Subfertility

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Subfertility

It can be defined as failure of a couple to conceive after regular unprotucted sexual intercourse for one or two years Subfertility can be primary, in couples who have never conceived, or secondary, in couples who have previously conceived.

On average, subfertility affects one in seven couples .

The causes of subfertility can be male, female or mixed

The cumulative spontaneous pregnancy rate for a couple is approximately 57 per cent after three months, 72 per cent after six months, 85 per cent after one year and 93 per cent after two years Accordingly, only 50 per cent of couples failing to conceive during the first year will conceive in the second year, which justifies starting investigations for infertility after one year. However, if the physician or the patient has a reason to suspect impaired fertility, the process should be started sooner.
Furthermore,
if the female partner is 35 years of age or older, the investigations should not be delayed, given the rapid decline of female fecundity

Natural conception

- For a woman with a normal menstrual cycle of 28 days, ovulation occurs around day 14. The average survival time of the oocyte is around 24 hours, while after ejaculation sperm may survive for up to 7 days in the female reproductive tract.

Factors affecting natural conception

- Several general factors may adversely affect the natural conception rate. These are:
- • Age: natural conception declines significantly in
- the female after 35 years of age. This is due to the
- decline in oocyte quality and numbers.
- • Smoking: reduces fertility in females and semen
- quality in males.
- • Coital frequency: stress and anxiety may affect
- libido and coital frequency and thus impact on
- fertility. Recommended coital frequency is two to
- three times per week.
- • Alcohol: excessive alcohol is harmful to the fetus,
- and can also affect sperm quality.
- • Body weight: Over or under weight can affect
- ovulation; women with a body mass index (BMI)
- of >29 or <19 will have difficulty conceiving.
- • Drugs:
- • non-steroidal anti-inflammatory drugs (inhibi ovulation)

Factors affecting natural conception

- • chemotherapy (destroys rapidly dividing cells
- e.g. gametes);
- • cimetidine, sulphasalazine, androgen injections
- (affects sperm quality).
- • Occupational hazards: exposure to chemicals and
- radiation adversely affects male and female fertility.
- Therefore, it is very important to optimize one's health before conception. Besides giving patients life style advice regarding conception, it is also imperative to advise them to take peri-conception folic acid up to 12 weeks gestation as this reduces the risk of neural tube defects; and also offer women rubella screening
- so that those who are susceptible can be given rubella vaccination to avoid infants being affected with congenital rubella syndrome.

Causes of female subfertility

- The main causes of female subfertility can be related
- 1.to hypothalamic–pituitary–ovarian (HPO) axis dysfunction,
- 2..ovulatory disorders secondary to ovarian factors,
- 3… tubal disease and endometrial factors.

- 4… there is however, also a significant group of patients where their diagnosis is unexplained

1.Ovulation problems

- Ovulation is intricately regulated by the HPO axis. Gonadotrophin-releasing hormom (GnRH) controls the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland, and the process is regulated via a feedback loop. The surge of LH mid-cycle causes ovulation.

1.Ovulation problems

- The causes of anovulation can be classified
- according to the clinical findings when the level of disruption between the hypothalamic–pituitary axis and the ovary
- is assessed. This divides the causes of anovulatory infertility
- into three main categories –
- 1, ovulatory dysfunction,
- 2. hypogonadotrophic hypogonadism and

- 3.Hypergonadotrophic hypogonadism,

Ovarian dysfunction

- The most common presentation of anovulation is associated
- with normal gonadotrophin concentrations. Such normogonadotrophic anovulation is usually seen in polycystic ovary
- syndrome. PCOS is the most common endocrine disorder in
- women of reproductive age. In its classic form – a combination
- of oligomenorrhoea/anovulation and hyperandrogenism – it
- is estimated to affect >5 per cent of the female population.
- PCOS is also associated with a metabolic disturbance, central
- to which is peripheral insulin resistance and compensatory
- hyperinsulinaemia. Significant abnormalities in the very earliest stages of folliculogenesis may be the root cause of anovulation

