The subfertile couple

A guide to investigations

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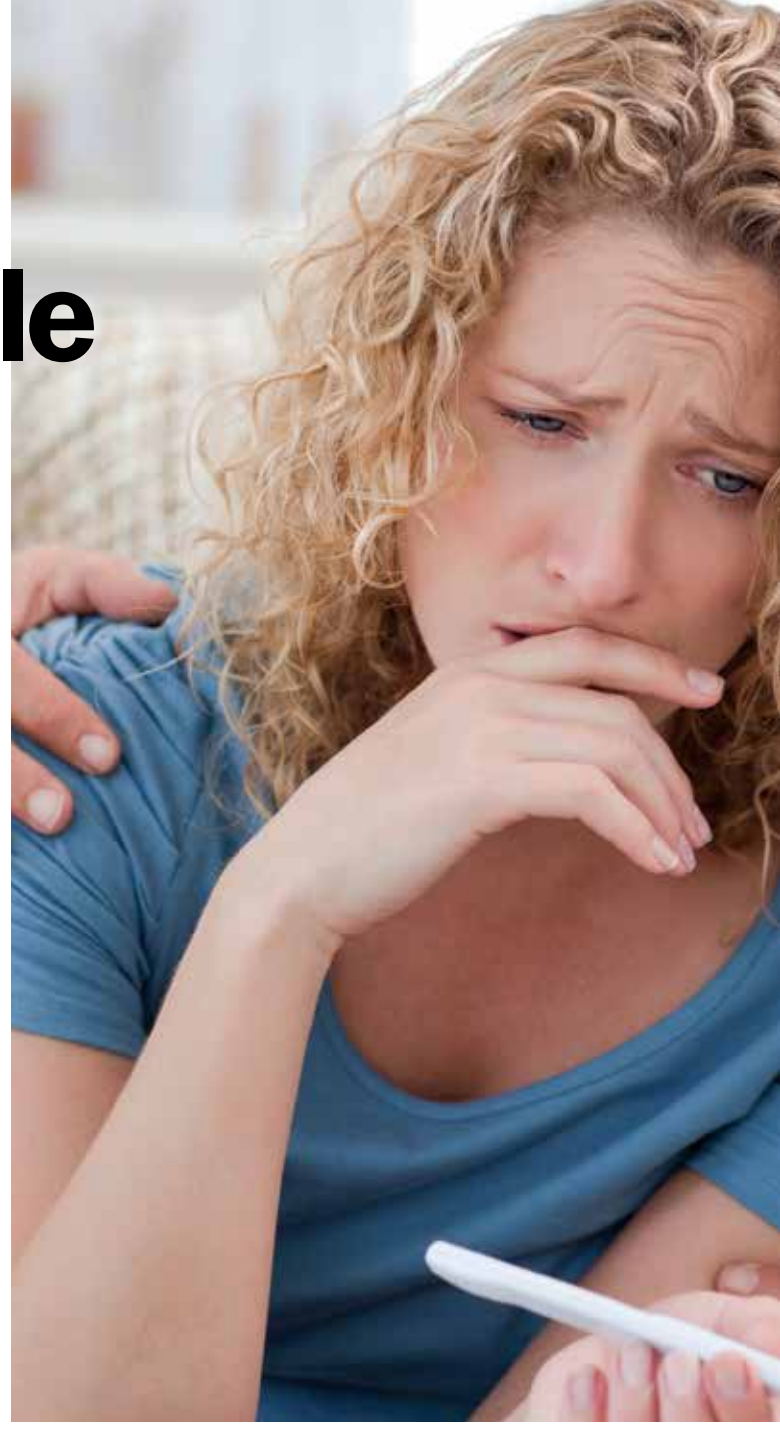
A delay in identifying and treating many subfertile couples is associated with poorer outcomes because of a reproductive decline with increasing female age and prolongation of the associated psychological stress. Early investigation of both partners in general practice is therefore important to expedite the diagnosis and facilitate specialist review for tailored treatment.



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Delay in childbearing is a progressively common reason for specialist referral to a fertility clinic. There is a highly significant effect of increased female age on the chance both to conceive and to carry a pregnancy to full term. This results in a heightened need to expedite fertility investigations and treatment in couples who have intentionally delayed childbearing.

It is reported that 84% of couples will conceive within 12 months of regular intercourse and no contraception.[1] Consequently, about one in six couples have difficulty achieving a pregnancy after 12 months and may wish to seek fertility advice. Clinicians need to be up to date with advances in assisted reproduction therapy to optimise a couple's chance of success in conception.

Although fertility treatment requires subspecialist expertise, preliminary workup in general practice is invaluable. Medical consultation is often delayed and only sought after exhaustion of nonproven treatments following advice from well-meaning friends, social media or alternative practitioners. The GP has an important role to ensure appropriate investigation of both partners is commenced as soon as patients seek advice, to help promptly identify the cause of their subfertility and to direct them if necessary for specialist review. This will minimise the lost opportunity to conceive caused by giving priority to inappropriate and alternative therapies.

