A. Title: Best Practice Article: Investigation and management of subfertility

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Abstract

Subfertility affects 1 in 7 couples and is defined as the inability to conceive after one year of regular unprotected intercourse. This article describes the initial clinical evaluation and investigation to guide diagnosis and management.

The primary assessment of subfertility is to establish the presence of ovulation and patent fallopian tubes in women, and normal semen parameters in men. Ovulation is supported by a history of regular menstrual cycles (24-35 days) and confirmed by a serum progesterone >30nmol/L during the luteal phase of the menstrual cycle. Common causes of anovulation include polycystic ovary syndrome (PCOS), hypothalamic amenorrhoea (HA) and premature ovarian insufficiency (POI). Tubal patency is assessed by Hystero-Salpingo-Graphy (HSG), Hystero-Contrast-Sonography (HyCoSy), or more invasively by laparoscopy and dye test.

The presence of clinical or biochemical hyperandrogenism, serum gonadotrophins (LH / FSH) and oestradiol, and pelvic ultrasound to assess ovarian morphology and antral follicle count, can help establish the cause of anovulation. Ovulation can be restored in women with PCOS using letrozole (aromatase inhibitor), clomifene citrate (oestrogen antagonist), or exogenous gonadotrophin administration. If available, pulsatile gonadotrophin releasing hormone (GnRH) therapy is the preferred option for restoring ovulation in HA. Spermatogenesis can be induced in men with hypogonadotrophic hypogonadism with exogenous gonadotrophins. Unexplained subfertility can be treated with *in vitro* fertilisation (IVF) after 2 years of trying to conceive.

Involuntary childlessness is associated with significant psychological morbidity; hence expert assessment and prompt treatment is necessary to support such couples.

Contents

Background

Subfertility is defined as the inability to conceive after 1 year of regular unprotected intercourse and it affects 1 in 7 couples in the UK[1]. Subfertility is not an absolute state and its definition simply reflects the likelihood of conception with time; 84% of couples will conceive within 1 year of trying and 92% within 2 years[2]. A couple who have not conceived after 1 year of regular unprotected sexual intercourse should be offered further clinical assessment. Owing to the prognostic impact of the female partner's age, NICE recommends that referral should be made sooner if the female partner is aged ≥36 years, or if either partner have a known cause of subfertility that would make further attempts to conceive without assistance futile e.g. amenorrhoea (absent periods), previous salpingectomy (removal of the fallopian tubes following previous ectopic pregnancy), azoospermia (absent sperm), or predisposing factors for subfertility.[1] In the UK, the most common causes of subfertility are 'male factor' subfertility (30%), ovulatory dysfunction (25%), tubal (20%), and uterine / peritoneal disorders (10%); however, 25% remain 'unexplained' following standard investigations.[1]

It is preferred that couples are reviewed in the consultation together as both partners are impacted by the investigation and treatment of subfertility.[1] Initial assessments can be commenced in primary care, however NICE recommends that couples have access to a specialist service as this improves effectiveness of management and patient satisfaction.[1]

History

For both partners, a history of prior conception establishes if subfertility is primary (no previous conception), or secondary (previous conception). Other important aspects of the history include: age, the duration of 'trying to conceive', the frequency of sexual intercourse, medication history (including over-the-counter medications), alcohol, smoking and illicit drug use (see Table 1). If pubertal development was incomplete, further history should include parental height, family history of disordered pubertal development, or anosmia that could suggest Kallmann syndrome.[3]

History in the female partner should also include: a full menstrual history (including average cycle length, number of menses per year and age of menarche) to establish the presence of oligomenorrhoea (cycle length >35 days or <8 cycles per year) or amenorrhoea (≥3 months without menses or < 3 menses per year). Regular menstrual cycles usually indicate ovulatory cycles in a young woman without hyperandrogenism. Symptoms of hyperandrogenism (e.g. hirsutism, acne) are consistent with polycystic ovary syndrome (PCOS).[4] Weight gain causing insulin resistance and a family history can increase the likelihood of PCOS.[4] Duration of hirsutism is important; a sudden severe onset of hyperandrogenism should prompt consideration of an androgen secreting tumour. Congenital adrenal hyperplasia (CAH) can be partial and is frequently underdiagnosed; thus CAH should also be excluded in women with hyperandrogenism. Hypothalamic amenorrhoea (HA) is caused by a combination of low body weight, psychological stress, excessive exercise and genetic predisposition. Thus, assessment of change in body weight, and in particular whether energy expenditure through exercise is likely to exceed energy intake from diet, as well as family history of menarche and menstrual disturbance, can help assess the likelihood of HA. A history of headaches, galactorrhoea, or visual field disturbance in combination with oligo/amenorrhoea could indicate a raised prolactin level due to pituitary pathology. Dyspareunia (pain during intercourse), dysmenorrhoea (painful menses), or pelvic pain could indicate endometriosis.

