Infertility and Sterility – Causes, Diagnosis and Management

Many young couples suffer from an unfulfilled wish to bear children. Men, as well as women, may be the physiological cause of this barrenness; regardless, undesired childlessness always implies a great amount of emotional distress for both partners. The diagnostic process involves extensive testing of both the man and the woman, including a hormone analysis of the blood and physical examinations. The terminological distinction between sterility and infertility has to be considered. Treatment consists in artificial insemination techniques, such as IVF or ICSI.

Definition of Sterility and Infertility

With regard to terminology, infertility has to be distinguished from sterility. Sterility is the inability to conceive after two years of regular intercourse. It is further sub-divided into primary and secondary sterility. Primary sterility is the complete inability to become pregnant, while secondary sterility refers to the failure to conceive after a previous successful pregnancy.

Infertility, on the other hand, is the inability to successfully carry a baby to term and give birth; i.e., conception is feasible but the pregnancy cannot be completed. This may take the form of miscarriages or extrauterine pregnancies.
Epidemiology of Sterility and Infertility

Sterility and infertility affect about 10 - 15% of couples. This number has been rising continuously over the last few years. This may partly be due to the fact that the average age at which women give birth to their first child also keeps rising because of occupational preferences and longer periods of education.

Etiology of Sterility

Causes of sterility can be manifold and diverse. In a third of cases, the reason lies only with the man; in another third, it is because of the woman; and in the rest of the cases, it is a combination of both, or the cause is unknown.

Causes of Sterility in Men

To assess the causative factors of sterility in a man, a semen analysis is performed. The resulting sperm count (also called spermiogram) allows identifying various pathologies.

- **Oligozoospermia** refers to a low sperm count under 20 million per milliliter.
- **Asthenozoospermia** refers to reduced sperm motility.
- **Teratozoospermia** is when there are a large number of sperms with abnormal morphology.
- A combination of all of these conditions is accordingly termed **oligoasthenoteratozoospermia** or short **OAT syndrome**.

Spermiogenic defects may also be a cause of sterility. Here, the hormones **FSH** (= follicle stimulating hormone) and **LH** (= luteinizing hormone) play an important role. The Leydig cells in the testicles control the LH, and the cells build androgens.

Malformations are the primary organic causes of sterility. This includes injuries to the testicles, epididymides, prostate, or the urethra. Often, **varicoceles** or past infections such as **mumps orchitis** are the cause of sterility.

Especially in men, **psychological explanations** should be considered as they are frequently the cause of sexual dysfunctions. Most typical are decreased libido, erectile dysfunction, orgasmic dysfunction, and ejaculatory dysfunction. Studies have shown that psychological issues contribute to reducing the sperm quality.
Causes of Sterility in Women

In women, the classification of possible causes is much more complex. Clinical examinations start with ovarian causes of sterility. A hypothalamic-hypophyseal ovarian failure can lead to a reduced GnRH production, which, in turn, leads to an insufficient release of LH and FSH. Consequently, amenorrhea, an anovulatory cycle, and corpus luteum deficiency can develop. The reduced release of gonadotropin is often triggered by stress, physical strain such as high-performance sports, and anorexia nervosa.

Hyperandrogenemic ovarian insufficiency is characterized by an immoderate production of androgen. The patients often suffer from appearances of virilization and manlike hair patterns. A typical disease is polycystic ovarian syndrome.

Due to increased levels of prolactin, the pulsatile release of GnRH is inhibited. Prolactinomas or the intakes of dopamine antagonists (typical antipsychotics for example) cause hyperprolactinemia. An ovarian insufficiency can also occur from the decreased release of gonadotropins.

The cause of sterility can also be found in the tubes. Transitions of the tube mucosa with luminal adhesions develop from recent infections of the genitalia involving the adnexa. Adhesions with the surrounding tissue can develop as well, and reduce the motility of the tubes.

A typical infection is particularly the adnexitis from Chlamydia, but also infections from Trepona pallidum (lues) and Neisseria gonorrhoea should be kept in mind. Peritubaric adhesions can be caused by endometriosis.

