Subfertility
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Definition:

Failure to conceive with unprotected regular intercourse in 1 year.
Primary subfertility: couples who had no previous conception.

Secondary subfertility: couples who had previous conception.
**Table 45.1 Diagnostic categories in infertility**

<table>
<thead>
<tr>
<th>Category</th>
<th>Primary (%)</th>
<th>Secondary (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anovulation</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Tubal</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Unexplained</td>
<td>30</td>
<td>20</td>
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</table>
50% of couples will conceive spontaneously after receiving advice and simple treatment. The remainder require more complex assisted conception techniques. 4% of couples will remain involuntarily childless.
Factors that reduce the chance of spontaneous conception

1. The age of female partner, the fertility reduced rapidly in woman over 35 years old.
2. Duration of infertility > 2 years
3. Low coital frequency and inappropriate timing of intercourse to ovulation
4. No previous pregnancy in current relationship
5. Smoking, alcohol, drugs.
6. Body mass index outside the range 20-30 (weight Kg/length 2 m2)
Causes of female subfertility

**Ovulation problems:**
Can be classified according to the clinical findings when the level of disruption between the hypothalamus-pituitary axis & the ovary is assessed.
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 mechanism by oestradiol & inhibin B from a developing follicle results in excessive secretion of FSH (follicular stimulating hormone) & LH (luteinizing hormone).
- Causes of Hypergonadotrophic hypogonadism: premature ovarian failure, resistant ovarian syndrome.
- Neither premature ovarian failure, resistant ovarian syndrome is treated by injection of FSH.
Due to hypothalamic disorders, when the pulsatile secretion of the GnRH is slowed or stops.

Causes:

Excessive exercise, psychological stress & anorexia nervosa.
Failure of the pituitary gland to produce gonadotrophins

Causes:

1. Destruction of the anterior pituitary gland by tumor (craniopharangioma, benign non-functioning adenoma).

2. Pituitary inflammatory reaction as in tuberculoses, sarcoidosis.

3. Ischemic changes as in Sheehan syndrome.


5. Surgical causes at the time of hypophysectomy for pituitary tumor.

6. Damage during cranial irradiation.
Ovarian dysfunction:
The commonest cause of anovulatory subfertility is PCOS (polycystic ovarian syndrome), the diagnosis is based on the biochemical abnormalities (low sex hormone binding globulin concentration & high androgen concentration), with U/S appearance of the ovaries (an enlarged ovaries, multiple subcapsular follicles & dense stroma).
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 adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome)
Marker of ovarian reserve

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. 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 ovaria response to gonadotrophin stimulation for *in vitro* fertilization, namely poor and hyper-response.
Other causes:

Endocrine disorder, e.g.: hyperprolactinemia, both hypothyroidism & hyperthyroidism
Tuba l infertility:
Tubal damage may be caused by:
1: Pelvic infection which is caused by:
   Sexual transmitted disease caused by Chlymedia
   trachomatis, gonococci & other microorganism can
   lead to tubal damage.
   Pelvic sepsis following appendicitis or peritonitis.
2: Endometriosis, this lead to mechanical damage of
   the tube because of adhesions formed.
3: Pelvic surgery.
(a) Photograph of a normal fimbriae end of a Fallopian tube during laparoscopy. (b) Photograph of a right hydrosalpinx.
Disorder of implantation:

- Endometrial polyp
- Submuocosal fibroid
- Asherman syndrome (intrauterine adhesion)
- Congenital abnormal uterine cavity.
Magnetic resonance image of a large fibroid within the cavity of the uterus (yellow circle).
Unexplained infertility:

Completion of routine investigation of infertility fails to reveal a cause in 15-30% of cases.

Causes of male subfertility:

Disorder of spermatogenesis
Impaired sperm transport
Ejaculatory dysfunction
Immunological & infective factors
Management:

**History:**

**Personal & social history:**
The couple's age, occupation of the male, exposure to high temperature, chemicals, ionizing radiation may affect the production of the sperm. Smoking, alcohol, drugs.

**Menstrual history**, age of menarche, regularity, duration, of the cycle, any associated pain (dysmenorrheal).

**Obstetric history:** include history about the previous pregnancy from current & previous relationship, the pregnancy outcome, any difficulties in getting pregnant & ask about the breast feeding.
Contraception history: the use of oral contraception pills & long acting progesterone may associate with a period of amenorrhea. The use of intrauterine contraceptive device increases the risk of pelvic infection.

Past medical history: any medical problem should be discussed prior to pregnancy, use of antidepressant drugs increase prolactin secretion & NSAID may affect the ovulation.

Sexual history: Frequency of intercourse around the period of ovulation.
Examination:

An examination of both partner is essential to ensure normal reproductive organs.

Assessment of body mass index.