History in the male partner should encompass symptoms of testosterone insufficiency e.g. libido, potency, frequency of shaving, gynaecomastia and past medical history of risk factors for testicular dysfunction from infection (mumps orchitis, or sexually transmitted infections), previous cryptoorchidism, trauma, or previous oncological treatments (see Table 1).

Examination

Body mass index (BMI) should be evaluated to assess the likelihood of HA, PCOS, or obesity hypogonadism. The presence of secondary sexual characteristics should be assessed in both partners. Visual fields should be examined in patients with headaches, galactorrhoea, or other symptoms

consistent with pituitary dysfunction. Features of hyperandrogenism, including hirsutism assessed by the modified Ferriman Gallwey score[5], and pelvic examination should be performed in women. In men, assessment of testicular volume with a Prader orchidometer is a key examination to determine whether normal pubertal development has occurred. Obstructive azoospermia may be suggested by at least one testis >15ml, enlarged or hardened epididymis, or nodularity of the epididymis or vas deferens. Gynaecomastia (presence of firm glandular tissue behind the nipple) and body hair distribution can indicate low testosterone levels.

Investigations

Semen analysis

Semen analysis is essential in the diagnostic work-up of all subfertile couples. It should be performed after 2-5 days of sexual abstinence (see Table 2 for normal values). The results can be highly variable and thus usually at least 2 samples are required to confirm an abnormal result. A mildly abnormal result should be repeated in 12 weeks to allow time for a further cycle of spermatogenesis, however a severe abnormality e.g. azoospermia (absent sperm) should be repeated sooner. Abnormal values may prompt more detailed assessments of sperm function in a specialist centre. Often abnormalities may occur together (see Table 2); if oligozoospermia (low concentration), asthenozoospermia (low motility), and teratozoospermia (increased abnormal morphology) co-aggregate in the same patient, this is described as oligo-astheno-teratozoospermia (OAT). Urine microscopy and culture should be assessed in men with leukocytospermia. Post ejaculatory urine samples can be used to assess for retrograde ejaculation. Sperm antibodies in semen do not need to be measured routinely.[1]

Biochemistry

Confirmation of ovulation

Almost all young women with a history of regular menstrual cycles are ovulatory, however only 60% of women with hyperandrogenism and regular cycles are ovulatory. Thus, a serum progesterone in the mid-luteal (7 days after ovulation, or 7 days before predicted menses) should be measured as evidence of ovulation. A value >30 nmol/L is commonly used to confirm ovulation, however lower values may also indicate ovulation has occurred. A single serum progesterone level ≥15.9 nmol/L has a sensitivity of 89.6% and a specificity of 98.4% for detecting ovulation[6].

Anovulatory women

In all patients with amenorrhoea, the commonest cause is pregnancy and thus this should be excluded prior to further evaluation. PCOS is often associated with increased GnRH pulsatility (raised serum LH), whereas HA or hyperprolactinaemia is associated with reduced GnRH pulsatility (low serum LH).[7] Serum oestradiol is often preserved in women with PCOS, but can be reduced in women with HA, hyperprolactinaemia, or premature ovarian insufficiency (POI). Raised androgens could indicate PCOS, or congenital adrenal hyperplasia (CAH). A low serum sex hormone binding globulin (SHBG), which increases free androgen levels, can occur in overweight or insulin resistant women and thus can also be a feature of PCOS. A 17-hydroxy-progesterone (17-OHP) level should be assessed during the follicular phase in women with hyperandrogenism and if not low, referred to an endocrinology specialist service for further assessment with a stimulated level in a short Synacthen test.

