value of these new tests has yet to be established. Controlled trials are needed to assess whether they improve the chance of conception or assist in directing a couple to seek advice. While these tests may be accurate, it does not necessarily follow that their use improves the likelihood of conception. Previous work has shown no difference in pregnancy rates following donor insemination whether insemination was timed using a kit to predict levels of luteinising hormone predictor kit or timed by the woman's pre-ovulatory surge in cervical mucus production.[21] Showing clear evidence of benefit is important because couples experiencing a delay in conception are vulnerable and will often try anything that they believe might increase their chance of pregnancy.

Management options

Sperm dysfunction

Couples in which the man has sperm dysfunction need early referral for in vitro fertilisation, usually with intracytoplasmic sperm injection, the direct injection of a

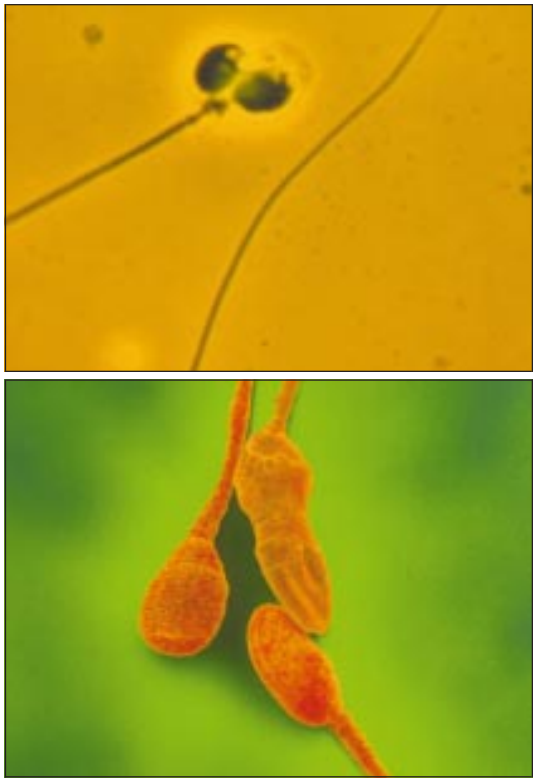

Fig 1 Deformed sperm. Light micrograph showing a spermatozoon with two heads (top). Coloured scanning electron micrograph showing a "hockey stick" spermatozoon with abnormal residual cytoplasm and two healthy sperm (bottom). While all men have some deformed sperm, large numbers may cause male infertility

single sperm into each egg. Where such treatment is not available donor insemination is a possibility.

Ovulation disorder

Treatment for disorders of ovulation depend on the underlying cause. Polycystic ovary syndrome accounts for most cases of oligomenorrhoea and about a third of those of amenorrhoea. History, examination, and first line investigations usually establish the diagnosis. Although a transvaginal ultrasound scan provides supportive evidence, the diagnosis should not be made solely by ultrasound scan as a polycystic ovarian appearance has been reported in 10-20% of the normal female population.[22 23]

In primary care more can be done for ovulatory dysfunction than for other causes of subfertility. Simple treatments to induce ovulation include clomifene citrate and, for women with hyperprolactinaemia, bromocriptine. Clomifene citrate (usually given on days 2-6 of the cycle) acts mainly by blocking oestrogen receptors in the pituitary. This promotes the release of additional follicle stimulating hormone and luteinising hormone to stimulate follicular development. The starting daily dose should not exceed 50 mg, and probably never 100 mg daily except in very obese women. Mid-luteal serum progesterone measurements can be used to check for an ovulatory response. Some clinicians consider that follicle numbers should also be monitored by ultrasound scans, but there is no evidence that this reduces the risk of multiple pregnancy (mainly twins) with clomifene, which is about 8%. Because of a possible association with later borderline ovarian tumours,[24] clomifene should not be prescribed in nulliparous women for more than 12 months.

Dopamine agonists such as bromocriptine and cabergoline are safe and effective treatments for hyperprolactinaemia. However, the diagnosis and monitoring of women with presumed hyperprolactinaemia can be sufficiently complicated to warrant specialist referral. It is worth considering pharmacological causes for hyperprolactinaemia—such as dopamine antagonists, some antihypertensives, and major tranquillisers—before referral. It is unlikely that dopamine agonist treatment will overcome iatrogenic cause of raised prolactin levels.