Rotterdam criteria for diagnosis of PCOS

- Revised 2003 criteria (2 out of 3 for diagnosis)
- 1. Oligo- or anovulation
- 2. Clinical and/or biochemical signs of
- hyperandrogenism
- 3. Polycystic ovaries on ultrasound and exclusion
- of other aetiologies (congenital adren hyperplasia, androgen-secreting tumors Cushing syndrome)

Marker of ovarian reserve

In the ovary, anti-Müllerian hormone (AMH) is produced by the granulosa cells. AMH levels can be measured in blood and are shown to be proportional to the number of small antral follicles. In women, serum AMH levels decrease with age and are undetectable in the post-menopausal period. AMH levels represent the quantity of the ovarian follicle pool and are a useful marker of ovarian reserve. AMH measurement can also be useful in the prediction of the extremes of ovarian response to gonadotrophin stimulation for in vitro fertilization, namely poor and hyper-response

Hypogonadotrophic hypogonadism

- Failure of the pituitary gland to produce gonadotrophins
- will lead to lack of ovarian stimulation. There are a number
- of disorders of the anterior pituitary gland that lead to failure of production of FSH. These include destruction of the
- anterior pituitary by a tumour (e.g. a benign non-functioning
- adenoma or craniopharyngioma), by a pituitary inflammatory reaction as in tuberculosis, or following ischaemia
- as in Sheehan's syndrome. Rare congenital causes include
- Laurence–Moon–Biedl, Kallmann's and Prader–Willi syndromes. The pituitary can also be damaged by cranial irradiation or surgically at the time of hypophysectomy for a pituitary tumour

- Hypogonadotrophic hypogonadism will also occur if pulsatile secretion of GnRH is slowed or stopped.
- This is seen in hypothalamic dysfunction, commonly secondary to excessive exercise, psychological stress or anorexia nervosa

Hypergonadotrophic hypogonadism

- This occurs as a result of failure of the ovary to respond
- to gonadotrophic stimulation by the pituitary gland. The absence of negative feedback (by oestradiol and inhibin B) from a developing follicle results in excessive
- secretion of the gonadotrophic hormones FSH and LH.
- Concentrations of these hormones reach menopausal levels. Hypergonadotrophic hypogonadism classically results from premature ovarian failure with exhaustion of the ovarian follicle pool.

- A variant of the condition, resistant ovary
- syndrome, describes the occurrence of elevated levels of serum gonadotrophins in the presence of a good reserve of follicles. Abnormalities in the FSH receptor may produce this picture. Neither premature ovarian failure nor resistant ovary syndrome is treatable by FSH injection

- Other discrete causes Endocrine disorders, most commonly hyperprolactinaemia and hypothyroidism, are possible causes of anovulation and should be excluded by appropriate biochemical testing.

2..Tubal infertility

- Tubal damage underlies infertility in approximately
- 14 per cent of couples and 40 per cent of infertile women [C].
- Any damage to the Fallopian tube can prevent the sperm from
- reaching the oocyte or the embryo from reaching the uterine cavity, leading to infertility and tubal ectopic pregnancy,
- respectively. The Fallopian tube is more than just a ‘tube’: a
- number of key events occur within the tube, including capacitation of the sperm, fertilisation and the early development
- of the zygote and embryo. Therefore, the Fallopian tube may
- maintain its patency but lose the ability to promote these
- other functions. Currently accepted investigations can only
- test tubal patency, and not its function

2..Tubal infertility

- The main causes of tubal damage are either pelvic inflammatory disease (PID) or iatrogenic causes. PID remains
- the major cause of tubal damage in the western world, with
- Chlamydia trachomatis infection the prime pathogen in most
- cases. Pelvic infection or abscess caused by appendicitis, other
- bowel disorders or septic abortion is responsible for a lesser
- proportion of cases. Fallopian tubes can be damaged iatrogenically either directly, as in tubal ligation for sterilisation,
- or indirectly as a consequence of pelvic surgery. Other rare
- causes of tubal damage include tuberculosis, schistosomiasis,
- viral infection and abdominal inflammatory disorders, such
- as Crohn’s disease.