Serum prolactin levels exhibit a diurnal variation with highest values typically during sleep, however levels are similar during waking hours and prolactin can be measured at any time of day.[8] A mildly elevated serum prolactin level (500-1000 mIU/L) can occur due to the stress of venepuncture,[9] hence it should be repeated in the first instance (perhaps by a cannulated prolactin if available). Drugs that antagonise dopamine e.g. some antipsychotic and antiemetic medications, and non-functioning pituitary adenomas causing ‘disconnection hyperprolactinaemia’, are also common causes of a raised prolactin level, in addition to a prolactin-producing pituitary adenoma (prolactinoma). A prolactin level that is persistently >1000 mIU/L, particularly in the context of amenorrhoea, galactorrhoea, visual field abnormality, or headaches warrants referral to endocrinology.[9] Macroprolactin (presence

of a large prolactin aggregate often complexed with an immunoglobulin that has decreased bioactivity) that causes a benign elevation in serum prolactin due to assay interference, should be excluded in all patients with a raised prolactin level.

Most women will undergo menopause between the ages of 45-55 years old.[10] Only 1% of women undergo menopause before the age of 40 years and thus if this occurs, this is termed 'premature'.[10] In women under 40 years of age, a serum FSH level >25 IU/l on two occasions at least 4 weeks apart indicates POI.[11] The clinical course of POI is more variable than following the natural menopause with up to 20% of women conceiving spontaneously and hence this condition is termed ovarian 'insufficiency' rather than the previously used 'failure'.[11] The cause of POI will require further investigation, as well as exclusion of possible autoimmune, or hereditary predispositions e.g. Fragile X syndrome premutations.[11] Thus, women with POI should be referred to a specialist service for further investigation of aetiology, to discuss prognosis, as well as to ensure appropriate management to prevent osteoporosis.[11]

Cushing's syndrome is a rare cause of menstrual disturbance with hyperandrogenism and weight gain, but if clinically suspected (reddish purple striae, plethora, proximal muscle weakness, bruising with no obvious trauma, and unexplained osteoporosis)[12], referral to an endocrinologist for further assessment is recommended. Overt thyroid dysfunction can lead to menstrual and ovulatory disorder associated with subfertility,[13] however NICE recommends only testing thyroid function in women with symptoms of thyroid disease.[1]

Ovarian reserve testing

The female partner's age hugely impacts both the chance of subfertility and the response to treatment. Ovarian reserve reflects the number of oocytes remaining within the ovaries and serves as an estimate of a woman's fertility potential. However, markers of ovarian reserve often do not predict fertility-related clinical outcomes such as 'time to conception', or 'time to menopause', more accurately than age alone.[14] Thus, measurement of ovarian reserve markers as part of a 'fertility M.O.T.' is not advocated. Ovarian reserve markers do correspond to the follicle pool capable of responding to

gonadotrophin stimulation during assisted reproduction, and thus can be used to predict the number of oocytes retrieved during IVF treatment. Thus, measurement of ovarian reserve markers prior to IVF treatment is indicated to ensure that appropriate dosing of gonadotrophins to manage the risk of over-response (potentially leading to ovarian hyperstimulation syndrome; OHSS), and of under-response (leading to insufficient follicular growth).

Total antral follicle count (AFC) on ultrasound (number of small antral follicles 2-10 mm) measured during the follicular phase, or serum anti-Mullerian hormone (AMH) levels can serve as useful markers of ovarian reserve. Serum AMH and total AFC correlate well to each other and thus either value can be used, although both are prone to measurement error for technical reasons. Serum AMH levels fluctuate only minimally across phases of the menstrual cycle and thus can be measured at any time, whereas AFC is best measured during the follicular phase. Assays for serum AMH have progressed over recent years to become more reliable. Currently, an international standard for AMH has yet to be agreed and different assays report different values. Thus, guidance from the local pathology service is required when interpreting AMH values.[15] However, NICE recommend that <5.4 pmol/L (Beckman Coulter generation II assay) is predictive for a low response during IVF treatment and >25.0 pmol/L a high response.[1] Similarly, a total AFC <4 is suggestive of a predicted reduced response and >16 an increased risk of hyper-response during IVF treatment. Serum AMH levels are also increased in PCOS and they are likely to form part of future criteria for diagnosis of PCOS,[16] although their measurement for this indication is not currently recommended.[4]

