Infertility and Sterility: Causes, Diagnosis, and Management

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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.

Definitions of Sterility and Infertility

Infertility must be distinguished from **sterility**. Sterility is the **inability to conceive** after two years of regular intercourse. It is further subdivided into primary and secondary sterility. **Primary sterility** is the complete inability to become pregnant, whereas **secondary sterility** refers to a failure to conceive after a previous successful pregnancy.

Infertility, on the other hand, is an **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. The number has been rising continuously over the past few years, perhaps partially due to the fact that the average age at which a woman gives birth to her first child also keeps rising, which is largely attributed to 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, the cause is only with the woman; in the rest of cases, the cause is a combination of both or is unknown.

Causes of sterility in men

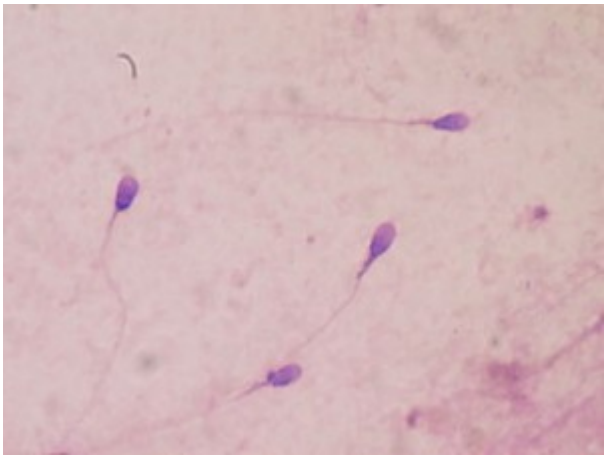

Image: “Colorized sperm sample under the light microscope,” by Bobjgalindo. License: CC BY-SA 4.0

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

- **Oligozoospermia** refers to a low sperm count under 20 million per milliliter.
- **Asthenozoospermia** refers to reduced sperm motility.
- **Teratozoospermia** refers to a large number of sperm with abnormal morphology.
- Combination of all of those conditions is accordingly termed **oligoasthenoteratozoospermia** or **OAT syndrome**.

Spermiogenic defects also may cause sterility. Follicle-stimulating hormone (**FSH**) and luteinizing hormone (**LH**) play important roles. The Leydig cells in the testicles control LH, and the cells build androgen.

Malformations are the primary organic causes of sterility, such as injuries to the testicles, epididymides, prostate, or 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 dysfunction. The most typical are decreased libido, erectile dysfunction, orgasmic dysfunction, and ejaculatory dysfunction. Studies have shown that psychological issues contribute to reduced sperm quality.

Causes of sterility in women

In women, classification of possible causes is much more complex. Clinical examinations start with ovarian causes of sterility. **Hypothalamic-hypophyseal ovarian failure** can lead to reduced production of gonadotropin-releasing hormone (GnRH), which, in turn, leads to an insufficient release of LH and FSH. Consequently, amenorrhea, an anovulatory cycle, and corpus luteum deficiency can develop. 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 immoderate production of androgen. Such patients often suffer from appearances of virilization and manlike hair patterns. Common example is **polycystic ovarian syndrome**.

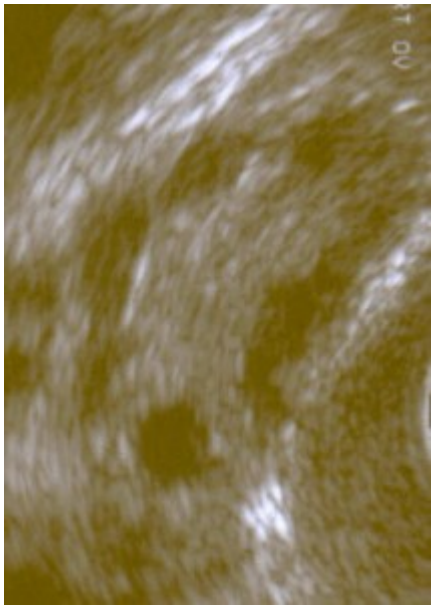

Image: “Polycystic ovary in a sonogram,” by Ekem. License: public domain

Due to increased levels of prolactin, the pulsatile release of GnRH is inhibited. **Prolactinoma** or intake of dopamine antagonists (antipsychotics, for example) may cause **hyperprolactinemia**. Ovarian insufficiency can also occur from a decreased release of gonadotropins.