Initial assessment

Investigation of the subfertile couple requires a thorough clinical history. The duration of infertility is a good indicator of the possible need for medical intervention. General health is important for conception and conditions including extremes of weight (obesity or

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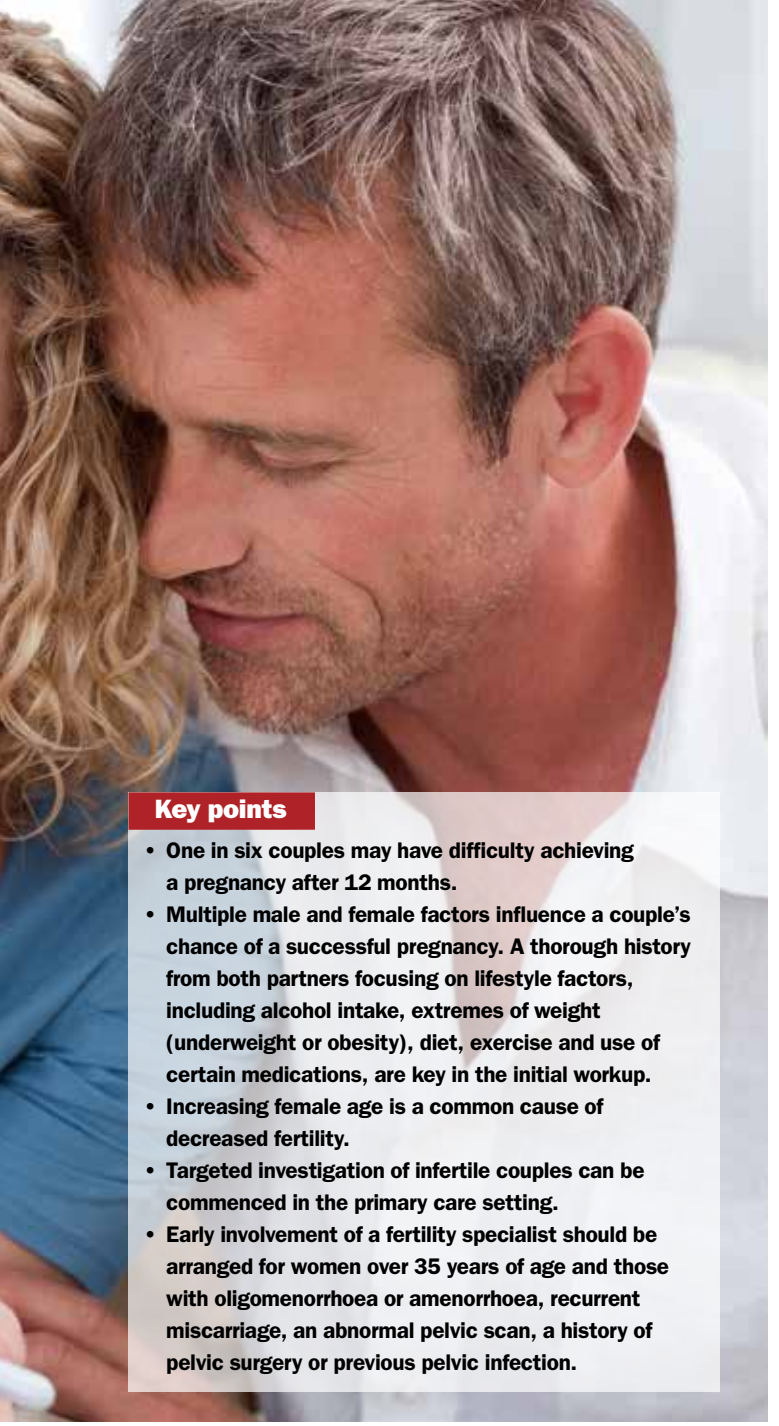

Key points

- **One in six couples may have difficulty achieving a pregnancy after 12 months.**
- **Multiple male and female factors influence a couple's chance of a successful pregnancy. A thorough history from both partners focusing on lifestyle factors, including alcohol intake, extremes of weight (underweight or obesity), diet, exercise and use of certain medications, are key in the initial workup.**
- **Increasing female age is a common cause of decreased fertility.**
- **Targeted investigation of infertile couples can be commenced in the primary care setting.**
- **Early involvement of a fertility specialist should be arranged for women over 35 years of age and those with oligomenorrhoea or amenorrhoea, recurrent miscarriage, an abnormal pelvic scan, a history of pelvic surgery or previous pelvic infection.**

underweight), diabetes, hypertension and inflammatory or autoimmune disease can contribute to sexual dysfunction and either poor gamete quality or impaired endometrial receptivity. Lifestyle choices including alcohol intake, smoking and use of recreational or body building drugs can be detrimental.[1] Similarly, stress, recent changes in weight, use of certain medications (e.g. category D drugs, sulfasalazine, drugs associated with elevated prolactin levels, long-term use of anti-inflammatory drugs and previous chemotherapy), diet and exercise habits can all influence fertility outcomes.[1-3]

Subfertility is determined by the length of time a couple have been attempting conception, as well as the frequency and timing of intercourse. The definition of infertility is formally applied to couples who have been unsuccessful in achieving pregnancy after 12 months. Investigation is advisable after six months in women aged over 35 years to minimise the delay in commencing effective treatment.[2]

Couples should be encouraged to have intercourse approximately every two days in the week before the expected time of ovulation. Any problems with intercourse need to be assessed. The clinician should also ascertain a history of previous pregnancy from each partner as this may help diagnose male or female fertility impairment or a combination of both. Contraceptive history, its type, duration of use and reason for discontinuation may also provide a clue to some underlying pathology (e.g. occasional pelvic infection associated with use of an intrauterine device). Use of intramuscular depot progesterone preparations may be associated with a delay to the return of regular ovulation in some women.[4]

Further history taking can be divided into male and female factors and then classified into hormonal, functional and structural details.