A raised serum FSH (>8.9 IU/L) during the early follicular phase is reflective of reduced ovarian reserve, albeit it is a relatively late feature.[1] NICE recommends against using ovarian volume, ovarian blood flow, serum inhibin B, or oestradiol as predictors of any outcome of fertility treatment.[1]

Gonadal function estimation in men with abnormal semen analysis

In males, the following blood tests should be requested to evaluate testicular function following 2 abnormal semen analysis results: fasting testosterone before 10 am (testosterone can fall physiologically during the afternoon and in response to a glucose load[17]), LH, FSH, albumin and SHBG. Testosterone

should be measured using equilibrium dialysis method if available, or free testosterone can be calculated using albumin and SHBG in patients with borderline testosterone values).[18,19] Testosterone levels can vary from day to day and thus at least 2 measurements are required to diagnose hypogonadism based on a low testosterone level.[19] Hypogonadotrophic hypogonadism (low serum testosterone <9.2 nmol/L with low or inappropriately normal FSH/LH) should prompt referral to an endocrinologist to exclude hypopituitarism. Iron studies (serum ferritin, transferrin saturation) should be performed as an initial screening test for haemochromatosis in patients with hypogonadism.

LH acts on Leydig cells to produce testosterone, which in turn negatively feeds back on LH secretion. FSH stimulates testicular Sertoli cells for spermatogenesis, which in turn produce inhibin B to negatively feedback on FSH secretion. Thus, a raised FSH level (>7.6 IU/L) in the context of hypogonadism is suggestive of primary gonadal failure, however FSH levels can be normal in up to 40% of men with impaired spermatogenesis.

Karyotyping

Karyotyping should be performed in women with ambiguous genitalia, or evidence of primary ovarian insufficiency, or clinical features suggestive of Turner syndrome (45X0). In men with testicular failure of unknown aetiology, a karyotype should be obtained to identify Klinefelter syndrome (47 XXY).

Microbiology

Chlamydia trachomatis[20] and gonorrhoea are frequent causes of tubal subfertility. Each episode of acute pelvic inflammatory disease (PID) causes subfertility in 10–15% of cases. A positive test should prompt both partners to be treated. HIV and Hepatitis B and C status should also be determined before the use of assisted reproduction.

Imaging

A transvaginal ultrasound (TVUS) provides information on uterine / ovarian anatomy, ovarian morphology and ovarian reserve (total AFC).[4] Access to the ovaries for transvaginal surgical retrieval of oocytes following controlled ovarian stimulation during IVF treatment can be confirmed. Tubal patency should be assessed in women with confirmed ovulation and partners with normal semen analysis by either Hystero-Salpingo-Graphy (HSG), Hystero-Contrast-Sonography (HyCoSy), or by 'laparoscopy and dye' test. HSG offers a robust assessment of tubal patency, however HyCoSy has the advantage of avoiding radiation exposure. Laparoscopy is an invasive test, but can be indicated to identify the presence of other pelvic pathology such as endometriosis.[21]

In males with azoospermia and normal testosterone and gonadotrophin levels, a scrotal US scan should be performed to exclude obstructive causes of male subfertility. Men with isolated congenital bilateral absence of vas deferens (CBAVD), frequently (~80%) have mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[22]

Management

Preconception advice

Alcohol

Alcohol consumption should be restricted to ≤4 units per week for women and ≤3 units per day for men, however it should be noted the Department for Health Chief Officers' guideline advise that the preferred approach is to not drink alcohol at all if planning conception.[23]

Smoking

Smoking has been shown to reduce female fertility[24, 25], therefore women should be offered referral to a smoking cessation service.[1] There is also an association between smoking and reduced semen quality in men[26] although the impact of smoking on male fertility remains uncertain.

Drugs

A number of prescription, over-the-counter and recreational drugs interfere with fertility and thus consideration should be given to minimising as many of these as possible [27, 28].