The cause of sterility also may be found in the **tubes**. Transitions of the tube mucosa with luminal adhesions may develop from recent infections of the genitalia involving the adnexa. **Adhesions** with the surrounding tissue can develop as well, reducing tube motility. Examples include adnexitis from **chlamydia**, syphilis, and gonococcus. Peritubaric adhesions can be caused by **endometriosis**.

Abnormalities of the uterus, such as uterus bicornis, uterus septa, or hypoplasia, less frequently result in contraceptional barriers but can cause **miscarriages**. The endometrium can be damaged from previous curettages or infections, such as endometritis. Complete build-up of the endometrial mucosa may no longer be possible. Furthermore, a myoma in the uterus can lead to occlusions of the lumen and cause sterility.

Cervix uteri also can cause infecundity. Former cervical disruptions or infections of the cervical canal are possible causes. Lack of estrogen brings about decreased spinnbarkeit

of the cervical mucus. This averts normal ascension and motility of sperm.

Furthermore, **immunological causes** in cervical mucus are possible. Antibodies against sperm in the cervical mucus occur particularly often in sterile marriages.

Psychological causes are possible in women, as with men. However, most patients are in the normal range; such cases are classified as idiopathic sterility.

Diagnosis of Sterility

An important part of diagnosis is a **detailed medical history** and **routine gynecologic examination**. The history should include sexual behavior that relates to ovulation. Completing a basal temperature curve over 3 cycles can be helpful to identify anovulatory cycles.

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

To analyze possible tubal causes of sterility, different methods may 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. This method also can localize tubal obstructions.

Motility, adhesions, and foci of endometriosis can be assessed precisely by **laparoscopy** with blue instillation. Benefits of laparoscopy include the possibility to simultaneously remove adhesions in one session.