Female factors

Female factors account for more than a third of cases of infertility in couples.[2] Issues can be grouped into the following: ovulatory dysfunction; endometrial functional abnormalities; uterine and tubal abnormalities; and peritoneal factors (Box 1).

Ovulatory dysfunction

Lack of regular ovulation accounts for 25 to 50% of cases of female infertility and hence assessment of ovulatory function is integral in the diagnostic workup.[2,3] In most cases, regular menstrual cycles between 26 and 34 days, with appropriate variation in cervical mucus (thin at mid cycle and thicker in the luteal phase) suggest ovulation is occurring.[5] In women with regular cycles, the time of ovulation may be accurately identified by the use of home ovulation urine tests. These test kits are less useful in women with oligomenorrhoea associated with polycystic ovary syndrome (PCOS) because of persistently high luteinising hormone (LH) levels giving multiple weak false-positive results. Documentation of a mid-luteal phase progesterone level greater than 30 nmol/L is a strong indicator of ovulation.[3] The timing of this test is usually day 21 for women with 28-day cycles. In women with longer cycles, progesterone levels should be checked seven days before expected menses.[3,6] A normal follicular phase progesterone level is less than 5 nmol/L. A normal luteal progesterone level is above 15 nmol/L, and a level between 5 and 15 nmol/L either reflects poor timing of the test or poor function of the corpus luteum.

Amenorrhoea is associated with anovulation and is described as primary (never had spontaneous menses) or secondary (more than six months of no menses), established by clinical history and examination.

Suspected ovulatory dysfunction requires biochemical and sonographic evaluation (see case 1, Box 2).[7] Measurement of follicle-stimulating hormone (FSH), LH and oestradiol levels helps to identify ovulation disorders caused by primary hypothalamic–pituitary disease (hypogonadotrophic hypogonadism), primary ovarian disease (hypergonadotrophic hypogonadism) and other disorders of ovarian function with normal gonadotrophin levels

1. Female causes of subfertility

Ovulatory dysfunction

- Hypogonadotrophic hypogonadism (low oestradiol, low or inappropriately normal LH and FSH levels)
  - pituitary or hypothalamic tumours
  - suppression of the hypothalamic–pituitary axis (e.g. stress, malnutrition, chronic illness, extreme exercise, eating disorders)
  - hyperprolactinaemia
  - use of opiates, marijuana
- Hypergonadotrophic hypogonadism (high LH and FSH, low oestradiol levels)
  - premature ovarian failure, secondary to chemotherapy or radiotherapy, ovarian surgery, autoimmune disease, genetic disorders (Turner's syndrome, fragile X) or family history
- Eugonadotrophic ovulatory dysfunction (normal LH, FSH and oestradiol levels)
  - polycystic ovary syndrome, adrenal disease, thyroid dysfunction

Endometrial functional abnormalities

- Implantation abnormalities related to coagulation disorders or immunopathology (e.g. systemic lupus erythematosus, antiphospholipid syndrome)

Uterine and tubal abnormalities

- Tubal dysfunction (e.g. tubal ligation, obstruction, hydrosalpinx)
- Fibroids, endometrial polyps, uterine septum and other Mullerian tract abnormalities, adenomyosis, Asherman's syndrome

Peritoneal pathology

- Pelvic environment (e.g. endometriosis, adhesions, inflammatory bowel disease, appendicitis)

Abbreviations: FSH = follicle-stimulating hormone; LH = luteinising hormone.

(eugonadotrophic ovulatory disorders).[8] Most women with an ovulation disorder will be eugonadotrophic and have polycystic ovaries and clinical signs of androgen excess such as acne and hirsutism. These are features of PCOS, which is diagnosed when at least two of the three cardinal features (oligomenorrhoea or amenorrhoea, clinical or biochemical androgen excess and polycystic ovaries confirmed on ultrasound) are present and other causes, particularly adrenal disease (e.g. congenital adrenal hyperplasia, Cushing's disease and adrenal tumours) have been excluded.

For each of these broad categories – hypogonadotrophic hypogonadism, hypergonadotrophic hypogonadism and eugonadotrophic dysfunction – additional serum hormone measurements are needed to help define the cause of the ovulation disorder. These include testosterone and sex-hormone binding globulin levels and free androgen index, particularly in women with normal FSH, LH and oestradiol levels who may have clinical signs of androgen excess. A 17-OH progesterone level should also be checked to help identify congenital adrenal hyperplasia as a rare cause of eugonadotrophic ovulatory dysfunction.

Oligomenorrhoea or amenorrhoea may also be caused by other endocrine diseases, including thyroid dysfunction and hyperprolactinaemia.[8] High levels of prolactin can disrupt pituitary FSH and LH production, thus reducing ovarian oestrogen production. Similarly, thyroid dysfunction may elevate prolactin levels, alter sex-hormone binding proteins and/or directly impact ovarian function.[2,8]

Measurement of the serum level of anti-Mullerian hormone (AMH) is also useful in the assessment of women with ovulation disorders. AMH is produced by small growing ovarian follicles. The number of these follicles decreases with increasing female age and hence the AMH level is a good indicator of remaining ovarian function.[9] The AMH level does not fluctuate significantly during a menstrual cycle and therefore a measurement at any time is a more accurate indication of ovarian function than a serum FSH level measured between days two and six of the cycle. AMH levels also correlate with an ultrasonographically defined ovarian antral follicle count. Very low levels of AMH in women of childbearing age indicate premature ovarian insufficiency whereas elevated levels are associated with PCOS and hypothalamic dysfunction.[9] This interpretation only applies to women over 25 years of age because AMH is very low prepuberty, rises after puberty and reaches maximum levels in the mid-20s.[9] AMH levels can be mildly reduced in women taking long-term oral contraceptives and during pregnancy.[9]

Hypothalamic amenorrhoea is a common cause of subfertility and may be implicated in elite athletes, women who exercise excessively and those with a low body weight, including women with eating disorders.[2] Stress-induced hypothalamic amenorrhoea may arise following significant emotional or psychological trauma.[2] Circadian rhythm disturbances may be an issue in women who have varied sleep cycles such as shift workers and those who work in aviation. A thorough history will help in identifying these issues.

