Investigation and treatment of the infertile couple

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AETIOLOGY

Infertility, defined as the inability to conceive after 1 year of unprotected intercourse, is a common condition with psychological, medical and economic implications. This definition has historical roots in clinical practice and also practical implications. Using life table analysis, it has been calculated that the chances of conception for a given couple, assuming a 20% monthly probability, are 85% after 12 months and 95% after 24 months (in women younger than 35 years). Although the infertility rate has been stable over the years, this is likely to increase due to environmental effects, chemical exposure and delayed childbearing. In addition, there has already been an increase in the demand for infertility services. Infertility may be primary (no previous pregnancies) or secondary (previous pregnancy, irrespective of outcome). There are various causes leading to difficulty in conceiving, and very often several causes can be identified at the same time. The causes and factors contributing to infertility and their relative frequency are summarized in Figure 7.1 and are discussed below.

Age

The prevalence of infertility rises dramatically as age increases. The inverse relation between female age and fertility has been consistent in many populations. In Trussell and Wilson’s historical study, statistical modelling indicated a moderate decline in fertility rates until age 35 to 39, and a much steeper decline thereafter.

Anovulation

Ovulation dysfunction is usually indicated by amenorrhoea, oligomenorrhoea or polymenorrhoea, accounting for 21% of cases of infertility. It is important to make the correct diagnosis, as appropriate medical treatment is often effective in restoring fertility to near-normal levels. The causes of primary and secondary amenorrhoea are listed in Tables 7.1 and 7.2.
Figure 7.1
Causes of infertility. (From Hull and Cahill 1998,1 with permission.)

Table 7.1: Classification of primary amenorrhoea

<table>
<thead>
<tr>
<th>Class</th>
<th>Cause(s)</th>
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<tbody>
<tr>
<td>Structural anomalies</td>
<td>Müllerian agenesis (e.g. Rokitansky syndrome)</td>
</tr>
<tr>
<td></td>
<td>Vaginal septum</td>
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<td></td>
<td>Imperforate hymen</td>
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<tr>
<td>Chromosomal anomalies</td>
<td>Turner's syndrome (45XO or mosaics)</td>
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<td></td>
<td>XY gonadal dysgenesis</td>
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<tr>
<td>Ovarian causes</td>
<td>Premature ovarian failure (normal chromosomes)</td>
</tr>
<tr>
<td>Hypothalamic causes (hypogonadotrophic hypogonadism)</td>
<td>Systemic and chronic illness</td>
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<tr>
<td></td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>Intense exercise</td>
</tr>
<tr>
<td></td>
<td>Genetic (e.g. Kallmann's syndrome)</td>
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<tr>
<td></td>
<td>Idiopathic</td>
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<tr>
<td>Pituitary causes</td>
<td>Hyperprolactinaemia</td>
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<tr>
<td></td>
<td>Hypopituitarism</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Causes of hypothalamic/pituitary damage (hypogonadism)</td>
<td>Tumours</td>
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<tr>
<td></td>
<td>Cranial irradiation</td>
</tr>
<tr>
<td></td>
<td>Head injuries</td>
</tr>
<tr>
<td>Systemic causes</td>
<td>Chronic debilitating illness</td>
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<tr>
<td></td>
<td>Weight loss</td>
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<tr>
<td></td>
<td>Endocrine disorders</td>
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<tr>
<td>Delayed puberty</td>
<td>Constitutional or secondary</td>
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</table>
**Tubal factors**

These account for 14% of cases of infertility. Pelvic infections (pelvic inflammatory disease, PID), most commonly caused by *Chlamydia trachomatis*, result in severe tubal damage in:
- 10–30% of women after a first attack
- 30–60% after a second
- 50–90% after a third.

Chlamydial PID is often clinically ‘silent’ until severe pelvic adhesions and damage are identified during infertility investigations. The intrauterine contraceptive device (IUCD) may increase the risk of developing clinical PID by 50–100%, and this form of PID is often severe. Of all the different types, the progestogen-releasing IUCD (Mirena IUS) may minimize the risk of infection through its effect on cervical mucus. Because suction and medical termination of pregnancy are associated with a 5% risk of retained products of conception and hence pelvic infection, it is prudent to offer antibiotic prophylaxis to these women.

**Cervical mucus factor**

Around the time of ovulation, cervical mucus becomes both watery and stretchy due to the predominance of oestrogen and the lack of progesterone. At ovulation, the stretching
of the mucus, known as spinnbarkeit, should be at least 8 cm. A history of previous cervical surgery should be sought and testing for chlamydial infection should be undertaken when satisfactory mucus is not seen.

Male factors

Male factors alone may be responsible in 30% and contributory in a further 20% of subfertile couples. One of the central problems in male infertility is the difficulty in identifying genuine rather than presumptive aetiological factors.

INVESTIGATION OF THE INFERTILE COUPLE

It is very important to evaluate both the female and the male partner, as a diagnosis of infertility can be made only on the basis of the results of assessments of both partners. Some barriers to pregnancy are easily identifiable, such as azoospermia, bilateral tubal obstruction or amenorrhoea. In most cases, however, the situation is less clear. A standard infertility evaluation consists of a series of tests that, despite historical roots, have had little scientific validation in distinguishing between fertile and infertile couples. When infertility evaluation identifies factors that are thought to be associated with infertility but are not absolute barriers to pregnancy, then we should counsel the couple emphasizing the gaps in our knowledge about aetiology, treatment and outcome.

Evaluation of female infertility

Particular attention needs to be paid to the reproductive history, such as previous pregnancies and their outcomes, including terminations of pregnancy. Additionally, relevant past and current gynaecological history, including characteristics of the menstrual cycle, sexually transmitted infections and information on medical/surgical illnesses, drug use/misuse and family history should be obtained. Couples also need to be questioned about their sexual activity, such as frequency and timing of sexual intercourse or sexually related problems, including loss of libido, dyspareunia and erectile or ejaculatory problems.