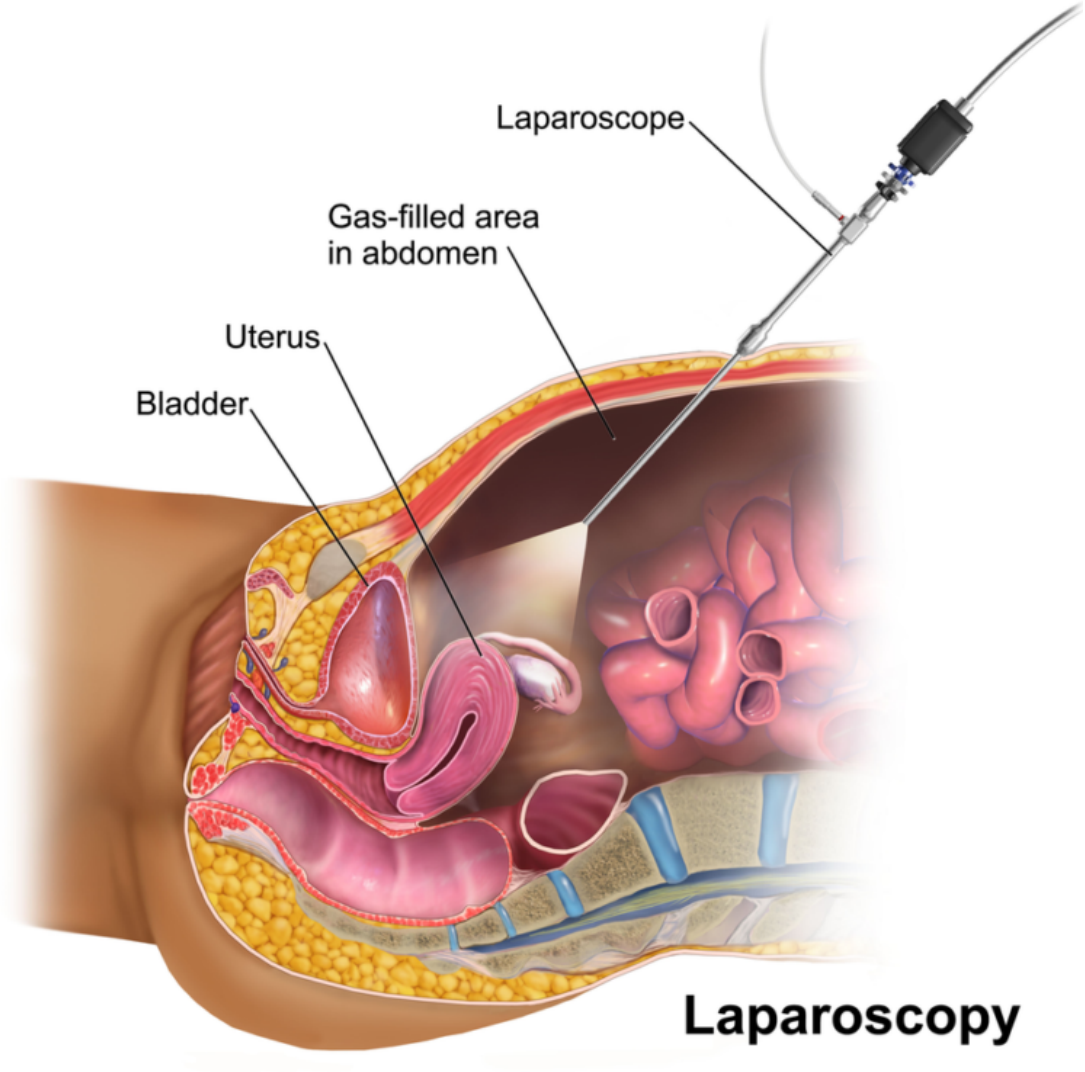

Image: “Laparoscopy,” by Bruce Blaus. License: CC BY 3.0

Detection of malformations, dysplasia, or hypoplasia of the uterus is possible with **hysterosalpingoscopy**. To ascertain a more precise assessment, **hysteroscopy** of the uterus may be used.

To examine sperm motility in the cervical mucus, a **postcoital** test may be used during ovulation. The test requires 3- to 5-day sexual abstention. On the day of ovulation, a mucus sample is taken after intercourse from the vaginal vault as well as from the cervical canal. Afterward, the mucus specimen is microscopically examined by phase. The test is rated positively when motile sperm can be proved in the mucus. A negative test with immotile sperm in the cervical mucus suggests rare immunological causes of sterility. Immotility of sperm can be caused by antibodies against the sperm.

Medicamentous Induction of Ovulation

Ovulation inductors are used to treat dysfunctions in the hypophyseal-hypothalamic area. The agents support follicular maturation and secretion of gonadotropins. Typical drugs are **clomifene**, **cyclofenil**, **tamoxifen**, and **epimestrol**, among others. The substances are used preferentially at the beginning of a cycle. The drugs are indicated for diseases like **corpus luteum insufficiency**, anovulatory cycles, and **normogonadotropic amenorrhea**. To achieve timely ovulation, ovulation inductors are combined with **human chorionic gonadotropin (beta-HCG)**.

Typical adverse effect is ovarian hyperstimulation. Additionally, multiple pregnancies may occur cumulatively after ovarian stimulation. Increased rate of miscarriage also is possible.

Ovarian Hyperstimulation Syndrome (OHSS)

Ovarian hyperstimulation syndrome may occur after treatment with ovulation inductors. Typical characteristics are **ascites** and **cyst formation** in the ovaries.