Endometriosis

- It is apparent that severe endometriosis can lead to mechanical tubal damage due to adhesion formation caused by the pelvic endometrial deposits. However, it is less certain whether the lesser degrees of endometriosis can lead to infertility. Both mild endometriosis and infertility are common, and
- may occur together as epiphenomena

Uterine factors

- Submucous leiomyomata, congenital uterine abnormalities,
- endometrial polyps and intrauterine adhesions are all potential causes of infertility. The presence of a fibroid that occludes
- or distorts the Fallopian tubes will lead to tubal infertility [D].
- Fertility outcomes are decreased in women with submucosal
- fibroids, and removal seems to confer benefit. Subserosal
- fibroids do not affect fertility outcomes, and removal does not
- confer benefit. Intramural fibroids appear to decrease fertility, but the results of therapy are unclear. Distortion of the
- uterine cavity, by a fibroid, a septum or in the T-shaped uterus
- following exposure of the female fetus to diethystilbestrol in
- utero, can lead to implantation failure and recurrent early
- miscarriage [D].

- Excessive uterine curettage after a miscarriage
- or abortion, especially in the presence of uterine infection, can lead to the destruction of the strata basalis endometrium.Intrauterine scarring and synechiae develop as a result, which is known as Asherman’s syndrome. This condition can also result after CS, uteroplasty or myomectomy. It has been difficult to demonstrate a relationship between endometritis and subfertility, except when the cause of endometritis is tuberculosis.

3. male subfertility

- In the human, the process of spermatogenesis starts
- at puberty and continues throughout life. The total
- process of spermatogenesis in humans takes 74 days
- within the seminiferous tubules. It takes a further ten
- days for the sperm to travel to the epididymis to be
- stored for use during ejaculation. The head of the
- epididymis stores 70 per cent of the mature sperm
- and, during ejaculation, the sperm exit via the vas
- deferens which then passes through the inguinal canal
- and opens into the urethra adjacent to the prostate

- The supporting cells of the testis are the Leydig and Sertoli cells. The Leydig cells are contained in the connective tissue of the testis and are the prime source of the male hormone, testosterone. LH from the pituitary gland regulates Leydig cell function by the negative feedback loop. The Sertoli cells arehighly specialized cells that maintain the integrity of the seminiferous epithelium (so that spermatogenesis can occur in an immune privileged area) as well as nourish the developing sperm.
- Approximately one in 20 men are subfertile, about 85 per cent have suboptimal semen quality, while azoospermia, coital dysfunction and immune factors contribute to the rest.

AETIOLOGY

- Primary testicular disease
- Obstructive male infertility
- Endocrinological causes of male Infertility
- Auto-immune causes
- Drugs
- Environmental factors
- Varicocele
- Ejaculatory disorders

Unexplained infertility

- Completion of standard investigation of infertility fails to reveal a cause in 15–30 per cent of cases [C]. This does not indicate absence of a cause, but rather the inability to identify it. The results of IVF have shown that there may be undiagnosed problems of oocyte or embryo quality or of implantation failure, neither of which can easily be tested unless IVF is undertaken. Unexplained infertility causes great distress to couples, who often find it harder to bear when a cause cannot

History taking and examination

- It is important to recognise that infertility is a problem that
- faces couples, and that both partners should be seen and investigated together whenever possible [E]. Consultations involving infertility require tact and sensitivity on behalf of the
- clinician, a quiet, private environment and sufficient clinical
- time to allow exploration of the couple’s anxieties and explanation of available treatments, as well as classical history taking. A rapport must be established before more personal a

Semen analysis

- Semen analysis should be performed after the patients have abstained from sexual intercourse for 3–4 days. Two abnormal test results are required to diagnose male subfertility.