Transvaginal high-resolution ultrasound examination in the early to mid-follicular phase of the menstrual cycle is used to count the number of small follicles in both ovaries (the 'antral follicle count'). This information is often not reported in routine pelvic ultrasound scans because of low resolution scanning or an inexperienced operator. It allows assessment of ovarian reserve and identification of other ovarian pathology, as well as uterine structural abnormalities (see below). A low antral follicle count suggests reduced ovarian reserve and a high antral follicle count indicates PCOS or hypogonadotrophic hypogonadism. In a patient with oligomenorrhoea or amenorrhoea in whom cycle length is indeterminable, the scan can be carried out at any stage but measurement of serum LH, oestradiol and progesterone levels may be needed to indicate cycle stage and help with interpretation. The presence of a single dominant follicle of more than 17 mm can indicate a preovulatory state.

Endometrial functional abnormalities

Abnormal implantation or implantation failure may be a cause of recurrent miscarriage or infertility in women with an autoimmune, thrombophilic or inflammatory condition, including systemic lupus

2. Case scenarios

Case 1. Investigation of subfertility in a woman with oligomenorrhoea and possible androgen excess

A 32-year-old woman and 36-year-old man present in general practice with 18 months of primary infertility. Her menstrual history includes oligomenorrhoea with cycles ranging from 28 to 60 days. A semen analysis is normal. The couple deny any issues with intercourse and have been attempting to conceive regularly (two to three times per week).

What other information would you like to know?

The woman's menstrual history includes menarche at the age of 13 years with oligomenorrhoea since then. Menses last for five to six days every 28 to 60 days without any associated dysmenorrhoea. She has poor knowledge of her fertile time. During her teenage years she suffered with acne and was treated by a dermatologist. She finds it difficult to lose weight, despite regular exercise. Her mother was diagnosed with type 2 diabetes in her 40s.

What examination would you perform?

The woman's height is 162 cm and she weighs 74.5 kg, with a body mass index (BMI) of 28.4 kg/m^2. Her blood pressure is 125/70 mmHg. She has mild facial scarring consistent with the history of previous acne. Abdominal examination is normal with no palpable masses. She has evidence of excess facial hair around the upper lip and chin. There is no acanthosis nigricans. Thyroid examination is normal with no evidence of goitre. There are no genital abnormalities and no evidence of galactorrhoea on breast examination.

What investigations would you order?

This woman's history is significant for oligomenorrhoea with examination findings of possible androgen excess. Preliminary blood tests including day 2 measurements of oestradiol, progesterone, follicle-stimulating hormone and luteinising hormone levels should be ordered. Testosterone levels, sex-hormone binding globulin levels and free androgen index are also important to measure. As this woman has features of hirsutism, 17-OH progesterone levels should be checked to exclude congenital adrenal hyperplasia. Endocrine causes of oligomenorrhoea including thyroid dysfunction and hyperprolactinaemia need to be excluded. Measurement of anti-Mullerian hormone level, although not essential, is helpful. The patient's results are presented in the Table on the next page.

What do the results show?

The results of the investigations show normal oestradiol and gonadotrophin levels. There is a mildly elevated testosterone level, low sex-hormone binding globulin level and a high free androgen index. The 17-OH progesterone level is normal; hence congenital adrenal hyperplasia is unlikely. Normal prolactin levels and thyroid function tests exclude hyperprolactinaemia and

Biochemical and clinical hyperandrogenism combined with oligomenorrhoea suggests polycystic ovary syndrome (PCOS). Transvaginal ultrasound may show a high antral follicle count and enlarged ovaries bilaterally although such findings may not be seen in all patients with PCOS. PCOS is diagnosed based on Rotterdam criteria (see Box below).[2] PCOS is the most common endocrinopathy in women, with one in 10 women affected. The diagnostic criteria should only be applied after exclusion of other disorders, including congenital adrenal hyperplasia (suggested by an elevated follicular phase 17-OH progesterone level) and androgen-secreting tumours (suggested by rapid androgenisation and significantly elevated testosterone levels e.g. more than 6 nmol/L). Women with Cushing's syndrome may also present with hirsutism, although this is usually accompanied by other features including rapid weight gain, thinning skin and violaceous abdominal striae. If these latter disorders are suspected, referral of the couple to a specialist is imperative.

How should this couple be managed?

This couple should be referred to a fertility specialist for consideration of ovulation induction therapy. Fertility, although reduced in women with oligomenorrhoea or amenorrhoea due to PCOS, is certainly possible with 75 to 80% of patients achieving ovulatory cycles with assistance. PCOS is associated with dyslipidaemia and insulin resistance, and hence measurement of fasting glucose, insulin and lipid levels may be warranted. Given this patient's family history of diabetes, an oral glucose tolerance test is important.