The general physical examination is important (Box 7.1). Women who have a normal body mass index (BMI; 20–25 kg/m²) are more likely to conceive and to have a normal pregnancy than those who are outside the normal range (Fig. 7.2). Women who are underweight become anovulatory and amenorrhoeic. It is usually easy to induce ovulation in underweight women, who may then conceive readily, but these pregnancies are more likely to miscarry or result in the premature delivery of growth-restricted babies. Obesity is the more common problem in western society. Not only does obesity reduce fertility, but it also increases the risk of miscarriage, gestational diabetes, hypertension, thromboembolic disease and complicated operative delivery. These women should be advised to reduce their BMI to less than 30 kg/m² before starting any treatment. Without doubt, weight loss improves overall reproductive function,
Box 7.1: General history and examination of the female partner

History
- Previous contraception and any problems (e.g. lost coil)
- Previous pregnancies and outcome
- Medical history (pelvic infection, Crohn disease)
- Surgical history (ovarian cyst, appendectomy)
- Gynaecological history (cone biopsy, cervical smear history)
- Current medical illness
- Drug history: prescribed and misuse
- Diet
- Smoking and alcohol consumption
- Galactorrhoea
- Hirsutism
- Menstrual regularity and menorrhagia
- Dysmenorrhoea
- Intermenstrual or postcoital bleeding
- Preovulatory cervical mucus recognition
- Coital frequency and timing

Examination
- Signs of endocrine disease:
  — acne, hirsutism, balding
  — acanthosis nigricans
  — virilization
  — visual field defects
  — goitre, signs of thyroid disease
- Body mass index
- Blood pressure
- Urinalysis
- Breast examination: lumps, galactorrhoea
- Abdominal examination: masses, striae, abnormal hair growth
- Pelvic examination: clitoral appearance, evidence of cervical and vaginal endometriosis, uterine and adnexal features

(After Cahill and Wardle 2002, with permission.)

Figure 7.2
Likelihood of spontaneous miscarriage and pregnancy following infertility treatment, analysed by body mass index. *95% confidence intervals do not cross unity. (After Wang et al. 2000, with permission.)

particularly in women with polycystic ovary syndrome (PCOS). A pelvic examination should be performed; endometriosis is suggested by the presence of nodules in the vagina, thickening of the posterior fornix, and tenderness and limited mobility of the pelvic organs.
Signs of hyperandrogenism (acne, hirsutism, balding) are suggestive of PCOS, although biochemical screening helps to differentiate other causes of androgen excess. A testosterone level less than 5 nmol/L excludes other causes of hyperandrogenism in the majority of patients. Hirsutism can be graded according to the Ferriman–Gallwey scoring system, although the complexity of this system means that it is rarely used in clinical practice and is generally confined to research studies. It is important to distinguish between hyperandrogenism and virilization (Box 7.2). Virilization suggests a more profound disturbance of androgen secretion than usually seen with PCOS and indicates a need to exclude androgen-secreting tumours, congenital adrenal hyperplasia and Cushing’s syndrome. Acanthosis nigricans is a sign of profound insulin resistance and is usually visible as hyperpigmented thickening of the skin folds of the axilla and neck. It is associated with PCOS and obesity (also Cushing’s syndrome and other disorders of insulin resistance). Amenorrhoic women may have hyperprolactinaemia with or without galactorrhoea, hence it is important to measure serum prolactin levels whether this sign is present or not. If there is suspicion of a pituitary tumour, the woman’s visual fields should be checked. Thyroid disease is common, and the thyroid gland should be palpated and signs of hypothyroidism or hyperthyroidism elicited.

Evaluation of male infertility

It is important to enquire about any children from previous relationships, and to search for a history of surgery or trauma to the testes, orchitis and exposure to toxins (such as paints) or irradiation.

General examination should again include an assessment of BMI, blood pressure and secondary sexual characteristics (Box 7.3). BMI is traditionally used as an indicator of overall obesity. Men who are significantly overweight might be expected to have fertility problems as, unlike the situation in women, in men there is an inverse relationship between serum testosterone levels and visceral fat mass. Increased central obesity in men is associated with relative hypogonadism. Obesity itself is one of the several conditions

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**Box 7.2: Hyperandrogenism versus virilization**

<table>
<thead>
<tr>
<th>Hyperandrogenism</th>
<th>Virilization</th>
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<tbody>
<tr>
<td>• Acne</td>
<td>• Acne</td>
</tr>
<tr>
<td>• Hirsutism</td>
<td>• Hirsutism</td>
</tr>
<tr>
<td>• Male pattern balding</td>
<td>• Male pattern balding</td>
</tr>
</tbody>
</table>

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that can result in a low sex hormone-binding globulin level and is also the most common cause of insulin resistance. As a result, total testosterone is frequently low, but the free testosterone is normal, suggesting that this is not a true clinical hypogonadism. Therefore most obese men are able to reproduce normally, provided that there is no physical impediment to intercourse.

The underlying mechanisms responsible for the reduced testosterone levels in obese men are unknown. The reduction in free testosterone seen in massive obesity is not accompanied by a reciprocal increase in luteinizing hormone (LH), suggesting a form of hypogonadotrophic hypogonadism. One hypothesis postulated for the decreased free testosterone in massively obese individuals is functional alterations at the hypothalamic–pituitary level characterized by decreased amplitude of the LH pulses. Some rare hypothalamic syndromes, such as Prader–Willi syndrome, are associated with both obesity and hypogonadotrophic hypogonadism. Another possible mechanism to explain the aetiology of low testosterone levels and the subsequent insulin resistance in obese men is hyperoestrogenaemia. There are increased serum levels of oestradiol and oestrone in obese men, which is primarily as a result of increased peripheral conversion of androgens to oestrogens through the action of the enzyme aromatase in the adipose tissue. This increase in serum oestrogen concentration is, however, not accompanied by overt signs of feminization. It is therefore possible that the increased oestradiol levels contribute to the insulin resistance in obese men.

Some chest diseases are associated with infertility (e.g. congenital absence of the vas deferens may be associated with cystic fibrosis or Kartagener syndrome with dextrocardia) and might be elicited at the time of the examination.