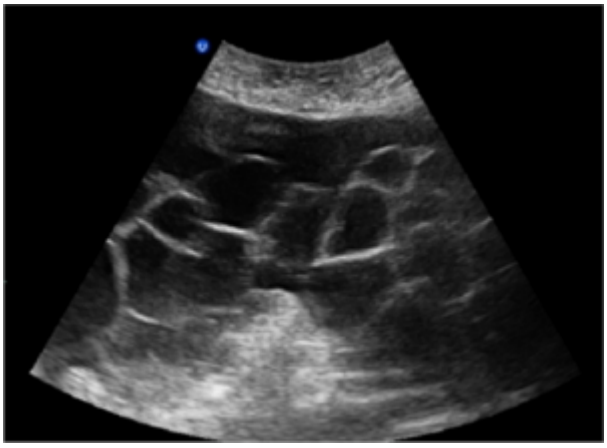

Image: “Bilateral multilocular cystic masses in a patient with ovarian hyperstimulation syndrome in a spontaneous pregnancy with invasive mole,” by Open-i. License: CC BY 2.0

Ovarian hyperstimulation syndrome is the most common complication of assisted reproduction. **Prevention** includes continuous sonographic and laboratory controls.

When the syndrome occurs, treatment addresses symptoms. To prevent thromboembolism, a sufficient intake of fluids is necessary; also, ascites and pleural effusions should not lead to restriction of fluids. Further backup measures are sufficient **thrombosis prophylaxis** with heparin and support of renal function.

Artificial Insemination

Artificial insemination usually is used only after previous therapies. If previous therapy is unsuccessful, individuals make the decision of whether to pursue artificial insemination and which form. With artificial insemination, male sperm is introduced into the female genital tract in order to achieve fertilization. The most common technique for artificial insemination in humans is intrauterine insemination. Two other approaches are described below.

In Vitro Fertilization (IVF)

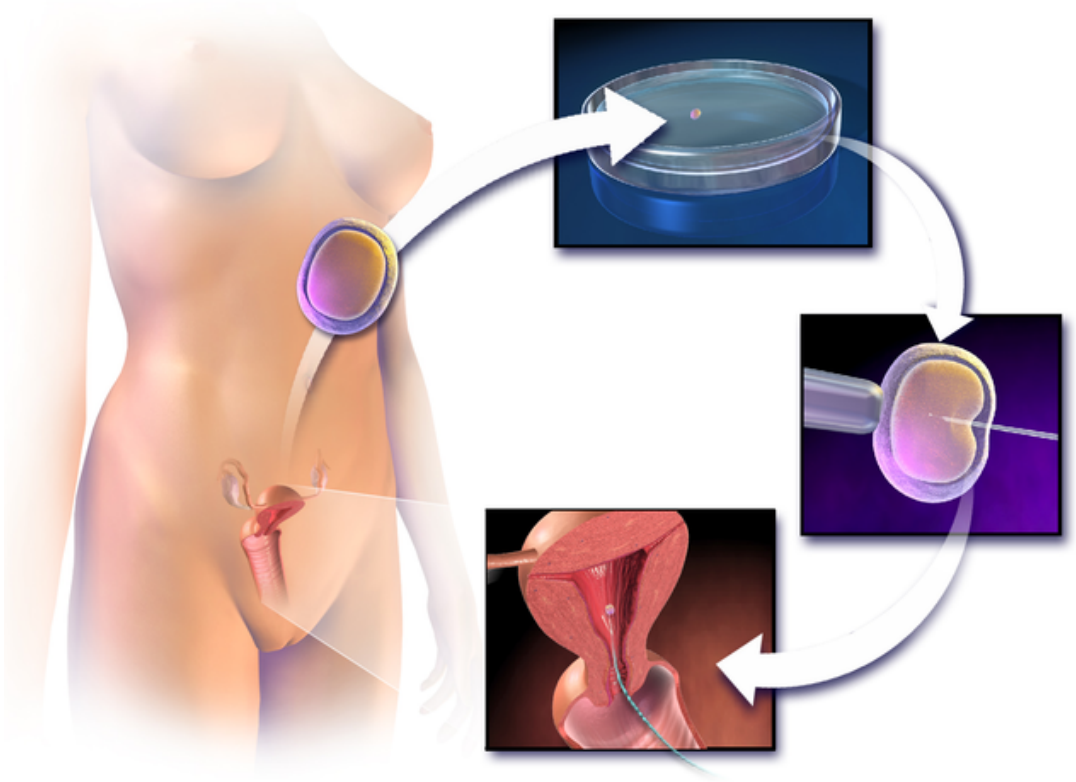

Image: “Assisted reproductive technology,” by Bruce Blaus. License: CC BY 3.0

IVF is a form of artificial insemination and requires different stages.