Most women (up to 90%) with PCOS and subfertility are overweight or obese and therefore diet and exercise should be tailored accordingly as optimisation of BMI can improve conception and pregnancy outcomes.[2]

Preconception counselling, including recommendation of folate and iodine supplementation, is necessary as per general guidelines.

Rotterdam criteria for diagnosis of polycystic ovary syndrome

Two of the following three features are required to diagnose polycystic ovary syndrome:

- oligo/anovulation
- hyperandrogenism
  - clinical (hirsutism or less commonly male pattern alopecia)
    or
  - biochemical (raised free androgen index or free testosterone)
- polycystic ovaries on ultrasound

Other causes must be excluded such as congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome, thyroid dysfunction and hyperprolactinaemia

2. Case scenarios continued

Case 2. Investigation of subfertility in a man with reduced libido and small testes

A 35-year-old woman and 36-year-old man present to their GP as they have been trying to conceive for 6 months. The woman has a 7-year-old daughter to a previous partner. She has regular menstrual cycles and no significant medical history. The man has never conceived a child and is a smoker.

What other information would you like to know?

The woman had no issues with conception of the first child. She has no past medical history, is of normal BMI, is a nonsmoker and drinks no alcohol. She denies any clinical features of androgen excess. Although the couple have been engaging in regular intercourse, the man admits to low libido and states he often has difficulty achieving an erection as a result. This is a long-standing problem.

What examination would you perform?

Both patients have normal blood pressure and BMI. The man is tall, with eunuchoid features and increased lower to upper body segment ratio. Examination reveals bilaterally small, firm testes (3 mL).

What investigations would you order?

The woman's history suggests no abnormality and given her previous successful pregnancy a female issue is less likely. However, ovulation should still be confirmed with a luteal phase progesterone measurement.

The man's history of reduced libido and clinical features including small testes are suggestive of testosterone deficiency. Hormones including luteinising hormone, follicle-stimulating hormone and free and total testosterone levels should be measured, and a semen analysis should be performed (see Table on this page).

What do the results show?

The woman's investigation results are normal. The man's results show hypergonadotrophic hypogonadism and azoospermia. In the context of his clinical features, Klinefelter's syndrome should be excluded. A blood karyotype analysis is ordered revealing 47,XXY, confirming Klinefelter's syndrome.

How should this couple be managed?

The couple should be referred to a fertility specialist for consideration of sperm aspiration. Given the woman's age of 35 years and the possible delay and uncertainty in any attempt to obtain his sperm, it is reasonable to refer them without delay. Some patients with Klinefelter's syndrome may have very low quantities of sperm that can be extracted via testicular sperm aspiration or testicular microdissection. If this is successful, the couple may be able to undergo assisted reproduction therapy with intracytoplasmic sperm injection. However, if no sperm are found or the couple do not wish to proceed with treatment with a highly uncertain outcome then donor sperm may be considered. Smoking cessation should also be encouraged.

Table. Results of investigations for cases 1 and 2

Investigation	Normal range[7]	Case 1	Case 2
Female			
FSH (follicular phase) (U/L)	5.0–15.0	6	3
LH (follicular phase) (U/L)	2.4–12.6	12	3
Oestradiol (follicular phase) (pmol/L)	<700	200	215
Progesterone (follicular phase) (nmol/L)	<4.0	2.0	2.2
17-OH progesterone (follicular phase) (nmol/L)	1.0–4.5	3.7	2.4
Testosterone (nmol/L)	<3.0	3.5	1.1
Free testosterone (pmol/L)	0–30	45	10
SHBG (nmol/L)	27–120	30	60
FAI	<6.0	11.7	1.8
TSH (mIU/L)	0.27–4.2	1.2	2.2
Thyroxine (T_4) (pmol/L)	12.0–22.0	13.5	14
Prolactin (mIU/L)	42–420	270	284
Anti-Mullerian hormone (pmol/L)	14–30	60	25
Male			
FSH (U/L)	1.0–9.0	5	25
LH (U/L)	1.7–8.6	4	30
Testosterone (nmol/L)	6.0–29.0	20	3
Free testosterone (pmol/L)	80–370	267	40
TSH (mIU/L)	0.27–4.2	1.9	1.6
T4 (pmol/L)	12.0–22.0	14.4	12.1
Prolactin (mIU/L)	95–500	310	290
Semen analysis			
Volume (mL)	1.5–6.0	4	3
Density (sperm/mL)	>15 x 10^6	39 x 10^6	0
Progressive motility (%)	≥32	44	0
Sperm morphology (%)	≥4	8	0

Abbreviations: FAI = free androgen index; FSH = follicle-stimulating hormone; LH = luteinising hormone; SHBG = sex-hormone binding globulin; TSH = thyroid-stimulating hormone.

3. Indications for structural imaging in women with subfertility

Tubal occlusion
- History of a sexually transmitted infection increasing the risk of pelvic inflammatory disease (e.g. chlamydia, gonorrhoea)
- Symptoms suggesting endometriosis (e.g. pelvic pain, abnormal bleeding or spotting)
- Previous ectopic pregnancy
- History of intra-abdominal infection, including inflammatory bowel disease, peritonitis, appendicitis

Uterine cavity configuration
- Symptoms including unusually heavy or prolonged menstrual bleeding, intermenstrual bleeding, severe pelvic pain or cramps during menstrual period, and infertility associated with normal ovulation and normal semen suggest structural abnormalities of the uterine cavity caused by submucosal fibroids, endometrial polyps or congenital abnormalities of uterine formation (intrauterine septum, bicornuate uterus)
- Previous dilatation and curettage, intrauterine infection, tuberculosis, adenomyosis may suggest structural and functional abnormalities of the endometrium

Pelvic adhesions impairing function
- History of previous pelvic surgery – possible adhesions
- History of a sexually transmitted infection increasing the risk of pelvic inflammatory disease (e.g. chlamydia, gonorrhoea)
- Symptoms suggesting endometriosis (e.g. dysmenorrhoea or dyspareunia)

erythematosus, antiphospholipid syndrome or other clotting abnormality.[10,11] Patients with a history of recurrent miscarriage or a suspected implantation disorder should be referred early for specialist review.