Tight-fitting underwear

There is an association between elevated scrotal temperature and reduced semen quality[29,30], however it is unclear whether wearing loose-fitting underwear improves fertility.[31]

Body mass index (BMI)

Men and women with a BMI >30 kg/m^2 should be advised that losing weight is likely to increase their chance of conception.[32,33, 34,35,36] Women with a BMI <19kg/m^2 with oligo/amenorrhoea should be advised that increasing body weight is likely to improve their chance of conception.[1] Women with HA and a BMI <18.5 kg/m^2 have an increased risk of foetal loss, small-for-gestational-age babies, and preterm labour during pregnancy, and thus should be encouraged to gain weight prior to ovulation induction.[37]

Timing of intercourse

The majority of pregnancies can be attributed to sexual intercourse occurring from 6 days before and including the day of ovulation [38,39], with the highest estimated conception rates occurring 2 days before ovulation.[40] However, timed intercourse can be emotionally stressful,[41] and ovulation can be difficult to predict[38], and thus is not routinely advised.[1] Consequently, couples should be advised that regular sexual intercourse 2 to 3 times a week optimises the chance of pregnancy as spermatozoa survive in the female reproductive tract for up to 7 days after insemination.[1] However, couples experiencing difficulties with intercourse every 2-3 days, or those using artificial insemination may benefit from the use of ovulation prediction kits.[42]

Folic acid supplementation

Women trying to conceive should take dietary supplementation with folic acid 400 micrograms daily up to 12 weeks' gestation to reduce the risk of foetal neural tube defects (5 mg daily if she has diabetes or is taking antiepileptic medications).[1]

Management of female subfertility

The World Health Organization (WHO) classifies ovulation disorders into three groups:[1]

- *Group I:* hypothalamic pituitary failure (e.g. HA, or hypogonadotrophic hypogonadism, or hyperprolactinaemia)
- *Group II:* hypothalamic-pituitary-ovarian dysfunction (e.g. PCOS)
- *Group III:* ovarian insufficiency (e.g. age-related or POI)

WHO Group I: Hypogonadotrophic hypogonadism

If a woman is not ovulating due to HA then advice on ensuring adequate energy availability for fertility (by avoiding excessive exercise and having adequate energy intake to achieve a BMI >19kg/m^2) can be recommended in the first instance.[37] Cognitive behavioural therapy (CBT) offers an option to restore ovulation and fertility without pharmaceutical treatment.[37] Provided that her BMI is ≥18.5 kg/m^2, and lifestyle advice has been trialled, then ovulation induction with pulsatile GnRH therapy (if available), or low dose gonadotrophins e.g. menotrophin can be attempted.[37] Women with hyperprolactinaemia should be offered treatment with a dopamine agonist e.g. cabergoline. Women with primary amenorrhoea and lacking pubertal development may have congenital hypogonadotropic hypogonadism (CHH). In these women, anosmia should be formally assessed with the University of Pennsylvania Smell Test to assess for evidence of Kallmann syndrome which can be treated with gonadotrophins to induce ovulation.[43]

WHO Group II: Normogonadotrophic hypogonadism

PCOS is the most common cause of normogonadotrophic hypogonadism with a relatively unchanged FSH level, often accompanied by a raised serum LH level (consistent with increased GnRH pulsatility). If overweight, weight loss of even modest amounts (5-10%) can improve rates of ovulation and should be encouraged. Ovulation can be restored using clomifene citrate, a selective oestrogen receptor modulator, which reduces oestradiol-induced negative feedback and thus increases FSH levels. Ultrasound monitoring for at least the first cycle is indicated to reduce the risk of multi-follicular growth and multiple pregnancy. If unsuccessful after 6 cycles, then IVF treatment can be considered. Although off-label for many years due to unfounded concerns of congenital birth defects, letrozole, an aromatase inhibitor, is an effective option for ovulation induction in PCOS.[44] Metformin can also be used as an adjuvant to aid in the metabolic dysfunction associated with PCOS.[4]

WHO Group III: Ovarian Insufficiency

For women with POI, spontaneous pregnancy can still occur, however the response to ovarian stimulation as part of IVF treatment is likely to be very poor. Thus, oocyte donation can be considered as an alternative option.