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**Box 7.3: History and examination of the male partner**

**History**
- Occupation (exposure to excessive heat or toxins)
- Medical history (mumps, venereal disease)
- Surgical history (orchidopexy, inguinal hernia repair, vasectomy)
- Current medical illness
- Drug history: prescribed and misuse
- Smoking and alcohol consumption
- Erectile or ejaculatory difficulty

**Examination**
- General: weight, height, blood pressure
- Secondary sexual characteristics
- Muscle bulk
- Signs of endocrine disease
- Gynaecomastia
- Abdominal examination: masses, hernia, scars, liver
- Genital examination: if sexual dysfunction or abnormal semen analysis

(After Cahill and Wardle 2002, with permission.)
Men with severe androgen deficiency of prepubertal origin will have a high-pitched voice, small soft testes and small penis, lack of pubic and axillary hair, and decreased muscle mass. They are often tall, with a large arm span that exceeds their height. If hypogonadism develops after puberty, the skin becomes fine and body and facial hair diminish. There may be gynaecomastia, as in Klinefelter’s syndrome, although the phenotype in Klinefelter’s syndrome can vary quite widely. Gynaecomastia may also occur with hyperthyroidism, liver disease, oestrogen- or human chorionic gonadotrophin (hCG)-producing tumours and as a side-effect of some drugs, such as cimetidine, spironolactone and digoxin. Abdominal examination should reveal the presence of abnormal masses, hernias or scars from herniorrhaphy. Genital examination is best performed in a warm room with the patient standing. This examination only needs to be performed if there are sexual difficulties, symptoms or signs of hypogonadism, or abnormalities with the semen analysis. A full neurological examination is also required when there are problems with sexual function.

**Investigations**

Attendance at the fertility clinic should be utilized for general health screening and preconception counselling. Particular attention should be paid to body weight, blood pressure, urinalysis, cervical cytology and rubella immunity.

**Ovarian function**

Regular menstrual cycles are a sign of ovulation in 95% of the cycles. However, the regularity of the cycles alone is not enough to characterize ovarian function. The number of follicles in the ovaries decreases from birth, resulting in a slow decline in fertility from the age of 30 onwards. This decline parallels the reduction in the number and quality of the follicles and oocytes. The first sign of reduced ovarian activity is the shortening of the follicular phase, which reduces the length of the ovulatory cycle. The decrease in the number of follicles is followed by hormonal changes: inhibin B is produced by the small antral follicles, and as their numbers decline, the ovarian output of inhibin B decreases. This is paralleled by a rise in follicle-stimulating hormone (FSH) level.

Tests of ovarian reserve include measurement of the early follicular phase FSH (normal <10 IU/L) and oestradiol levels (days 1–3 of cycle; normal <75 pmol/L) to determine the FSH:oestradiol ratio, measurement of day 3 inhibin B (normal >45 pg/mL) or antimüllerian hormone levels (normal >15.7 pmol/L), and undertaking early follicular phase antral follicle count. Other options include dynamic tests to evaluate the ovaries during clomiphene citrate challenge or gonadotrophin stimulation. These tests will help to determine the most suitable treatment and are useful in counselling the couple.

An elevated FSH level indicates reduced ovarian reserve. In general terms, if FSH levels are greater than 10 IU/L the ovaries are unlikely to be ovulating regularly and will also be resistant to exogenous stimulation. Levels greater than 25 IU/L are suggestive of the menopause or premature ovarian failure. An elevated serum concentration of LH may suggest that the patient has PCOS. Other causes of an elevated LH are the mid-cycle
surge and ovarian failure. The association of amenorrhoea with very low levels of FSH and LH (usually < 2 IU/L) suggests pituitary failure or hypogonadotrophic hypogonadism. Gonadotrophin measurements are best interpreted together with the findings of a pelvic ultrasound scan, as these will provide the diagnosis in most cases.

Ovulation can be documented in several ways. The easiest is to measure a mid-luteal phase progesterone level. The clinical menstrual history will give fairly reliable information about the presence or absence of ovulation. A progesterone concentration greater than 30 nmol/L suggests ovulation. If the progesterone is 15–30 nmol/L, then ovulation may be occurring but the timing of the measurement may have been incorrect. It is then necessary to check the timing of the blood test to subsequent menstruation (the test should be performed 7 days prior to menstruation) and repeated in the following cycle, sometimes with serial measurements.

Basal body temperature (BBT) charts work on the rationale that progesterone will raise BBT by 0.2–0.5°C, although between 10 and 75% of ovulatory cycles fail to show such a degree of rise in BBT. BBT charts are therefore a source of considerable stress and do not provide a prospective indication of the day of ovulation. Commercially available kits that detect the presence of LH in the urine are expensive and may also cause unnecessary anxiety but are more accurate in detecting the LH surge and timing of ovulation.

When the cycles are irregular, other hormonal measurements such as testosterone, dehydroepiandrosterone sulphate (DHEAS), 17-hydroxyprogesterone, cortisol, prolactin and thyroid function tests may be necessary. If the results of any of these tests are considered abnormal, appropriate biochemical and imaging studies should be conducted.

**Tubal assessment**

When ovarian function and semen analysis are normal, tubal status should be investigated, particularly in women with a history of pelvic surgery, sexually transmitted infections or tubo-ovarian disease. Laparoscopy is the gold standard for the evaluation of tubal patency, during which peritubal adhesions, the ovaries, the peritoneum and the liver surface should be assessed and endometriosis (Fig. 7.3) excluded.

Other procedures, such as hysterosalpingography or hysterosalpingo contrast sonography, can also be used to assess tubal patency. They are useful in evaluating isthmic (proximal) and total fimbrial (distal) blockage, but are less helpful than laparoscopy in the diagnosis of partial tubal obstruction, peritubal adhesions or other contributory factors of tubal infertility such as severe endometriosis and pelvic adhesions, from either non-tubal intra-abdominal infection or previous surgery.8

**Uterine evaluation**

Transvagal ultrasound is a routine part of the infertility work-up and is used to assess uterine outline, position and morphology, and the adnexa. Fibroids, polyps, congenital anomalies, abnormalities of the endometrium, hydrosalpinx and ovarian masses can be detected. It is also possible to instil a small volume of normal saline into the uterine cavity using a small catheter to more accurately delineate its outline and the precise size
and location of any intracavity focal lesions. Additional information may be obtained during hysteroscopy with direct visualization of the uterine cavity. Three-dimensional ultrasound has in recent years become a valuable medical imaging modality. Recent advances in three-dimensional ultrasound have made accurate non-invasive assessment of pelvic organs possible, with potential improvements in the assessment and management of infertility problems. A number of uterine abnormalities have been linked to infertility and/or spontaneous abortion, such as congenital uterine structural anomalies, fibroids, polyps and synechiae. Although each of these conditions may contribute to infertility, they are also seen in association with pregnancy; a causal link has therefore not been established.