Uterine and tubal abnormalities

Evaluation of uterine and tubal structure and function is an integral part of the workup of the infertile couple. Tubal abnormalities including obstruction, hydrosalpinx, tubal endothelial destruction or pelvic adhesions may be found in up to 14% of women with fertility problems.[5] Uterine fibroids are a common finding in women and are not often the cause of subfertility. However, the size and location of a fibroid, specifically if projecting into the uterine cavity (submucosal), can affect implantation. Other structural abnormalities of the uterus that may affect fertility, including endometrial polyps, adenomyosis, uterine septae and congenital uterine abnormalities, may also be identified by good quality imaging.[10] A history of postpartum dilatation and curettage, other previous uterine surgery, instrumentation or intrauterine infection should also be elicited as possible causes of intrauterine adhesions.[10]

Initial investigation for uterine and tubal abnormalities is best carried out by high-resolution ultrasound, which may include a 3D reconstruction scan. Imaging with contrast agents in x-ray (hysterosalpingogram) or ultrasound (sonohysterography and hysterosalpingo contrast sonography) is used to examine tubal patency. Pelvic MRI may be used to confirm hydrosalpinx and is currently preferred by many gynaecologists for the detailed assessment of fibroids before surgical treatment. Hysteroscopy may be required for confirmation of scan findings and for surgical correction of uterine cavity abnormalities. Tubal patency may also be assessed by the use of dye insufflation at laparoscopy.[5,10] Tests for tubal patency are somewhat invasive and therefore should be considered after semen analysis and ovulation assessment have been completed.[1] Indications for structural imaging that may warrant earlier investigation are shown in Box 3.

Peritoneal pathology

Peritoneal pathology including endometriosis may be suspected in subfertile patients with a history of severe dysmenorrhoea, dyspareunia, dyschezia, prolonged premenstrual spotting, heavy periods or intermenstrual bleeding.[12] Pelvic and adnexal adhesions can arise following pelvic infection, surgery or radiation.[10] Other conditions, including inflammatory bowel disease, appendicitis and sexually transmitted infections such as chlamydia, raise the suspicion of pelvic inflammatory disease, pelvic adhesions and tubal occlusion.[12] It should be noted, however, that peritoneal pathology may be asymptomatic and undetected before investigations are carried out for infertility.

The extent of investigation and need for pelvic surgery depends on the severity of symptoms (pain) versus the risk of surgery related to the individual patient's medical history. High-resolution pelvic ultrasound scanning carried out by an expert operator is a useful initial investigation if peritoneal pathology is suspected. The volume, position and mobility of the ovaries help not only in the assessment of ovarian function but can also provide evidence for other pelvic disease including endometriosis and pelvic inflammatory disease. A 'deep infiltrating endometriosis' scan may be requested to identify pelvic nodules and adhesions, which limit movement of the ovaries and uterus, and raise the possibility of endometriosis or adhesions being responsible for a patient's fertility impairment. Laparoscopy is required for a definitive diagnosis of peritoneal abnormalities. Gynaecological referral of the patient is necessary in such cases.

Male factors

Male factors including sexual dysfunction or abnormal semen are the dominant problem in up to 25% of couples with fertility problems.[2,12] Conditions may be temporary and reversible, irreversible although potentially suitable for IVF, and/or irreversible due to genetic abnormalities (Box 4). In men with azoospermia, investigations should be carried out to identify a possible cause of their azoospermia before they are referred for IVF treatment because the cause may have significant implications for the future health of their children. In some of these cases, consideration of adoption or sperm donation may be required.

4. Male causes of subfertility

Hormonal and endocrine causes

- Hypogonadotropic hypogonadism (low testosterone levels with low or inappropriately normal LH and FSH levels)
  - tumours or inflammatory disorders of the pituitary and/or hypothalamus
  - Kallmann's syndrome
  - suppression of the hypothalamic–pituitary axis (e.g. stress, malnutrition, illness, extreme exercise, eating disorders)
  - hyperprolactinaemia
  - opiates, marijuana, anabolic steroids
  - previous testosterone therapy
  - congenital
- Hypergonadotrophic hypogonadism (high LH and FSH levels, low testosterone levels)
  - primary testicular failure
  - Klinefelter's syndrome
  - testicular infection, orchitis, torsion
  - testicular cancer
  - previous radiotherapy
  - previous cryptorchidism

Post-testicular obstruction (eugonadotrophic male infertility)

- Obstruction of epididymis, vas or ejaculatory duct by vasectomy, epididymitis caused by infection
- Nonmotile sperm – immotile cilia syndrome (Kartagener syndrome)
- Absence of sections of vas, epididymis, seminal vesicles or ejaculatory duct associated with cystic fibrosis mutations

Structural pathologies

- Hydrocoele
- Hypospadias
- Varicocoele
- Cystic fibrosis (congenital absence of the vas deferens)

Genetic abnormalities

- Klinefelter's syndrome and other karyotypic abnormalities
- Y chromosome gene deletions
- Cystic fibrosis mutations

Abbreviations: FSH = follicle-stimulating hormone; LH = luteinising hormone.