- volume Lower reference limit
- Semen volume (ml) 1.5 (1.4–1.7)
- Total sperm number
- (106 per ejaculate)
- 39 (33–46)
- Sperm concentration
- (106 per ml)
- 15 (12–16)
- Progressive motility (PR, %) 32 (31–34)
- Sperm morpology (normal
- forms, %)
- 4 (3.0–4.0)
- Vitality (live spermatozoa, %) 58 (55–63)
- pH ³7.2

Examination of the female partner

- Unless there is an indication from the patient's history that examination would be of any value in establishing the cause o infertility, there would seem to be little to be gained from routine examination. Indications from the history, for example of cyclical pelvic pain or dyspareunia, should prompt pelvic examination. Other features of the physical examination, for example detection of an asymptomatic pelvic mass, have been supplanted by transvaginal ultrasound examination. Assessment of BMI is important, as both obesity and underweight can cause anovulation [C]. If the patient is found to be obese, central obesity can be assessed by measuring then waist:hip ratio [C

Laboratory investigations, endoscopy and imaging

- The aim of these investigations is to assess ovulation, tubal patency and uterine factors

Ovulation •

- A history of regular periods usually indicates ovulation. However, a reliable marker is useful to confirm that ovulation has occurred. After the release of the oocyte and the formation of the corpus luteum, progesterone levels rise sharply, reaching a peak level approximately 8 days after the LH surge. The detection of high levels of progesterone in serum or evidence of progesterone effect can be used as a secondary marker of ovulation. Historically, the effects of progesterone on basal body temperature, endometrial histology or cervical mucus were commonly used. Measuring serum progesterone at its peak in the mid-luteal phase is a reliable, safe and inexpensive test. Levels in excess of 30 nmol/L are diagnostic of ovulation [C];

Ovarian reserve tests

- Women with advanced age or history of prior ovarian surgery are at risk for diminished ovarian function or reserve. Given the relatively non-invasive nature of the testing, several practitioners are including the evaluation of ovarian reserve as first-line work up for infertility. The testing includes a cycle day 3 serum FSH and estradiol level, AMH or an ultrasonographic ovarian antral follicle count. However, NICE guidelines recommend that women who have high levels of gonadotrophins should be informed that they are likely to have reduced fertility. The results of these tests are not absolute indicators of infertility but abnormal levels correlate with decreased response to ovulation induction medications and lowered livebirth rates after IVF

Tubal patency tests •

- Although the Fallopian tube has functions other than as a conduit for the sperm, oocyte and embryo, it is not yet feasible to assess these functions in routine practice. Tubal patency can be assessed by three different methods: ultrasound scanning with hydrotubation; hysterosalpingography; and laparoscopy dye hydrotubation [D]

Ultrasound scan and hydrotubation

- HyCoSy (**hy**sterosalpingo **co**ntrast **so**nography) has recently been introduced as a method for studying tubal patency using ultrasonography. Ultrasonographic contrast medium is slowly injected into the uterine cavity under direct visualisation, with imaging of the cavity and of flow along the Fallopian tubes. This method does not require X-ray and allows the ultrasound assessment of the pelvic organs i.e. the uterus including the uterine cavity, tubes and ovaries. This screening method should be reserved for cases where history is not suggestive of tubal pathology. Finding a normal cavity and bilateral fill and spill of contrast is reassuring, but where there is doubt, hysterosalpingography or a laparoscopy and dye hydrotubation test should be performed.

Hysterosalpingography

- Hysterosalpingography (HSG)is a simple, safe and inexpensive X-ray-based contrast study of the uterine cavity and the
  Fallopian tubes with a 65 per cent sensitivity and 83 per cent specificity for detecting tubal blockage. The principle of this test is to inject a radio-opaque contrast medium through the cervix into the uterus and take abdominal X-rays at intervals during and after the injection. The images should reveal the uterine outline and passage of contrast along the tubes, with free spill into the peritoneal cavity. HSG is usually carried out in the first 10 days of the menstrual cycle, to avoid disruption of an early pregnancy in the secretory phase of the cycle. It will cause period-like pain in most patients and may occasionally lead to a vasovagal attack. The main complication of HSG is flare-up of PID. The overall risk of infection from this test in the normal population is approximately 1 per cent, rising to 3 per cent in high-risk patients. Therefore, it is wise to carry out laparoscopy and dye test in high-risk patients and to use prophylactic antibiotics to cover the test. RCOG recommends routine screening for chlamydia in any patient before carrying out any intrauterine instrumentation [E]. HSG is recommended by RCOG as the primary screening procedure in