Tubal subfertility

Tubal subfertility can be referred for surgical tubal reconstruction if mild, but otherwise can be bypassed with IVF treatment. Hydrosalpinx can reduce live birth rates during IVF treatment and should be treated laparoscopically prior to commencing treatment. Endometriosis can cause intra-abdominal inflammation and scar tissue and can lead to anatomical obstruction of the fallopian tubes. It may also cause subfertility by producing cytokines that may be toxic to sperm or embryos.[45] For women seeking fertility, surgical excision or ablation plus adhesiolysis for endometriosis not involving the bowel, bladder or ureter, improves the chance of spontaneous pregnancy.[46] If the woman has fibroids, a myomectomy may be required to aid fertility, but fibroid embolisation is not recommended.[47]

Management of male subfertility

Hypogonadotrophic hypogonadism

In men with hypogonadotrophic hypogonadism, the prognosis is altered by whether previous testicular exposure to FSH has occurred. Patients with congenital hypogonadotrophic hypogonadism (CHH) have not undergone the 'mini-puberty' that normally occurs during the early neonatal period. Thus, these patients can have very small volume testes, near undetectable serum inhibin B levels and an increased risk of cryptorchidism.[48] These men may benefit from an initial period of isolated FSH administration to improve the success of subsequent induction of spermatogenesis.[48] For most men with acquired or partial hypogonadism (testicular volume >4mls), spermatogenesis can be restored by providing LH-like exposure to increase intra-testicular testosterone levels. This is often achieved using subcutaneous human chorionic gonadotropin (hCG) given twice weekly for 6 months. Thereafter, a repeat semen

analysis is performed to assess response, although response can take up to 2 years. Serum testosterone is monitored every 8 weeks and the dose halved if levels exceed 30 nmol/L. If the man remains azoospermic, human menopausal gonadotrophin (hMG) (which has both LH and FSH activity) can be added. Combination treatment can then be continued for a further 18 months. FSH should induce an increase in testicular volume to the adult range (15 mls) bilaterally over the course of a year. If sperm is insufficient for either *in vivo* or *in vitro* fertilisation, then sperm banking and intra-cytoplasmic sperm injection (ICSI) can be used. Obstructive azoospermia (the cause of azoospermia in up to a fifth of men) is less common than non-obstructive azoospermia. The success of ICSI is reduced when using sperm from men with non-obstructive azoospermia when compared to that from men with obstructive azoospermia or freshly ejaculated sperm.

In men who use exogenous anabolic-androgenic steroids, negative feedback on the hypothalamic-pituitary-testicular axis can occur, with a subsequent reduction in intra-testicular testosterone concentration.[49] This, in turn, can lead to azoospermia, testicular atrophy and hypogonadotrophic hypogonadism[50]. Recovery of sperm count from azoospermia occurs by 6 months in approximately two thirds of men.[51]

Primary testicular failure

The most common congenital form of primary testicular failure is Klinefelter syndrome (47 XXY). Men with Klinefelter syndrome can require lifelong androgen replacement and fertility can be supported using intracytoplasmic sperm injection (ICSI). Other causes include cryptorchidism (75% of males with bilateral cryptorchidism are subfertile), orchitis secondary to mumps or HIV, testicular trauma, and following chemotherapy or radiotherapy. It is important not to treat men, who are seeking fertility and have mild hypogonadism plus reduced sperm concentrations, with testosterone replacement therapy, as this could reduce endogenous serum gonadotrophin levels (due to testosterone induced negative feedback) and thus further reduce spermatogenesis. Gonadotrophins are essential to maintain the high intra-testicular testosterone levels required to support spermatogenesis.

Idiopathic semen abnormalities

In obstructive azoospermia, microsurgery can lead to successful pregnancies in up to 25% of couples within 18 months of treatment. During surgery, sperm is retrieved and stored for possible ICSI. Treatment of varicocele is uncertain; however, the evidence indicates no benefit to fertility from varicocele treatment in subfertile men who have normal semen analysis, or in those with subclinical varicocele. Thus, a varicocele repair should only be considered if there is clinically apparent varicocele, with oligospermia, subfertility duration of over two years and no other cause of subfertility identified.[52] Men with very low sperm concentrations (<5million) should be tested for Y chromosome microdeletions.

Unexplained subfertility

Unexplained fertility is defined as subfertility despite normal sexual intercourse occurring at least twice weekly, with normal semen analysis, evidence of ovulation in several cycles and normal patent fallopian tubes demonstrated on laparoscopy. Women with unexplained subfertility should be offered IVF treatment after 2 years of trying to conceive, in preference to ovulation induction with clomifene citrate.