**Chlamydia testing**

Testing for *Chlamydia* may be undertaken with swabs or serology. *Chlamydia* serology is the best initial screen for tubal disease. A raised titre (>1:256) correctly predicts tubal damage in 90% of cases, over half of which give no history of PID. High antibody titres may indicate current or previous tubal infection. Treatment does not correct tubal damage but prevents reactivation if uterine instrumentation is performed.

*Chlamydia* screening may help identify women whose tubal status should be tested early in the investigative process and by a laparoscopy rather than the other methods. If the screen test is positive, the woman and her partner should be referred for suitable treatment and contact tracing. Swabbing for *Chlamydia* identifies active disease and when positive is an indication for treatment of the sexual partners and contact tracing.
Postcoital test

The postcoital test was introduced to provide information about the interaction between sperm and cervical mucus. However, review of the literature does not support its use in today’s practice.

Semen analysis

The evaluation of the male partner starts with a semen analysis, which should be performed after 3 days of abstinence. The volume of the semen, sperm number, motility and morphology assessment complete the examination. The World Health Organization (WHO) criteria for a normal semen analysis are outlined in Table 7.3. When one or several of these parameters are abnormal, the analysis should be repeated in 3 months, and further tests may be necessary. Azoospermia (absence of sperm) represents a barrier to natural conception, and further tests are necessary to determine the exact cause and prognosis. Clinicians must be cautious in interpreting low sperm values, especially if they are only mildly reduced below the range considered normal, as there are no data on where we should draw thresholds for normal and abnormal sperm parameters. Nineteen per cent of men in an infertile population will have a sperm count less than 20 million/mL, but so will 8% of men in a fertile population.

Trial sperm wash

The increasing number of men showing poor semen quality prompted the development of the trial sperm wash. This assessment is usually performed when the sperm concentration is 10 million/mL or less to help in deciding which treatment options are most suitable for the couple. The aim of the sperm preparation is to select motile and functionally competent spermatozoa from the ejaculate to improve the fertilization potential of the sample.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Volume</td>
<td>2.0 mL</td>
</tr>
<tr>
<td>pH</td>
<td>7.2–8.0</td>
</tr>
<tr>
<td>Sperm concentration</td>
<td>$20 \times 10^6$/mL</td>
</tr>
<tr>
<td>Total sperm count</td>
<td>$40 \times 10^6$ per ejaculate</td>
</tr>
<tr>
<td>Motility (within 60 min of ejaculation)</td>
<td>25% with rapid progression (A)</td>
</tr>
<tr>
<td></td>
<td>50% with forward progression (A and B)</td>
</tr>
<tr>
<td>Vitality</td>
<td>75% live (A, B and C)</td>
</tr>
<tr>
<td></td>
<td>25% dead (D)</td>
</tr>
<tr>
<td>Morphology</td>
<td>30% normal forms</td>
</tr>
<tr>
<td>White blood cells</td>
<td>$&lt;1 \times 10^6$/mL</td>
</tr>
<tr>
<td>Sperm antibodies</td>
<td>&lt;50%</td>
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</tbody>
</table>

(From World Health Organization 1999, with permission.)
Endocrine investigations in men

Gonadal status (testosterone, LH, FSH), prolactin and thyroid function should be measured in men with oligospermia (count less than 10 million sperm/mL) or if there are signs or symptoms suggestive of either androgen deficiency or endocrine disease. Serum testosterone levels undergo diurnal variation, with the highest levels in the morning. The normal range is 10–35 nmol/L. Recommendations for the evaluation of hyperprolactinaemia and male gonadal disease are given in Chapters 1 and 6, respectively. Normal serum concentrations of FSH and LH are less than 10 IU/L. The combination of azoospermia with normal levels of testosterone, FSH and LH indicates a mechanical obstruction and warrants urological assessment. An elevated FSH level indicates germinal cell insufficiency or, if combined with an elevated LH concentration and a low testosterone level, primary testicular failure. Low serum concentrations of all three hormones indicate hypothalamic or pituitary insufficiency, which may be amenable to hormonal therapy with hCG and FSH. Serum prolactin and thyroid function should be measured when testosterone and gonadotrophin levels are low or when there is gynaecomastia or there are signs of thyroid disease.

Men with primary gonadal failure or with severe male factor infertility (sperm count less than 5 million/mL) should undergo genetic testing (karyotype, Y chromosome microdeletions, cystic fibrosis gene mutation analysis). The incidence of sex chromosome or Y chromosome abnormalities is about 15% among men with azoospermia.

TREATMENT OF THE INFERTILE COUPLE

Tubal and uterine disease

The role of microsurgery for proximal tubal obstruction is debatable, as no randomized controlled trials or controlled observational studies are available to compare microsurgery with no treatment or with in vitro fertilization (IVF). Surgery for pelvic and tubal disease and its outcome depends on the age of the woman, the duration of and factors associated with infertility, and the availability of appropriate equipment and skilled surgeons, and is also linked closely to the severity of the damage, with better results achieved in those with filmy adhesions and limited damage. Most pregnancies occur between 12 and 14 months after surgery, and if no conception has occurred IVF would be indicated. Pregnancy rates after tubal surgery are comparable with those resulting from IVF, while the incidence of ectopic pregnancy varies from 8 to 23% following surgery for proximal and distal occlusion, respectively. The choice between surgery and IVF as the primary treatment will depend on careful patient selection according to the individual’s clinical circumstances and involving the couple in the decision-making process.

Tubal catheterization or cannulation for proximal tubal blockage may be achieved using either a radiographic approach (selective salpingography combined with tubal cannulation) or hysteroscopically. The National Institute for Health and Clinical
Excellence (NICE) has recommended that in women with proximal obstruction these techniques may be alternative treatment options, as they improve the chance of pregnancy.

Women with fibroids have lower spontaneous pregnancy rates than those without them or with other causes of infertility. Myomectomy appears to improve the pregnancy rate, although its impact on live birth rate is uncertain. Women with fibroids may also have a reduced pregnancy rate following assisted reproduction treatment (ART). The role of uterine artery embolization in improving the reproductive outcome of women with fibroids remains to be determined. Women with uterine septa and adhesions may benefit from surgery by improving the live term birth rate and reducing the miscarriage rate following spontaneous or ART conception.