Abnormalities of the uterus like the uterus bicornis, uterus septa or hypoplasia of the uterus less frequently result in contraceptive barriers but can cause miscarriages. The endometrium can be damaged from previous curettages or infections like endometritis. That is why a complete build-up of the endometrial mucosa is not possible anymore. Furthermore, myomas in the uterus lead to occlusions of the lumen and so cause sterility.
The cervix uteri can also cause infecundity. Old cervix disruptions or infections of the cervical canal are a possible cause. Lack of estrogen brings about decreased spinnbarkeit of the cervical mucus. This averts normal ascension and motility of the sperm.

Furthermore, an immunological cause in the cervical mucus is possible. Antibodies against the sperm in the cervical mucus particularly often occur in sterile marriages.

Psychic causes are possible in women just like they are in men. A majority of the results are in the normal range here which is why it is also called idiopathic sterility.

Diagnosis of Sterility

An important part of the diagnosis is a detailed anamnesis and the routine gynecologic examination. The anamnesis includes sexual behavior concerning ovulation here. To complete a basal temperature curve over 3 cycles can be helpful to identify anovulational cycles.

Furthermore, hormone analyses are made. The following hormones can be identified in the blood among others: FSH, LH, estradiol, prolactin, testosterone, DHEA-S and the thyroid hormones.

To analyze tubal causes of sterility, different methods can be considered. For hysterosalpingography, water-soluble contrast material is supplied into the cavum uteri. Afterward, radiographs are taken and the contrast material can be seen in the abdominal cavity if the tubes are pervious. Tubal obstructions can precisely be localized like this.

Motility, adhesions and foci of endometriosis can precisely be assessed by laparoscopy with blue instillation. Benefits of laparoscopy are especially the possibility to simultaneously remove adhesions in one session.
The reflection of malformations, dysplasia or hypoplasia of the uterus is possible with hysterosalpingoscopy. To ascertain a more precise assessment, a hysteroscopy of the uterus is run.

To examine the sperm motility in the cervical mucus, the postcoital test is made. This takes place during ovulation of the woman. A 3 to 5 days long sexual abstention is absolutely necessary for this. On the day of ovulation, a mucus sample is taken after intercourse. This is taken from the vaginal vault as well as from the cervical canal. Afterward, the mucus specimen is phase-microscopically examined. The test is rated positively when motile sperm can be proved in the mucus.

Negative tests with immotile sperm in the cervical mucus suggest rare immunological causes of sterility. Immotility of the sperm can be caused by antibodies against the sperm.

Medicamentous Induction of Ovulation

Ovulation inductors are used for dysfunctions in the hypophyseal-hypothalamic area. These are agents that support the follicular maturation and the secretion of gonadotropins. Typical drugs are clomifene, cyclofenil, tamoxifen, and epimestrol among others. The substances are preferentially used at the beginning of the cycle.
The drugs are indicated for diseases like **corpus luteum insufficiency**, anovulational cycles, and normogonadotropic **amenorrhea**.

To reach timely ovulations, ovulation triggers are combined with **chorionic gonadotropin** (beta-HCG).

A typical adverse effect can be ovarian hyperstimulation. Additionally, multiple pregnancies cumulatively occur after ovarian stimulation. An increased rate of abort is also possible.

### Ovarian Hyperstimulation Syndrome (OHSS)

The syndrome occurs due to treatment with medicamentous ovulation inductors. Typical characteristics are **ascites** and **cyst formation** of the ovaries.

![Bilateral multilocular cystic masses in a patient with ovarian hyperstimulation syndrome in a spontaneous pregnancy with invasive mole](https://example.com/image)

It is the most common complication of assisted reproduction. A causal therapeutic approach does not exist and an important component is the **prevention** of hyperstimulation syndrome. That is why a continuous sonographic control and also lab-medical controls are made.

When the syndrome occurs, the treatment is to be made symptomatically. To prevent thromboembolism, a sufficient intake of fluids is necessary; also, ascites and pleural effusions should not lead to the wrong track and lead to a restriction of fluids.