Assisted reproductive techniques (ART)

Prior to commencing treatment, initial screening includes testing both partners for HIV, hepatitis B, hepatitis C, and, if indicated, thalassaemia and sickle cell.[1]

Intrauterine insemination (IUI)

IUI involves the injection of washed and prepared sperm into the uterine cavity through a catheter around the time of ovulation (either spontaneous or induced by hormonal treatments). It is indicated for couples who have barriers to vaginal intercourse (either due to a physical disability or a psychosexual problem), or following sperm washing where the man is HIV positive, or for couples in same-sex

relationships using donor sperm. Over half of women aged under 40 years will conceive within 6 cycles of IUI and 75% within 12 cycles. Ovulation induction (hormonal induction of ovarian follicular growth) may improve success rates but is associated with an increased risk of multiple pregnancy.

In vitro fertilisation (IVF)

Ovarian stimulation to induce growth of multiple follicles with ultrasound monitoring of the ovarian response to exogenous FSH is the first step in IVF treatment. Following controlled ovarian stimulation, oocytes are retrieved under ultrasound guidance and fertilised with sperm *in vitro*. The embryos are then incubated for 3-5 days, before the strongest embryo is selected for transfer into the uterine cavity. Remaining high-quality embryos can be cryopreserved for transfer in subsequent cycles. Luteal phase support in the form of progesterone supplementation is administered at least until confirmation of pregnancy to improve the chance of implantation. Women aged under 40 years who have had 2 years of regular unprotected intercourse should be offered up to three cycles of IVF treatment. Women aged 40-42 years should be offered one cycle of IVF treatment, provided that they do not have evidence of low ovarian reserve. On average, approximately one quarter of all IVF treatment cycles result in a live birth[53]. The chance of success reduces with increasing age of the female partner. The human fertilisation and embryology authority (HFEA) has issued guidance to discourage the use of multiple embryo transfers, which has been a successful strategy causing rates of multiple pregnancy to decline.[54]

Intracytoplasmic sperm injection (ICSI)

ICSI is predominantly reserved for the treatment of 'male factor' subfertility, as only a single spermatozoon of normal appearance is required to fertilise the oocyte. A viable spermatozoon is extracted from the sample and injected directly into the oocyte. ICSI is thus more labour intensive but can be indicated in men with low sperm counts, or in couples where fertilisation was poor in a previous IVF cycle.

Donor insemination

Donor insemination may be considered in azoospermia (not amenable to treatments), where there is a high risk of transmitting a genetic disorder (if pre-implantation genetic diagnosis (PGD) is not possible), or infection, or in the case of severe rhesus isoimmunisation.

Oocyte donation

Conditions where oocyte donation may be appropriate include: POI, gonadal dysgenesis, bilateral oophorectomy, or cases where there is a high risk of transmitting a genetic disorder to the offspring (if PGD is not possible).

Complications of ART

The most serious complication of IVF treatment is ovarian hyperstimulation syndrome (OHSS).[55] Women with a high serum AMH level, high AFC or polycystic ovary morphology, are at particularly increased risk of ovarian hyper-response and OHSS. OHSS occurs predominantly due to the use of hCG to 'mature' oocytes in preparation for retrieval. It results in leakage of fluid into the third spaces of the body, manifesting as lower abdominal discomfort, nausea, vomiting, ascites and pleural effusions. It can result in the need for organ support on the intensive care unit and rarely even mortality. Recently, kisspeptin has been used in place of hCG to avoid the occurrence of OHSS even in women at increased risk.[56] The use of elective single embryo transfer has helped reduced the risks associated with multiple pregnancy.

Conclusion

Subfertility can inflict significant psychological morbidity on affected couples and sensitive expert management is necessary to support such couples. For most couples, reduced fertility is not absolute; the diagnosis represents a reduced chance of conception rather than a complete inability to conceive. Thus, adequate time to conceive must be allowed before a delay in conception is medicalised. However, care must also be taken to ensure that those with very impaired chance of conception with expectant management, have prompt access to investigation and fertility treatment. The initial evaluation is to ensure the female partner is ovulating and has patent fallopian tubes, whilst the male partner has normal sperm parameters. In the absence of these, subfertility is termed ‘unexplained’, although for many couples more than one cause of subfertility may co-exist. The female partner’s age has a dominant impact on the success of treatment for subfertility. Overall, the prognosis is promising, but multiple treatment cycles may be required before a successful conception is achieved.