General & pelvic examination
Investigation:

Assessment of ovulation:

- Temperature
drops at the time of menses
rises two days after the lutenizing hormone (LH) surge

An early follicular phase (day 2-5) measurement of (FSH&LH) assesses the reserve of oocyte.

Measure of mid luteal progesterone level.
Serial U/S to assess the size of the follicle.

Look for endocrine abnormality by measuring thyroid hormones level, androgen & prolactin level.
FIGURE 39.3. Ovulation associated biphasic basal body temperature pattern.

*Preferred time for hysterosalpingogram (HSG) testing.
†Preferred timing for sonographic assessment for ovulation.
‡Optimal interval for serum progesterone measurement for ovulation.
Assessment of tubal patency:

Hystrosalpingography: by injection of radio-opaque contrast medium through the cervix into the uterus & take abdominal X-ray at intervals during & after injection.

Is usually carried after completion of the menstrual blood flow during the 1st 10 days of the cycle.

2: Hystro contrast sonography (HyCoSy):

Ultrasonographic contrast medium is slowly injected through the cervix, visualization done by US, this method does not require X-ray.

3: Laparoscopy: the principle of this procedure is to visualize the passage of methylene blue dye through the tubes, direct visualization of the fimbrial ends & pelvic structures.
Assessment of the uterine cavity:
By hysterosalpingography & hysteroscopy.
Post coital test:

Has limited prognostic value & is rarely used today it involves the assessment of the peri ovulatry cervical mucus & sperm in sample obtained from female partner 6-10 hours after coitus.
Semen analysis:

- Volume: 2-5 ml
- Liquification time: within 30 minutes
- Sperm concentration: 20 million/ml
- Sperm motility: >50% progressive motility
- Sperm morphology: >30% normal forms
Treatment:

Ovulation problems:

• Those with hypothalamic disorder from excessive weight gain or low body weight should optimize their weight.
• Those with stress should modify their lifestyle.
• Patient with hyper prolactineamia should do full investigation to exclude medical & physiological causes.
• With PCOS, insulin sensitizing drugs like metformin may lead to resumption of normal ovarian activity.
• Ovarian drilling by use of thermal needle is use lapnic roscopically to make multiple small holes in the surface of the ovary.
• Restore ovulation
  • Administer ovulation inducing agents
• Clomiphene citrate
  • Antiestrogen
  • Combines and blocks estrogen receptors at the hypothalamus and pituitary causing a negative feedback
• Increases FSH production
  • stimulates the ovary to make follicles
• Ovulation induction can be made by anti oestrogen medication including clomiphene citrate, tamoxifin or exogenous gonadotrophin to stimulate the development of one or more mature follicle.

• Clomiphene citrate is administrated during the follicular phase of the menstrual cycle. It is effective in inducing ovulation in 85% of cases.

• Ovulation induction can be induced by exogenous gonadotrophin by daily injection from the beginning of the cycle, the dose is titrated against the individual response.
If no response with clomid then gonadotropins- FSH (e.g. pergonal) can be administered intramuscularly
This is usually given under the guidance of someone who specializes in infertility
This therapy is expensive and patients need to be followed closely

Adverse effects
Hyperstimulation of the ovaries
Multiple gestation
Fetal wastage
Surgical treatments
Lysis of adhesions
Septoplasty
Tuboplasty
Myomectomy
Surgery may be performed
laparoscopically
hysteroscopically
If the fallopian tubes are beyond repair one must consider in vitro fertilization
Tubal disease:
the aim is to restore the normal anatomy of the tubes.
The success rate depends on the severity, location of the damage as well as the skills of the surgeon.
Male fertility depends on sperm quality rather than the absolute number of sperm present. Men with hypogonadotrophic hypogonadism are treated with exogenous gonadotrophins and hCG to restore testicular volume and spermatogenesis.

Hormonal therapy is, however, ineffective at restoring sperm production or function in men with idiopathic oligospermia.

In these men intrauterine insemination with ovarian stimulation may be an appropriate treatment.
• Alternatively, couples may choose to proceed to IVF with intracytoplasmic sperm injection.

Men with obstructive azoospermia can be offered sperm aspiration followed by IVF with ICSI treatment. Although 25 per cent of men with abnormal sperm parameters have a varicocele, there is no evidence that surgical ligation improves fertility.
Assisted conception

Assisted conception techniques have, since their introduction in the late 1970s, enabled more than a million babies to be conceived.

These conceptions have depended on the development of laboratory, clinical and pharmaceutical advancements that have simplified and improved the treatment of subfertility. Intrauterine insemination, IVF and ICSI are widely used throughout the world to assist conception.
Meet Louise, the world’s first test-tube arrival

SUPERBABE

Wide-eyed Louise Brown pictured in hospital 18 hours after she was born. Today she’s doing well. See Page Three
A typical IVF-Embryo transfer cycle

- Initial consultation
- Pituitary down-regulation
- Superovulation ovarian stimulation
- Ovulation trigger with hCG trigger
- Oocyte collection
- Insemination of oocytes
- Embryo transfer
- Luteal support
- Pregnancy test
Pituitary down-regulation

Pituitary down-regulation is essential to prevent a natural LH surge during follicular stimulation as this would result in follicular rupture prior to egg retrieval. Treatment with GnRH analogues, given by daily injection, implant or nasal spray, prevents the natural LH surge and is continued throughout the treatment cycle.