**Patients with endometriosis: medical and surgical treatment**

Medical treatment of minimal and mild endometriosis with ovulation suppression agents (medroxyprogesterone, gestrinone, combined oral contraceptives, gonadotrophin-releasing hormone, GnRH, analogues) does not improve clinical pregnancy rates in women with endometriosis-associated infertility and should not be offered.

Women with minimal or mild endometriosis benefit from laparoscopic ablation or resection of endometriotic deposits plus adhesiolysis, and their ongoing pregnancy and live birth rates increase compared with diagnostic laparoscopy only. In women who have mild endometriosis as their only infertility factor, the pregnancy rate is higher after laser laparoscopy and laparotomy compared with medical treatment. However, the benefits of surgery should be balanced against the risks of general anaesthesia and surgical complications.

In women with moderate or severe endometriosis, laparoscopic surgery may improve the spontaneous pregnancy rate compared with laparotomy. In women with ovarian endometriotic cysts, NICE has recommended that these women should be offered laparoscopic cystectomy as opposed to drainage and coagulation, as it improves their spontaneous pregnancy rate. However, the value of surgery in women selected for IVF or intracytoplasmic sperm injection (ICSI) cycles is debated and is not supported by the available evidence. Postoperative medical treatment does not improve pregnancy rates and is not recommended.

**Management of ovulatory dysfunction**

Women with WHO group 1 ovulation disorders (hypothalamic–pituitary failure, amenorrhoea or hypogonadotrophic hypogonadism) should be offered pulsatile GnRH or gonadotrophins with LH, because these are effective in inducing ovulation.

Women with a BMI of more than 29 kg/m² are likely to take longer to conceive, and those who are not ovulating should be informed that losing weight would recommence ovulation and is likely to increase their chance of conception. Equally,
women who have a BMI of less than 19 kg/m² and who have irregular or absent menstruation should be advised that increasing body weight is likely to improve their chance of conception.

Ovulation induction aims to achieve unifollicular ovulation in the correction of anovulatory infertility, the commonest cause of which is PCOS. In these women, NICE guidelines advise the use of antioestrogens (clomiphene citrate or tamoxifen) for up to 12 months as a first-line therapy, because it is likely to induce ovulation. The cumulative pregnancy rates continue to rise after six treatment cycles before reaching a plateau, and are comparable with those of the normal fertile population. It has been suggested that at least one cycle of therapy should be monitored with ultrasound to ensure that response is assessed and that drug doses are adjusted to minimize the risk of multiple pregnancy. Adverse effects of antioestrogens include hot flushes, ovarian hyperstimulation syndrome (OHSS), abdominal discomfort and multiple pregnancies. Women who ovulate with clomiphene citrate but who do not conceive should be offered clomiphene citrate-stimulated intrauterine insemination (IUI).

A Cochrane Database systematic review of 15 randomized controlled trials concluded that in women with clomiphene-resistant PCOS and a mean BMI above 25 kg/m², metformin as a single agent was not found to increase clinical pregnancy rate when compared with placebo. However, treatment with both metformin and clomiphene citrate did increase clinical pregnancy rate compared with clomiphene citrate alone, hence these women should be offered the combined treatment. Metformin as a single agent was found to induce ovulation when compared with placebo, and in combination with clomiphene citrate was also effective in inducing ovulation compared with clomiphene citrate alone. The effectiveness of pulsatile GnRH in women with clomiphene citrate-resistant PCOS is uncertain and is therefore not recommended outside a research context.

Women prescribed metformin should be informed of the side-effects associated with its use, such as nausea, vomiting and other gastrointestinal disturbances. To minimize these, patients should initially be commenced on a low dose (500 mg once daily), building up gradually to a maintenance dose of 500 mg twice daily and subsequently, if tolerated, a maximally effective dose of 1 g twice daily. If these women remain non-responsive, they may be offered laparoscopic ovarian drilling, because it is as effective as gonadotrophin treatment and is not associated with an increased risk of multiple pregnancies. However, this treatment is associated with surgical risks, its benefits wane with time and the long-term effects are poorly understood.

Treatment with gonadotrophins, human menopausal gonadotrophin, urinary FSH and recombinant FSH are equally effective in achieving pregnancy, and consideration should be given to minimizing cost when prescribing. The use of adjuvant growth hormone treatment with GnRH agonist and/or human menopausal gonadotrophin during ovulation induction in women with PCOS who do not respond to clomiphene citrate is not recommended, as it does not improve pregnancy rates. Women who are offered ovulation induction with gonadotrophins should be informed about the risk of multiple pregnancy and OHSS before starting treatment. Women with ovulatory disorders due to
hyperprolactinaemia should be offered treatment with dopamine agonists such as bromocriptine or cabergoline (see Chapter 1).

Ovarian ultrasound monitoring to measure follicular size and number should be an integral part of patient management during gonadotrophin therapy to reduce the risk of multiple pregnancy and OHSS. Women who are offered ovulation induction should be informed that a possible association between ovulation induction therapy and ovarian cancer remains uncertain.

The role of intrauterine insemination: homologous and donor sperm

Intrauterine insemination involves timed insemination of sperm into the uterus in natural (unstimulated) cycles or following stimulation of the ovaries using oral antioestrogens or gonadotrophins. It is often undertaken following unsuccessful ovulation induction treatment in women with patent tubes but who suffer from unexplained infertility, ovulatory dysfunction or endometriosis, or when there is a degree of sperm factor dysfunction (count and motility) that requires sperm preparation prior to insemination. Success rate following IUI is dependent on:

- the age of the woman
- the number of developing follicles
- the endometrial thickness
- the duration and type of infertility
- the progressive motility of the sperm sample.

While there is debate over the true relevance of some of these factors, it is clear that the number of developing follicles is important, with a multifollicular response improving pregnancy rates. This multifollicular response is only possible if controlled ovarian stimulation is performed.

In male factor infertility, there are no set criteria for minimal sperm parameters to be used for insemination; however, it is recognized that a sperm preparation of $>2 \times 10^6$ motile sperm per mL is sufficient for IUI. When male factor is the sole cause of infertility, the pregnancy rate is similar following IUI in natural and stimulated cycles, but on both occasions better than timed intercourse. However, when multiple factors are present, stimulated IUI improves the pregnancy rate (although multiple pregnancy rates increase). Multiple pregnancies contribute significantly to perinatal mortality, morbidity and National Health Service costs.