First, **ovarian stimulation** takes place. A patient is pretreated with **GnRH antagonists**. The hypophysis is blocked and insensitive to the body’s own GnRH. Follicles grow evenly under therapy. Stimulation of follicular maturation is continued with human menopausal gonadotropin or FSH. Growth is monitored sonographically. At a specific point, **beta-HCG** is administered. Ovulation is induced.

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

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

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 a risk of multiple pregnancies. The success rate of live birth with IVF is 40% among women younger than 35 years. However, disadvantages of IVF include failure to conceive, hyperstimulation, and cost.

Intracytoplasmatic Sperm Injection (ICSI)

ICSI is another form of artificial insemination, particularly indicated for male sterility. The typical indication is **oligoasthenoteratozoospermia**. For IVF, 100,000 sperm are necessary, but for ICSI, **only a few are required**.

The patient is prepared in a similar way to IVF, first with ovarian stimulation and follicle

puncture. The obtained oocytes are released from their follicles, and adhesive granulocytes are removed with an enzyme, then **seminal filaments** are injected with a glass pipette. Afterward, the embryos are incubated again and then transferred to the cavum uteri.

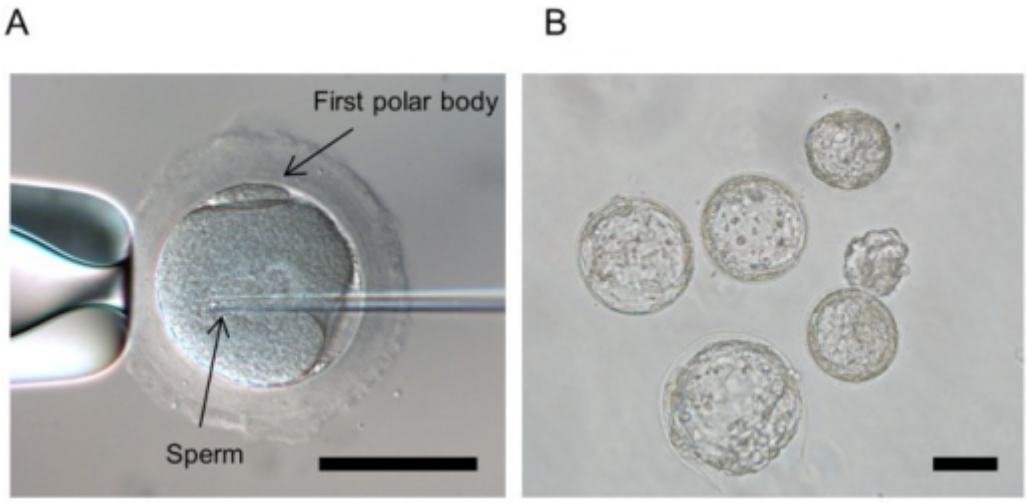

Image: "ICSI of marmoset oocytes after *in vitro* maturation," by Open-i. License: CC BY 4.0 (A) The zona pellucida was drilled with piezo pulses, the pipette was inserted deep into the oocyte, and a single piezo pulse was applied. Sperm were inserted into the oocyte (bar = 100 µm). (B) Marmoset blastocysts produced by ICSI (bar = 100 µm)

ICSI offers a high pregnancy rate; with the technique, 70%–80% of eggs are fertilized. Drawbacks of ICSI include unknown risks to eggs or embryos and damage to embryos.

References

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Correct answers: 1A, 2D, 3B

Notes