Alternatively, GnRH antagonists can be administered during the mid- and late follicular phases of a super ovulation cycle to prevent the LH surge. A low serum oestradiol level (< 100 \( u/L \)) or thin endometrium on ultrasound scan are used to confirm down-regulation of the pituitary.
Ovarian stimulation

- Ovarian stimulation is achieved by daily injections of gonadotrophins (either recombinant or urinary). The injections are continued for 11-14 days until the lead follicles are 18 mm in diameter on transvaginal ultrasound scan.
Ovulation trigger with hCG

- In the stage of ovulation trigger with HCG, HCG is used in place of LH to trigger ovulation. The oocytes are retrieved 34-38 hours after the injection.
Oocyte collection

Oocyte collection is normally an outpatient procedure carried out under transvaginal ultrasound guidance with the woman under intravenous sedation.

The follicular fluid is aspirated from each follicle using a controlled pressure vacuum pump. Using a microscope, the embryologist identifies the oocytes removed in the follicular fluid and then transfers these to culture medium in an incubator.
During sperm preparation, the sperm sample is washed to remove seminal plasma, leukocytes and bacteria. A laboratory process that allows the sperm to mature and undergo capacitation is performed, and the motile sperm can then be selected for use in the insemination process.
Insemination

In insemination the prepared sperm is mixed with the oocytes 4-6 hours after collection and incubated. For ICSI the eggs require an additional step to remove the surrounding cumulus cells prior to the injection of a single sperm into the cytoplasm of each oocyte.

Whatever the process of insemination, the next stage involves incubating the oocytes with the sperm for 16-18 hours.

Next is fertilization and embryo cleavage. The oocytes are examined for fertilization on the day after oocyte retrieval. The presence of two pronuclei and two polar bodies indicates normal fertilization. After 48 hours in culture, the embryos are examined for cleavage, and any cleaved embryos are assessed for quality. An embryo with minimal fragmentation will be graded more highly than one with many fragments.
Embryo transfer

In embryo transfer, the embryos are transferred into the uterus using a transcervical catheter on the second or third day of culture. In the UK regulations permit only two embryos to be transferred, except in exceptional circumstances.

Any spare embryos of good quality can be subject to embryo cryopreservation, with storage in liquid nitrogen for use in a frozen embryo replacement cycle in the future. The embryos can remain in storage without deterioration until they are required.
Luteal support and establishment of pregnancy

Luteal support can be provided by progesterone supplements in the form of vaginal pessaries, suppositories or injections. Alternatively, low-dose hCG injections are used to stimulate progesterone production by the ovary. Pregnancy is detected by a urinary pregnancy test or by analysis of the serum HCG 14 days after embryo transfer.
Intrauterine insemination

Intrauterine insemination involves the placement of a sample of purified sperm in the uterus at the time of ovulation. It is most successful if it is combined with ovarian stimulation to produce up to three mature follicles.

Close monitoring of the treatment is essential as there is a high risk of multiple pregnancy if treatment continues when more than three follicles have formed. It is used to treat mild male factor subfertility as well as unexplained subfertility. Although the success rate varies between assisted conception units, approximately 10-15 per cent of couples manage to conceive by this method.
Complications of assisted conception

Complications of assisted conception include the development of ovarian hyperstimulation syndrome, ectopic pregnancy and multiple pregnancy.

**Ovarian hyperstimulation syndrome**

Ovarian hyperstimulation syndrome develops in women who have had an exaggerated response to the exogenous gonadotrophins or gonadotrophin analogues used for superovulation. Women who develop 20 or more follicles or have pcos are more likely to develop the condition.

It occurs after the administration of exogenous hCG or after the natural rise in hCG with conception. Patients present with abdominal pain and distension, nausea, bowel disturbance, shortness of breath and poor urinary output. These patients may require inpatient care by a specialist team.
Ectopic pregnancy

Four per cent of pregnancies arising from IVF treatment will be ectopic, with an increased risk in women with known tubal damage. The embryos may migrate to the Fallopian tubes or are inadvertently placed there during the embryo transfer procedure.
Multiple pregnancy

Assisted conception often results in a twin or higher order pregnancy. This condition can be prevented by prevent the transfer of more than two embryos except in exceptional circumstances, when three may be transferred.

In stimulated intrauterine cycles or in ovulation induction with gonadotrophins or anti-oestrogens, careful monitoring is paramount in avoiding multiple pregnancies. Multiple pregnancies have increased morbidity and mortality for both the mother and the fetus.