Laparoscopy and dye test •

•

A laparoscopy and dye hydrotubation (‘lap and dye’) test is the most reliable, albeit expensive, tool used to diagnose tubal subfertility. The principle of this procedure is to visualise the passage of methylene blue dye through the Fallopian tubes The procedure enables inspection of the fimbrial ends of the tubes and the pelvic structures for the presence of endometriosis or adhesions. Combining this procedure with electrocoagulation of any endometriotic spots or adhesiolysis adds therapeutic value. Hence, it is advisable that such procedures are carried out in centres where the necessary expertise is available [E].

- Laparoscopy and dye test requires general anaesthetic and carries the risk of bowel or visceral injury. It is therefore not recommended as a first-line screening test [E].
  However, it should be considered in patients with a history suggestive of endometriosis, previous PID or previous pelvic surgery. Furthermore, if the HSG reports abnormal results, verification should be carried out with diagnostic laparoscopy [E].
  When comparing HSG with laparoscopy, keep in mind that both procedures provide extra information in addition to the assessment of the Fallopian tubes. HSG provides information about the status of the uterine cavity, whereas laparoscopy allows inspection of the intra-abdominal cavity, excludes peritoneal disease and allows laparoscopic treatmen

Assessment of the uterus •

- Uterine anatomy can be visualised by saline hysterosonography, HSG or hysteroscopy. Conventional TVS may not always
provide a good-quality image of the cavity, but 3D ultrasound, when available, can provide an accurate assessment of the uterine cavity. This may outline intrauterine polyps or synechiae. Routine hysteroscopy for infertile patients has been discouraged by RCOG [E].

Management of female infertility

- Any discussion about the management of infertility should begin with an explanation of the physiology of the cycle, with information about the ‘fertile period’. Among healthy women trying to conceive, nearly all pregnancies can be attributed to intercourse during a 6-day period ending on the day of ovulation.
  Lifestyle issues, including advice on smoking, alcohol consumption and ‘fitness for pregnancy’, should be raised. Further planning of treatment protocols will depend on the presumed cause of the problem

Management of tubal infertility

- Tubal infertility can be treated with tubal surgery, IVF and embryo transfer (IVF-ET) or selective salpingography.
  Although tubal surgery is no longer recommended for severe tubal disease since the introduct The cost, success rate, complications and benefits must be assessed in every case individually. Decision making may be altered in favour of IVF by the presence of other causes of infertility, particularly male factor and ion of IVF-ET, it still has a place in less severe forms of the disorder
- successful tubal surgery requires surgical skill and experience.
  The decline in the number of suitable cases has reduced training opportunities, and some advocate restriction of this practice to tertiary centres to allow concentration of expertise
  The success rate after tubal surgery depends on the underlying disease, site of damage (proximal or distal) and patient's age. NICE guidelines have suggested that for women with mild tubal disease, tubal surgery may be more effective than no treatment. In centres where appropriate expertise is available, it may be considered as a treatment option

- The cost of a single cycle of IVF has been calculated to be comparable to that of tubal surgery and, apart from patients with mild tubal disease, the cost-effectiveness argument is in favour of IVF-ET. However, tubal surgery, if successful, offers less risk of multiple pregnancy and ovarian hyperstimulation syndrome (OHSS), and avoids the ethical issues that fertilisation *in vitro* can engender. Patients should be informed that the risk of ectopic pregnancy after tubal surgery is significantly higher than after IVF-ET [C

IVF-ET

- Absent or irreparably damaged Fallopian tubes were the main reason for the development of IVF-ET. A lower pregnancy rate after IVF-ET in tubal-infertility couples compared to other causes of infertility has been reported. The reason is not entirely clear, but it is possible that fluid from a hydrosalpinx could be hostile to embryo development and implantation. Salpingectomy of an ultrasonographically visible hydrosalpinx should therefore be considered to improve the success rate of IVF treatment [C], although careful counselling is needed before performing salpingectomy for an infertile patient, even if the tubal damage is severe