Further backup measures are sufficient **thrombosis prophylaxis** with heparin and the support of the renal function.

### Artificial Insemination

In this process, male sperm is introduced into the female genital tract in order to achieve fertilization. The most common technique of artificial insemination in human beings is intrauterine insemination.

### In-Vitro Fertilization (IVF)
This concept is a form of artificial insemination. It is classified into different phases.

First, **ovarian stimulation** takes place; therefore, the patient initially is pre-treated with **GnRH-antagonists**. The hypophysis is blocked and insensitive to the body’s own GnRH. Follicles evenly grow under therapy. The stimulation of follicular maturation is continued with HMG or FSH. The growth is sonographically monitored. As soon as it reaches a specific size, the **administration of beta-HCG** takes place. Ovulation is induced like this.

The next phase is the **follicle puncture**. This can be made laparoscopically as well as sonographically. First-line therapy is the ultrasound-guided **transvaginal puncture**. The follicles are suctioned and microscopically examined afterward. The mature oocytes are put onto a special culture medium and stored in the incubator.

Next is the **in-vitro cultivation**. After 3-6 hours, the sperm is added to the oocytes. They are incubated in the culture medium. After 48 hours, usually, 3 embryos develop.

Afterward, the **embryo transfer** follows with a sterile special catheter into the cavum uteri. To assist in the luteal phase, the patient is given beta-HCG or progesterone.

Due to the transfer of several embryos, there is the danger of multiple pregnancies. The success rate of IVF for live birth is 40% among women under 35 years of age. Disadvantages of IVF include failure to conceive, OHSS and expensiveness.

**Intracytoplasmatic Sperm Injection (ICSI)**

An intracytoplasmatic sperm injection is also a form of artificial insemination. It is particularly indicated for male sterility. The typical indication is the **oligoasthenoteratozoospermia** here. For in-vitro fertilization, a 100,000 of sperm are
necessary and, for the intracytoplasmatic sperm injection, **only a few sperms are required**.

The patients are prepared in a similar way to in-vitro fertilization, firstly with ovarian stimulation and follicle puncture.

The obtained oocytes are released from their follicles and adhesive granulocytes are removed with an enzyme, and then the **injection of seminal filaments** is made with a glass pipette.

![Image: "ICSI of marmoset oocytes after in vitro maturation." by openi. License: CC BY 4.0](image)

(A) The zona pellucida was drilled using piezo pulses, and the pipette was inserted deep into the oocyte and a single piezo pulse was applied. Sperm were inserted into the oocyte (bar = 100 µm). (B) Marmoset blastocysts produced by ICSI. (bar = 100 µm).

Afterward, the embryos are incubated again and then transferred to the cavum uteri of the woman.

The application of artificial insemination usually is made after previous medicamentous treatment. If this is unsuccessful, the decision which form of artificial insemination is going to be used is made individually.

ICSI offers a high pregnancy rate and 70—80 % of eggs are fertilized through this technique. Drawbacks of ICSI include unknown risks to the egg or embryo and damage to the embryo.

**Review Questions**

The answers can be found below the references.

1. **A woman comes to your consultation-hour and you diagnose an ovarian hyperstimulation syndrome. What is a typical characteristic?**

   A. Ascites  
   B. Petechial bleedings  
   C. Weight loss  
   D. Visual disorders  
   E. Gait pattern in small steps

2. **Which is no phase of in-vitro fertilization?**

   A. Follicular puncture
B. Embryo transfer
C. Ovarian stimulation
D. Postcoital test
E. In-vitro cultivation

3. Which drug can be used for induction of ovulation?

A. Trastuzumab
B. Clomifen
C. Donepezol
D. Setralin
E. Venlafaxin

References
Stauber, Weyerstahl: Duale Reihe, Gynäkologie und Geburtshilfe, 2. Auflage
O. Bauer, K. Dietrich: Komplikationen der assistierten Reproduktion, Springer

Correct answers: 1A, 2D, 3B

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