Recently, there has been interest in the use of metformin to treat polycystic ovary syndrome. It has been shown to increase levels of sex hormone binding globulin, thought to be a secondary response of reducing hyperinsulinaemia[25] and thus reducing free testosterone levels in circulation. It also reduces luteinising hormone concentrations and ovarian sensitivity to luteinising hormone. Over 90% of women with oligomenorrhoea or amenorrhoea are reported to return to normal cycles with treatment, with 20% conceiving within six months.[26]

The starting dose of metformin is 500 mg daily. At this dose many women get more regular ovulatory cycles. If not the dose may be increased to 500 mg twice daily for a minimum of three months. If cycles become regular, it is worth continuing for six months at this dose. If a woman's cycle remains irregular the dose can be increased to 500 mg three times daily or 850 mg twice daily. Serum progesterone measurements, at five day intervals from day 21 will indicate whether normal ovulation is occurring. Ovulation should be expected in about 30-40% of women with metformin treatment alone. Women still without periods or ovulatory progesterone levels can be given additional clomifene as described above. The combination of metformin and clomifene induces ovulation in about 90% of women with polycystic ovary syndrome.[26] Side effects of metformin include mild nausea, diarrhoea, and abdominal bloating. These are minimised by the gradual increase in dose and are almost always transient. Metformin should be stopped when a woman has a positive pregnancy test, although no teratogenic effects have been reported from it being taken in early pregnancy.

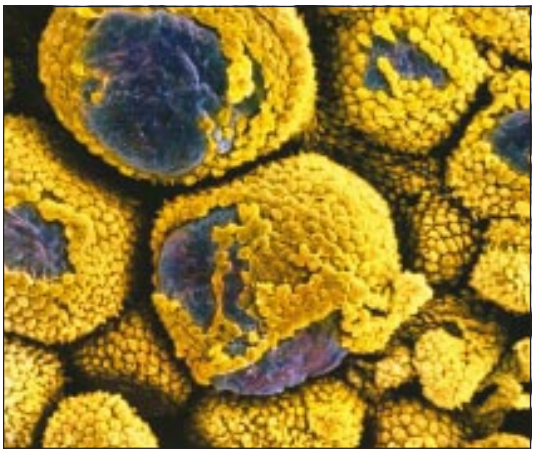

Fig 2 False colour scanning electron micrograph of a polycystic ovary, showing several cystic follicles bulging from the wall of an ovary

Box 2: Indications for early referral to a specialist fertility clinic

- Woman's age >38 years
- Duration of infertility >3 years
- Serum chlamydia antibody titre >1:256
- Follicle stimulating hormone concentration in early follicular phase >10 IU/l
- Luteinising hormone concentration in early follicular phase >10 IU/l
- Abnormal seminal fluid analysis:
Sperm count $<20\times10^6$/ml
Sperm motility <50% motile, <25% progressively motile
Sperm appearance <15% normal

The best treatment for infertile women with endometriosis is a matter of debate. When the principal symptom is pain, ovulation suppressing agents are useful. Although women with endometriosis may have a reduced chance of conceiving, current evidence shows that no medical treatment (to suppress ovulation) improves fertility. Clomifene has been advocated to optimise fertility, but it is probably best prescribed for women whose duration of subfertility is less than three years. For the remainder, in vitro fertilisation is probably the most effective treatment to achieve a pregnancy, and early referral to a specialist clinic is advised.

Fallopian tube damage

When positive chlamydia serology or hysterosalpingography suggest fallopian tube damage, appropriate antibiotic treatment for chlamydia followed by early referral for specialist opinion is indicated.

Objectives of management

These include diagnosing any definitive cause of subfertility; giving a realistic prognosis (with and without treatment); providing information, support, and counselling (to cope with the stress of treatment and possible failure); advising about treatment appropriate to the couple's needs (by duration, age, wishes) and valid alternatives (including non-intervention), and arranging prompt referral for couples who need specialist help (see box 2).

Additional educational resources

Professional information resources

- Balen A, Jacobs H. *Infertility in practice*. Edinburgh: Churchill Livingstone, 1997
- Centre for Reproductive Medicine, Bristol (www.repromed.org.uk)

Patient information resources

- Harris C, Carey A. *PCOS: A woman's guide to dealing with polycystic ovary syndrome*. London: Thorsons, 2000
- Cahill DJ, Wardle PG. *Understanding infertility*. Banbury: Family Doctor Publications, BMA, 2000
- Chambers R. *Fertility problems; a simple guide*. Oxford: Radcliffe Medical Press, 1999
- CHILD, the National Infertility Support Network (www.child.org.uk)
- Verity, the Polycystic Ovaries Self Help Group (www.verity-pcos.org.uk)
- NetDoctor (www.netdoctor.co.uk), a useful site containing articles written by specialists for patients (particularly www.netdoctor.co.uk/womenshealth/fertility/index.shtml)
- IVF-infertility.co.uk (www.ivf-infertility.co.uk), designed by infertility specialists primarily for couples who are experiencing difficulty in having a child and think that they might need medical help
- ReproMed, fertility calculator (www.repromed.co.uk/Fertility/Prognosis/prognosis.html), shows you how to calculate your likelihood of conception

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