Selective salpngography and tubal cannulation

- These procedures can be carried out under image intensification or at hysteroscopy. These methods were originally developed for diagnostic purposes, but were subsequently proven to be useful in treating proximal tubal damage, for which surgery yielded disappointing success rates. The outcome of these procedures in terms of regaining tubal patency is immediately known. According to NICE guidelines, for women with proximal tubal obstruction, selective salpingography plus tubal catheterisation, or hysteroscopic tubal cannulation, may be treatment options because these treatments improve the chance of pregnancy.

Management of anovulatory infertility

- Normalisation of bodyweight in underweight and obese patients can help to regain ovulation without the need for medical intervention [B]. Medical treatment of prolactinoma can also help regain normal ovulation [A]. Ovulation induction in patients with hypogonadotrophic hypogonadism can be achieved with the pulsatile administration of GnRH or by daily injection of gonadotrophin [C]. Ovulation induction in PCOS patients (80 per cent of anovular women) can be achieved by weight normalisation in obese patients [C] (40–60 per cent of PCOS patients)

The most common anti-oestrogen agent used is clomifene citrate (CC). CC induce gonadotrophin release by occupying the oestrogen receptors in the hypothalamus, thereby interfering with the normal feedback mechanisms, increasing the release of FSH and so stimulating the ovary to produce more follicles. Approximately 70 per cent of women on CC will ovulate, with a pregnancy rate of 15–20 per cent. There is a risk of multiple pregnancies (10 per cent) and therefore women on CC should be monitored by ultrasound scans to track the growth of their follicles

- medical or surgical methods. The medical methods include the use of clomiphene citrate or gonadotrophins .
  Assisted reproduction. NICE has recommended that women with WHO group II ovulation disorders (hypothalamic pituitary gonadal dysfunction), such as PCOS, should be offered treatment with clomifene citrate (or tamoxifen) as the first line of treatment for up to 12 months because it is likely to induce ovulation [A]. Additionally, women undergoing treatment with clomifene citrate should be offered ultrasound monitoring during at least the first cycle of treatment to ensure that they receive a dose that minimises the risk of mul tiple pregnancy.

- The surgical methods are either ovarian drilling or wedge resection. Stein and Leventhal suggested ovarian wedge resection in 1935. Their theory was that the thick tunica albugenia prevented the release of the ovum, hence the anovulation in PCOS patients. Although pregnancies resulted, the operation (performed by laparotomy) led to complications, including tubal damage and adhesion formation, and fell into disrepute. Ovarian drilling involves focal local destruction of the ovarian stroma with laser or diathermy, applied laparoscopically. The route of access reduces morbidity and postoperative complications. Ovarian drilling achieves equivalent ovulation and pregnancy rates to medical ovulation induction. Predictors of success have included LH level >10 IU/L, normal BMI and shorter duration o

- Economic analyses of two RCTs suggest that treating women with CC-resistant PCOS by laparoscopic ovarian drilling(LOD) resulted in reduced direct and indirect costs. On the other hand, the long-term advantages and risks of ovarian drilling require further assessment. Destroying ovarian tissue inevitably leads to destruction of primordial follicles and reduction of the ovarian reserve

Management of uterine factor infertility

- Congenital defects, leiomyomas and intrauterine adhesions and polyps are the only treatable uterine factors. However, before offering surgical treatment, the impact of such findings on the couple's fertility should be carefully assessed [E]. Myomectomy can be carried out either laparoscopically or by laparotomy
with similar postoperative pregnancy rates [A]. Entry into the uterine cavity should be avoided if possible, and adhesion barriers and microsurgical technique should be used to reduce the risk of postoperative adhesions. The risk of a scar rupture dur ng pregnancy is less if the endometrial cavity remains intact at
Submucous fibroids can successfully be resected hysteroscopically
Hysteroscopic division of intrauterine adhesions and excision of polyps are usually straightforward, with low morbidity.