In women with unexplained infertility, controlled ovarian stimulation and IUI results in higher pregnancy rates compared with natural cycles or with intracervical insemination only. Similarly, gonadotrophin-stimulated IUI increases the chance of pregnancy compared with gonadotrophins plus timed intercourse. In women with minimal or mild endometriosis, pregnancy and live birth rates are significantly higher with stimulated IUI cycles, although this is again associated with high multiple pregnancy rate. It is hypothesized that oocyte quality or other factors associated with endometriosis adversely affect the spontaneous pregnancy rate.
IVF and ICSI treatments

The decision to offer IVF or ICSI treatment should be based on the results of previous investigations and the precise diagnosis and duration of infertility, taking into consideration the probability of spontaneous pregnancy without treatment. However, a number of studies have shown higher pregnancy and live birth rates when couples resort to IVF treatment sooner rather than later. Current indications for IVF and ICSI treatments are summarized in Box 7.4.

Procedures involved in IVF and ICSI

In vitro fertilization treatment involves a number of principal steps that have remained relatively unchanged over the past 25 years. These include:

- superovulation (commonly called ovulation induction)
- oocyte retrieval
- IVF
- embryo transfer
- luteal phase support.

However, considerable refinements have taken place over the past decades, leading to significantly improved pregnancy rates.

Controlled ovarian stimulation

Superovulation protocols have evolved over the years – from the use of clomiphene citrate with or without gonadotrophins in the early years to more complex regimens using GnRH agonist and antagonists with subcutaneously administered recombinant gonadotrophins. Typical regimens now comprise a long down-regulation protocol using GnRH agonist with subsequent recombinant FSH or human menopausal gonadotrophin injections to induce scheduled follicular recruitment and growth of a cohort of mature follicles. Recently introduced GnRH antagonists have some advantages over the agonist group, namely shorter duration of treatment, absence of a flare-up effect and of pituitary down-regulation when used for a short interval, and lower risk of OHSS. However, they have been associated with lower clinical pregnancy rates. Follicular development must be monitored closely using ultrasound scans with or without hormone assays.

Box 7.4: Indications for in vitro fertilization or intracytoplasmic sperm injection treatments

- Tubal disease when surgery has not been successful or has been considered inappropriate
- Male factor infertility that is not correctable through other measures
- Endometriosis when other treatments have been deemed unsuitable or been unsuccessful
- Unexplained infertility when less invasive measures such as medical treatment or intrauterine insemination have not been successful
- Ovulatory disorders when other options have been exhausted and unsuccessful
- Egg donation due to premature ovarian failure or poor oocyte quality
- Intracytoplasmic sperm injection is indicated when there is severe impairment of sperm quality or number, or obstructive or non-obstructive azoospermia, and when previous in vitro fertilization treatment was accompanied by failed or very poor fertilization
Oocyte retrieval

Luteinizing hormone is given 34–37 h before oocyte retrieval to trigger the final stages of oocyte maturation. The transvaginal route is now the accepted standard technique for oocyte retrievals (Fig. 7.4), and the procedure is carried out mostly under conscious sedation for pain relief, administered by trained staff in the unit without the need for an anaesthetist as long as they follow guidelines published by the Academy of Medical Royal Colleges. NICE guidelines recommend that women undergoing transvaginal retrieval should be offered conscious sedation, as it is a safe and effective method.

Embryo transfer: day of transfer and technique

Embryo transfers may be carried out on day 2 or 3, or day 4 or 5, after oocyte retrieval. Ultrasound-guided embryo transfer has been shown in meta-analyses to increase the clinical pregnancy rates when compared with clinical touch technique, with the patient resting for about 20 min afterwards before resuming normal activity.

Luteal phase support

Superovulation protocols including GnRH agonists or antagonists would benefit from hCG and intramuscular progesterone supplementation, which result in higher clinical pregnancy and live birth rates. However, hCG is associated with a higher risk of OHSS and is generally not routinely recommended.

Success rates: IVF and ICSI

In 2006, the Human Fertilization and Embryology Authority (HFEA) reported the outcomes of 29,688 patients undergoing 38,264 IVF cycles between 1 April 2003 and 31 March 2004 and resulting in the successful births of 10,242 children. The average live birth rates for IVF treatment using fresh eggs ranged from 28.2% for women under the age of 35 years to 10.6% for those aged 40–42 years. The live birth rates following frozen embryo replacement cycles ranged from 16.8 to 6.9% for the same age groups.

Figure 7.4
Transvaginal oocyte collection showing needle within a follicle: (a) follicles, (b) needle tip, (c) ovarian tissue.
respectively. The multiple birth rate (twins and triplets) following fresh and frozen cycles for the same period was 23.6%.

Ectopic pregnancy rates based on analysis of 110,538 IVF treatment cycles that were registered by the HFEA between January 1995 and March 1999 and involved use of the woman’s own eggs and fresh embryo transfer showed an overall ectopic pregnancy rate per treatment cycle of 0.5% (18–25 years, 0.9%; >35 years, less than 0.3%).

Miscarriage rates based on analysis of the above 110,538 IVF treatment cycles showed an overall miscarriage rate per treatment cycle of 2.7%, while the miscarriage rate in women aged more than 35 years was 2.4%. Calculations based on numbers of pregnancies indicate a miscarriage rate per pregnancy of:

- 10.5% at 30 years
- 13.1% at 35 years
- 22.7% at 40 years
- 40.7% at 43 years.

These rates are comparable with those following spontaneous pregnancies.

**Clinical factors affecting success**

Analysis of the HFEA database and other national surveys has demonstrated that outcomes are affected by the following factors.