History

A developmental history is important when investigating subfertility in men. A history of issues including undescended testes, hypospadias and varicocoele, inguinal hernia, testicular injury or torsion, painful swelling of the testis at any age and previous chemotherapy or radiotherapy may provide important clues as to the cause of subfertility.

A thorough history of sexual function should also be taken to identify an erectile or ejaculatory problem. There are many potential contributors to erectile dysfunction including endocrinopathies such as diabetes, use of medications (e.g. some antidepressants and beta blockers) and psychological stress.[13] This problem may not be volunteered during the initial consultation. Premature ejaculation may be described as erectile dysfunction by the patient. Recent onset erectile dysfunction may also be an early indication of macrovascular disease.[13] If psychological factors are implicated then sexual counselling may be useful.[13]

Semen analysis

Semen analysis is the single most important laboratory investigation of the male patient. Because of the high variability of results from one man, an initial abnormal semen analysis result should be confirmed by analysis of a second sample, collected after two to six days' abstinence.[6,14] Current WHO standards for a normal semen analysis include an ejaculate volume of at least 1.5 mL, a sperm concentration of 15 million per mL or more, with 32% or more of sperm having progressive motility and 4% or more having normal morphology.[6] The sample should be collected in a sterile container and examined without delay, preferably within one hour of collection. This is best achieved by collection being carried out in very close proximity to the testing laboratory and transported at normal body temperature.[15] Abnormalities may be attributed to collection inexperience, poor handling of the sample after collection, previous testicular injury, torsion, exposure to gonadotoxins or other anatomical, endocrine or genetic causes affecting the testes or the hypothalamic–pituitary–testicular axis. Regular use of marijuana or cocaine is a possible cause of very poor sperm motility. A standard semen analysis may not identify abnormalities of sperm quality.

Lifestyle modification

Lifestyle modification, particularly smoking cessation, moderation of alcohol intake, diet and exercise, is important in improving sperm quality. These factors should be addressed in every patient. Some supplements containing antioxidants may be beneficial to some sperm parameters, although the evidence to date is conflicting and larger, robust trials are necessary.[16,17] Antioxidants have not been shown to improve sperm concentration.

Causes of male infertility

Hormonal and endocrine causes

Endocrine conditions, although uncommon, should be considered in men with semen abnormalities, impaired sexual function or other findings in the history or physical examination suggesting a specific endocrine disorder (e.g. clinical symptoms and signs of androgen deficiency, erectile dysfunction, gynaecomastia or galactorrhoea suggesting hyperprolactinaemia).[15]

Measurement of LH, FSH and testosterone levels allows identification of hypothalamic–pituitary disease (hypogonadotrophic), primary testicular disease (hypergonadotrophic) or post-testicular obstruction (eugonadotrophic), as the probable cause of an abnormal semen analysis result (Box 4).

Hypogonadotrophic hypogonadism

Hypogonadotrophic hypogonadism is an uncommon cause of subfertility and may be congenital or acquired. Hypothalamic or pituitary

Table. Investigations to be considered in couples with subfertility

Investigation	Timing	Note
Woman		
Serum LH, FSH, oestradiol, progesterone, testosterone, SHBG, FAI, 17-OH progesterone	Ideally collected on day 2 of the cycle if menses can be predicted If patient is amenorrhoeic, collect at any time	Investigations should be modified by clinical findings
Anti-Mullerian hormone	Can be collected at any time of the cycle	Currently not funded by Medicare Not essential although a useful test
Serum prolactin	Can be collected at any time of the cycle Best collected in the morning	Consider in patients with oligomenorrhoea/ amenorrhoea or galactorrhoea
Thyroid function tests	Can be collected at any time of the cycle	Subclinical hypothyroidism important to diagnose and treat in early pregnancy
Transvaginal ultrasound examination	Ideally performed in the follicular phase	Request comment on antral follicle count, volume, position and mobility of the ovaries and any uterine abnormality
Tests for tubal patency – hysterosalpingo contrast sonography, hysterosalpingography, laparoscopy	Pre-ovulation	Should only be considered after investigations for ovulation and semen analysis have been performed Consider tests early if patient has severe pain or risk factors for tubal occlusion (e.g. previous chlamydia infection or ectopic pregnancy) Usually performed after review by fertility specialist
MRI pituitary		Should be considered if primary pituitary abnormality is suspected and before specific treatment commenced Pituitary enlarges in pregnancy
Man		
Seminal fluid analysis	Collect after 3 days' abstinence. If a second analysis is needed, sample should be collected after 6 weeks	Best collected in close proximity to the laboratory
Serum FSH, LH, testosterone, SHBG	Sample should be collected in the morning, and test repeated if any abnormality	Consider in cases of low male libido, abnormal clinical findings such as small testes, abnormal seminal fluid analysis or any history to warrant clinical suspicion of hypogonadism
Serum prolactin	Best collected in the morning	Consider in cases of hypogonadotrophic hypogonadism or if clinical features of hyperprolactinaemia
Testicular ultrasound examination		Should be performed in all men with azoospermia or severe oligospermia or if any palpable testicular mass or abnormality of the vas deferens