507 **Table 1: History, Examination and Investigation of female and male subfertility**

	Female	**Male**	**Both**
History			
	Ovulatory Cycles: Average menstrual cycle length (usually within ±2 days for most women), Number of menses per year, Contraception history. **Hypothalamic Amenorrhoea:** Weight loss, Excessive exercise, Psychological stress, Family history. **PCOS / CAH:** Hirsutism, Acne, Oligomenorrhoea **Endometriosis:** Dyspareunia, Dysmenorrhoea, Cyclical pelvic pain. **Pelvic Inflammatory Disease (PID)** Pelvic pain, discharge, STIs.	**Testosterone deficiency:** Libido, Potency / Erectile dysfunction, Shaving frequency, Gynaecomastia. **Risk factors for testicular dysfunction:** History of mumps / orchitis History of STIs Trauma Previous oncological treatments.	**General questions:** Duration of trying to conceive. Fecundity, Frequency of sexual intercourse, Pubertal milestones. Medical History, Medications, Alcohol, Smoking, Illicit drug use. **Prolactinoma:** Headaches, Galactorrhoea, Visual field impairment. **Kallmann syndrome:** Anosmia, Incomplete pubertal development. Can be associated with other features depending on specific cause e.g. hearing impairment, renal agenesis, synkinesia.
Examination			
	Signs of hyperandrogenism: Ferriman-Gallwey score for hirsutism. Acne. Pelvic examination.	Testicular volume with Prader orchidometer. Epididymal hardness / thickening. Presence of Vas Deferens.	Secondary sexual characteristics BMI
Investigations			
Male factor		Semen analysis	
Microbiology	Rubella serology		Chlamydia swab / urine test

Bloods	Mid-luteal Progesterone level **Oligomenorrhoeic / anovulatory:** FSH, LH, oestradiol, SHBG, testosterone, prolactin, follicular phase 17-OHP, serum AMH.	Pre-10am fasting testosterone FSH, LH, SHBG, albumin Iron studies for haemochromatosis.	*If undergoing ART:* HIV, Hepatitis B & C Thalassaemia / Sickle cell.
Imaging	TVUS, HyCoSy, HSG to assess tubal patency.	Scrotal US / Doppler for varicocele or obstructive causes.	

Abbreviations: AMH anti-Müllerian hormone, BMI body mass index, CAH congenital adrenal hyperplasia, FSH follicle stimulating hormone, HA hypothalamic amenorrhoea, HIV human immunodeficiency virus, HSG hystero-salpingo-graphy, HyCoSy hystero-contrast-sonography, LH luteinising hormone, 17-OHP 17- hydroxyprogesterone, PCOS polycystic ovary syndrome, PID pelvic inflammatory disease, SHBG sex hormone binding globulin, TVUS transvaginal ultrasound, US ultrasound.

Table 2. Semen analysis reference values (World Health Organization criteria)[57]:

	Normal Value	Description of Abnormality	Further specialist tests to be considered if abnormal
Semen volume	≥1.5 ml	Oligospermia	Consider obstructive causes / CBAVD- CFTR mutation. Aspermia (no ejaculate)– assess prostate and for retrograde ejaculation with post-ejaculatory urine analysis.
pH	≥7.2		
Sperm concentration	≥15 million spermatozoa per ml	Oligozoospermia <15million Severe oligozoospermia <5million Azoospermia (no sperm)	*If <10million:* Endocrine evaluation (FSH / LH / 10 am fasting testosterone) / Clinical examination / US Doppler for Varicocele. *If <5milion:* Chromosomal Analysis / PCR for Y microdeletions.
Total motility	≥40% motile	Asthenozoospermia	Anti-sperm antibody. Sperm viability and membrane test.
Vitality	≥58% live spermatozoa		
Morphology	≥4% normal forms	Teratozoospermia	Sperm penetration assay.

Abbreviations: CBAVD congenital bilateral absence of the vas deferens, CFTR cystic fibrosis transmembrane conductance regulator, FSH follicle stimulating hormone, LH luteinising hormone, PCR polymerase chain reaction, US ultrasound.

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