- Increasing duration of infertility significantly decreases live birth rate, irrespective of age.
- Male or multiple infertility factors are associated with lowest outcomes, but those with tubal, endocrine and unexplained infertility have comparable success rate with the probability of natural conception in young, fertile couples. Women with hydrosalpinges will benefit from pre-IVF salpingectomy and, equally, those with secondary infertility have higher pregnancy and live birth rates than those with primary infertility.
- Pregnancy and live birth rates following IVF decrease with advancing female age, irrespective of whether fresh or frozen embryos are used, with optimal treatment age between 23 and 38 years. Lowest pregnancy rates occur in women aged 40 or above. However, older women with good ovarian response, producing more than three embryos suitable for transfer, may have a pregnancy rate similar to that of younger patients, whereas cycles yielding less than three embryos have a poor prognosis.
- The transfer of a higher number of embryos results in a higher number of fetuses that might be born. This higher multiple pregnancy risk has its health risks on mother and babies, as well as economic implications. At present, the HFEA guidance is that no more than two embryos should be transferred during any one cycle of IVF. There are indications that an elective single embryo transfer policy should be adopted to further lower the risk of multiple pregnancy.
- Each IVF attempt has a similar success rate to the other; however, with increased number of treatment cycles advancing female age determines the outcome, and hence lower pregnancy and live birth rates may be observed.
• There is no evidence to suggest that tubal embryo transfer, zygote intrafallopian transfer or gamete intrafallopian transfer result in higher pregnancy or live birth rates.
• There are also differences in the success rates between the various centres.

Lifestyle factors
• Alcohol consumption in excess of one unit per day reduces the effectiveness of ART.
• Smoking by either partner has a negative effect on the outcome of treatment.
• Caffeine consumption has an adverse effect on outcome.
• NICE has recommended that the BMI of the female partner should be 19–30 kg/m² before commencing fertility treatment, as the likelihood of success is reduced outside this range.

Oocyte donation
Egg donation is an effective treatment for women with primary or secondary premature ovarian failure, gonadal dysgenesis such as Turner’s syndrome, following oophorectomy, and chemo- or radiotherapy-related ovarian failure, and when repeated failure of fertilization is attributed to poor oocyte quality. In addition, oocyte donation might be employed in women with markedly diminished ovarian reserve or to avoid the risk of transmission of a genetic disorder in cases in which the carrier status of both partners is known.

High pregnancy rates have been reported following oocyte donation for Turner’s syndrome patients. However, these women have a significantly higher biochemical pregnancy rate and early miscarriages, and lower clinical pregnancy and delivery rates, when compared with other women with premature ovarian failure. An important factor in the establishment of pregnancy is an endometrial thickness of greater than 6.5 mm. Other factors include the number of previous natural conceptions and live births, and the fertilization rate, but not advancing female age. Women with Turner’s syndrome should also be screened before their treatment to exclude phenotypic manifestations of the syndrome that might jeopardize successful pregnancy, including aortic dilation and cardiac lesions. All oocyte donors should be screened for both infectious and genetic diseases in accordance with guidance issued by the HFEA, and in view of the considerable emotional and social effects on both the donor and the recipient, counselling must be offered for all involved by someone who is independent of the treatment unit.

Male factor infertility
Gonadotrophins have been shown to improve fertility in men with hypogonadotrophic hypogonadism (e.g. secondary testicular failure, Kallmann’s syndrome). Pulsatile GnRH may be as effective in enhancing sperm production in some of these men. Injections of hCG are administered thrice weekly, with regular monitoring of testosterone response. FSH is added thereafter to induce spermatogenesis. The response is variable and depends on the precise cause, severity, time of onset and clinical features, and it may take months or years for sperm counts to increase to within the normal range.
However, no other drugs have been shown to be effective for idiopathic sperm abnormalities or antisperm antibodies. Furthermore, antibiotic therapy should not be used routinely for leukospermia unless a specific pathogen is isolated. Surgery for obstructive azoospermia improves fertility and is an appropriate alternative to percutaneous epididymal sperm aspiration (PESA) and IVF. However, surgery for varicoceles does not improve pregnancy rates. In men with anejaculation or retroejaculation, penile electrovibration or transrectal electroejaculation helps to retrieve motile sperm for IUI, IVF or ICSI, depending on its quality, and is preferred by many to medical therapy with its substantial side-effects. Should either or both approaches fail, PESA and IVF remain an appropriate alternative for these men. Anxiolytic drugs and/or sildenafil are recommended when ejaculatory failure is associated with erectile dysfunction of psychogenic origin.

**Risks associated with assisted reproduction treatment**

At each stage of ART, complications may occur, and some may even be life-threatening. Psychological and emotional effects are present before, during and after treatment and can adversely affect the couple’s relationship. They include concerns on the outcome of treatment, effects on the baby, multiple pregnancy and the risk of cancer.

The incidence of treatment-related complications varies. Adverse events during oocyte recovery and OHSS occur in 1.3–8.3% of cases. Operative complications associated with transvaginal oocyte retrieval include haemorrhage at the puncture site, serious intra-abdominal bleeding, bowel and ureteric injury, and pelvic infection. However, the most serious complication associated with ART is OHSS. Moderate or severe OHSS occurs in 0.5–10% of stimulation cycles, and up to 1% of all patients require hospitalization.

Identification of risk factors before treatment (young age, PCOS or thin body stature) and during treatment (excessive follicular development on scan and high oestrogen levels) is critical to the prediction and prevention of this life-threatening complication. Several strategies have been employed to prevent the development of OHSS, including use of a low starting gonadotrophin dose or dose reduction during treatment, close monitoring, coasting (withholding gonadotrophins for 24–64 h before the hCG injection), elective cryopreservation of all embryos, intravenous albumin administration during oocyte retrieval and avoidance of hCG for luteal phase support.

Treatment of established moderate or severe OHSS requires close monitoring of symptoms, biochemical profile and fluid balance. This may necessitate admission to hospital and treatment in a high-dependency unit if necessary. Additional measures for pain relief, thromboprophylaxis and paracentesis may be required.

Concerns have been expressed on the risk of ovarian, breast and endometrial cancers in women undergoing ovulation induction or IVF treatment. At present, there is no evidence of an increased risk of breast and ovarian cancer in women who have undergone IVF as compared with subfertile women. There does seem to be a small increased risk of endometrial cancer in those exposed to IVF, but this is also apparent in the unexposed group, suggesting a subfertility-related effect.
Obstetric complications are a further hazard of ART and extend throughout pregnancy itself and on to the peri- and neonatal periods. An overall early pregnancy loss of around 20% is comparable with spontaneous pregnancies, but there is a slightly increased ectopic pregnancy rate. A meta-analysis of 15 singleton pregnancy studies encompassing 1.9 million spontaneous and over 12,000 IVF pregnancies showed significantly increased rates of perinatal mortality, preterm delivery, low birth weight, placenta praevia, gestational diabetes and pre-eclampsia for IVF pregnancies. High multiple pregnancy rate following IVF is a significant contributor to adverse obstetric and perinatal outcomes, hence the HFEA guidance on reducing the number of embryos transferred to two only.