Abbreviations: FAI = free androgen index; FSH = follicle-stimulating hormone; LH = luteinising hormone; SHBG = sex-hormone binding globulin.

disorders, hyperprolactinaemia and medication use may be causative.[18] It can often be corrected by appropriate treatment (e.g. suppression of prolactin or gonadotrophin replacement treatment).[18] Use of testosterone supplements, particularly in the unsupervised or illicit setting, may be implicated in some patients.[19] These agents suppress endogenous gonadotrophin production. Such behaviour should be explored through a thorough patient history. Kallmann's syndrome, although rare, is a well-recognised genetic cause of hypogonadotrophic hypogonadism and secondary congenital failure of testicular growth and function.[19] It is often associated with anosmia (see below).[19]

Hypergonadotrophic hypogonadism

Primary testicular failure is a more common cause of poor semen quality and is usually associated with reduced testicular size or

consistency. Causes of hypergonadotrophic hypogonadism may include genetic abnormalities, previous cryptorchidism and acquired pathologies such as testicular trauma, torsion, orchitis (secondary to infection) and exposure to medications such as chemotherapy.[18] In some cases no cause is found and the diagnosis is idiopathic.

Obstruction (eugonadotrophic)

Obstructive azoospermia may result from epididymitis following infection such as chlamydia or gonorrhoea. Genetic conditions, including cystic fibrosis, may also be implicated. Iatrogenic injury to the vas following previous surgery is also a rare but possible cause of obstruction.

Structural abnormalities

Structural abnormalities may be noted on examination of the scrotum, including palpation of the testes, epididymis and vas deferens. Use of an orchidometer is helpful in assessing chronicity. Small testicular volume (<10 mL bilaterally) suggests Klinefelter's syndrome or long-standing pathology from childhood or adolescence, before pubertal maturation (e.g. cryptorchidism, torsion). Conversely, normal testicular size and penile anatomy usually indicate a more recent cause of the abnormal semen analysis result. Any palpable testicular or scrotal mass or vas deferens abnormality should be investigated with ultrasound examination to exclude malignancy.[15] Referral of the patient to a urologist may be necessary. Long-term severe oligospermia or azoospermia is associated with a slightly increased risk of testicular cancer.[16]

Genetic abnormalities

Kallmann's syndrome

Kallmann's syndrome is a rare but well-recognised complex genetic cause of hypogonadotrophic hypogonadism. At least 18 gene mutations involving control of gonadotrophin secretion have been described.[19] Complex genetic–environmental interactions have now been identified, which help explain individual susceptibility to environmental factors influencing gonadotrophin secretion.

Klinefelter's syndrome

Klinefelter's syndrome (47,XXY karyotype), the most common genetic cause of male hypogonadism, is characterised by small firm testes, gynaecomastia and hypogonadism (see case 2, Box 2).[20] It has an incidence of one in 660 newborn boys, and accounts for 3.1% of cases of male infertility.[20,21] Patients usually have azoospermia, although sperm may be found in up to 50% of these men via specialist testicular aspiration or microdissection techniques; hence infertility is not absolute.[20,21]

Cystic fibrosis

A cystic fibrosis gene mutation should be considered in any patient with azoospermia or severe oligospermia even in the absence of respiratory or gastrointestinal features of this disease and may be suggested by bilaterally impalpable vas deferens.[15] Mutations for cystic fibrosis are found in 4% of Caucasians.[22] Screening is important because of the implications for genetic abnormalities in future offspring. If detected, then the female partner also requires screening and the couple should be referred to a genetic counsellor.

Karyotype abnormalities

Karyotype abnormalities, including Klinefelter's syndrome, may account for 3 to 14% of cases of oligospermia and azoospermia.[23,24] Y-chromosome microdeletions are found in 6 to 18% of men with nonobstructive azoospermia or oligospermia.[25,17] If present, sperm from these men can be used successfully in IVF treatment; however, it is important that such patients are aware this gene deletion will be found in all of their sons.

The role of the GP

Delay in identifying and treating many subfertile couples is associated with poorer outcomes because of a reproductive decline with increasing female age and prolongation of the associated psychological stress. Early investigation, instituted by the GP, is therefore highly important to expedite specialist involvement if necessary. A summary of investigations to consider and their appropriate timing is shown in the Table.

Optimisation of general health through lifestyle changes should always be instituted early. Weight optimisation, smoking cessation and diet should be reviewed. General recommendations regarding antenatal vitamin supplementation, such as folic acid and iodine, should be reiterated.

Comorbidities that are known to affect fertility or to be associated with high-risk pregnancies all need optimisation. Diabetes, hypertension, obesity and autoimmune disease should be well controlled if possible, and specific specialist referral of the patient may be necessary to maximise improvement.

Early involvement of a fertility specialist should be arranged for women over 35 years of age and those with oligomenorrhoea or amenorrhoea, recurrent miscarriage, an abnormal pelvic scan, a history of pelvic surgery or previous pelvic infection.[6] Initial investigations must include a semen analysis irrespective of female factors for all couples experiencing a delay in conception.

Conclusion

Subfertility is an increasingly common problem and may be attributed to female factors, male factors or both. In many cases, fertility issues may be unexplained, but this does not necessarily predict a poor outcome from assisted reproduction. A thorough history can enable tailored investigation of both partners in general practice before specialist referral, particularly in circumstances in which time is crucial or there is associated psychological distress. **ET**

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A list of references is included in the website version of this article (www.endocrinologytoday.com.au).

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The subfertile couple
A guide to investigations

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