Acknowledgement

The publication of the National Collaborating Centre for Women’s and Children’s Health clinical guideline on the assessment and treatment of fertility problems on behalf of NICE has considerably influenced UK practice. The authors of this chapter have attempted to remain within the parameters of this guideline, which inevitably formed a principal source of the manuscript, and where appropriate presented alternative views based on more recent evidence.

References


Further reading

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National Collaborating Centre for Women’s and Children’s Health 2004 Fertility assessment and treatment for people with fertility problems. RCOG Press, London
SELF-ASSESSMENT

Patient 1

A 32-year-old woman with a history of oligomenorrhoea, hirsutism and weight gain is referred to you, having failed to spontaneously conceive for over 2 years.

**Question**

1. What factors would you wish to elicit in the history? What features should you look for during your examination? Which biochemical and radiological tests should you request?

**Answer**

1. Duration of symptoms. Other associated features (e.g. galactorrhoea, visual disturbance, headaches). Any features of virilization from history (e.g. deepening of the voice) or examination (e.g. increased muscle bulk, clitoromegaly)? Has the patient been hypertensive or diabetic? Does she have symptoms of easy bruising or proximal myopathy? Is there a relevant family history? Is she a smoker? Has there been any previous obstetric or gynaecological history of note, such as previous sexually transmitted disease or PID? Look for features of Cushing’s syndrome and hypothyroidism on examination. Check visual fields and examine for galactorrhoea.

Check prolactin, thyroid function tests, and gonadotrophin and androgen measurement (testosterone, DHEAS, androstenedione). Consider tests for Cushing’s syndrome (urinary free cortisol, dexamethasone suppression testing, salivary cortisol) and late-onset congenital adrenal hyperplasia (early morning follicular phase 17-hydroxyprogesterone). Perform urinalysis and measure fasting glucose. Request ovarian ultrasound scan if PCOS is suspected. Request magnetic resonance imaging (MRI) of pituitary gland if prolactin level is persistently elevated. Consider ovarian/adrenal MRI scans if testosterone is greater than 5 nmol/L.

The patient has a long history of oligomenorrhoea, dating back to the menarche. There is no galactorrhoea, visual disturbance or headache. Her hirsutism is mainly confined to the face and umbilicus, and there are no signs of virilization, Cushing’s syndrome or hypothyroidism. Her serum prolactin, thyroid function tests and 17-hydroxyprogesterone are normal and testosterone is 2.8 nmol/L, with a modestly raised androstenedione (14 nmol/L; normal range 4–10 nmol/L). Screening for Cushing’s syndrome is negative. Ovarian ultrasonography demonstrates 12 follicles of less than 10 mm in diameter at the periphery, with increased central stromal echogenicity. The patient’s BMI is 34 kg/m².

**Question**

2. What is the likely diagnosis? What would be your initial management strategy? How would you counsel her?
Answer
2. Polycystic ovary syndrome. Recommend weight loss and exercise, as well as smoking cessation if the patient is a smoker. Check rubella immunity. Begin folic acid (400 μg daily). Check for male factor infertility. Commence clomiphene citrate in the first instance if lifestyle measures are ineffective. If the patient fails to ovulate with clomiphene, then can add metformin. Counsel her that fertility is reduced and that weight loss is essential for improving fertility and other features of PCOS. Additionally, fertility can be improved with strategies comprising insulin sensitization, ovulation induction and/or IVF.

Despite clomiphene and metformin therapy, the patient does not become pregnant after 12 months.

Question
3. What other therapeutic options are there?

Answer
3. Gonadotrophin therapy with or without IUI, laparoscopic ovarian diathermy and IVF.

Patient 2

A 34-year-old woman and her 35-year-old partner are being seen in the fertility clinic with a 4-year history of primary infertility.

Question
1. What relevant information in the couple's history would you require, and what examination would you need to undertake in the initial assessment?

Answer
1. The female history would involve an assessment of previous contraception use and any associated problems (such as lost coil), previous pregnancies and outcome, medical history (e.g. pelvic infection, Crohn disease), surgical history (e.g. ovarian cyst, appendectomy), gynaecological history (cone biopsy, cervical smear history), current medical illness, drug history (prescribed and misuse), diet, smoking and alcohol consumption, galactorrhoea, hirsutism, menstrual regularity and menorrhagia, dysmenorrhaea, intermenstrual or postcoital bleeding, preovulatory cervical mucus recognition, and coital frequency and timing.

Examination would be general, with BMI, signs of endocrine disease, and abdominal examination. An ultrasound scan of the pelvis should be performed to assess uterine and ovarian morphology and to exclude any adnexal lesions such as hydrosalpinges.

The male history would assess occupation (exposure to excessive heat or toxins), medical history such as mumps and venereal disease, surgical history such as orchidopexy, inguinal hernia repair or vasectomy, current medical illness, drug history
(prescribed and misuse), smoking and alcohol consumption and any history of erectile
or ejaculatory difficulty. Examination would be general, with a BMI assessment.
Genital assessment is not necessary initially.

Question
2. What initial investigations would you obtain?

Answer
2. For the woman, day 1–3 FSH and LH levels, day 21 progesterone, Chlamydia
serology and rubella serology. For the man, semen analysis.

All these investigations are normal.

Question
3. What do you do next?

Answer
3. Tubal assessment: laparoscopy, or hysterosalpingogram or hysterosalpingo contrast
sonography.

Tubal assessment is normal. This couple therefore have a diagnosis of unexplained
infertility.

Question
4. What are the couple’s treatment options, and what are the success rates associated
with these?

Answer
4. Clomiphene citrate for 6–12 months; 40% of women will conceive within 12 months.
The main side-effects are hot flushes, pelvic discomfort and multiple pregnancy.

Intrauterine insemination has a 10–15% chance of success with each cycle. The main
risk is multiple pregnancy.

With IVF, the live birth rate is 20% per cycle. The main risks of this procedure are
ovarian hyperstimulation, multiple pregnancy, injury to bowel and blood vessels
during oocyte collection or, rarely, even death.