INFERTILITY AND PATH TO PARENTHOOD

Information about the medical causes, contributing factors and treatment options for infertility in women and men

GYN – A.R.T. AG
Center for Gynecology, Reproductive Medicine, Microsurgery and Minimal Invasive Surgery

Dear Reader,

The medical aspects of infertility are complex. The aim of this brochure is to provide you with an initial overview of the various causes of infertility and the treatment options available to women and men.

The brochure is designed to complement your in-person consultation. It is not intended to, or can ever, replace personalized medical advice. As your specialists, we are happy to assist you at any time.

Dr. med. Alice Andenmatten

Dr. med. Paola Minikus

Dr. med. Margarethe Rossmanith

Moritz B. Suerdieck

Dr. med. K. Blickenstorfer

PhD Mary Fahy-Deshe

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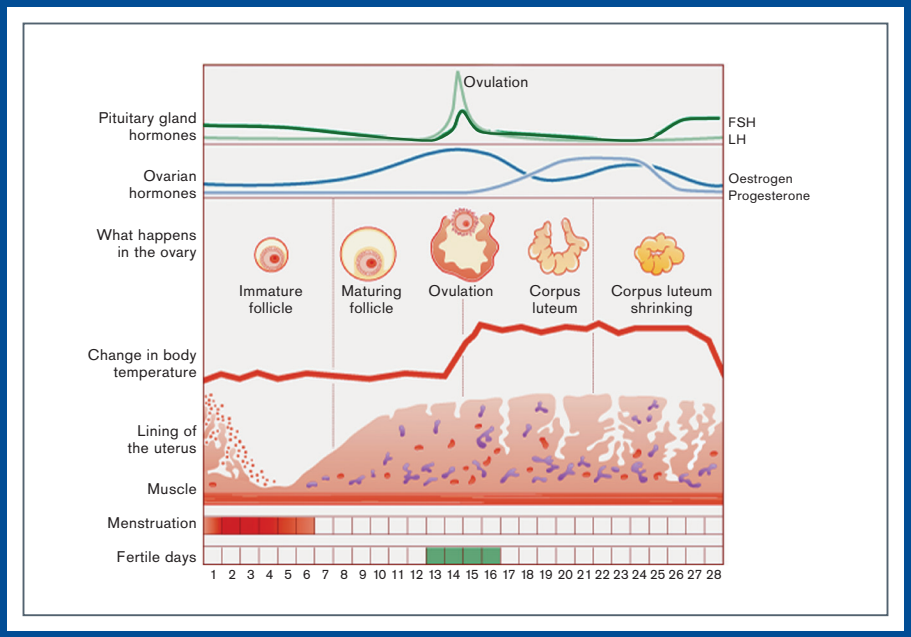
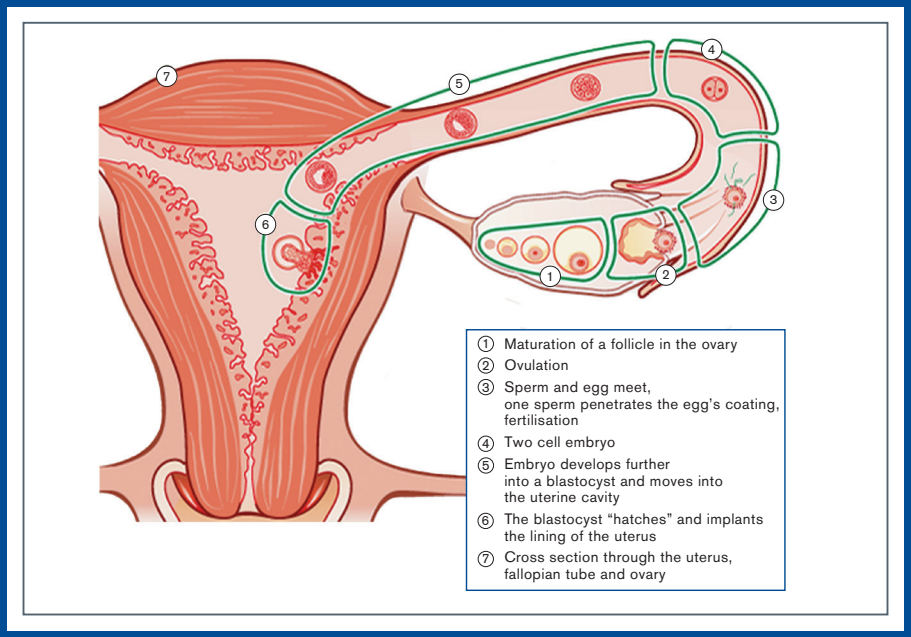




Fundamentals

The reproductive cycle

The reproductive cycle in women is a periodic process that prepares the body for reproduction. At sexual maturity, the pituitary gland (hypophysis) produces two sex hormones: follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

In the first half of the cycle, FSH stimulates the growth of a follicle in one of the ovaries, where the egg matures. The follicle also produces estrogen, which promotes the growth of the uterine lining. When the follicle reaches approximately 2 cm in size, a surge in LH triggers ovulation. This occurs around the 12th to 16th day of a regular cycle. The follicle ruptures, releasing the mature egg, which remains viable for fertilization for approximately 12–24 hours. The egg is then captured by the fimbriae of the fallopian tube. The remaining follicle transforms into the corpus luteum, which produces progesterone, preparing the uterine lining for a possible pregnancy.

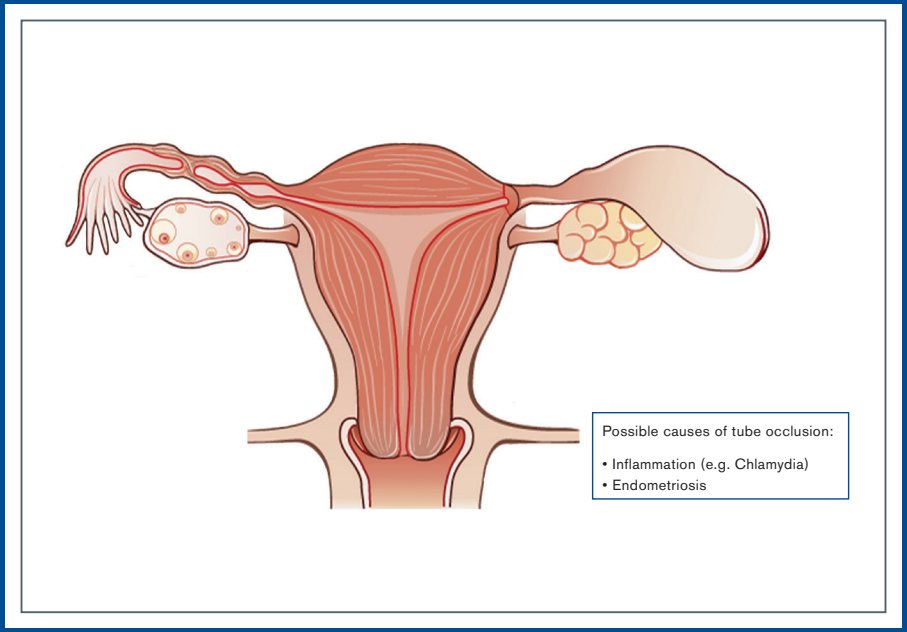
If the embryo does not implant, the signals needed to sustain pregnancy fail to materialize. As a result, the uterine lining is shed, and menstruation occurs.

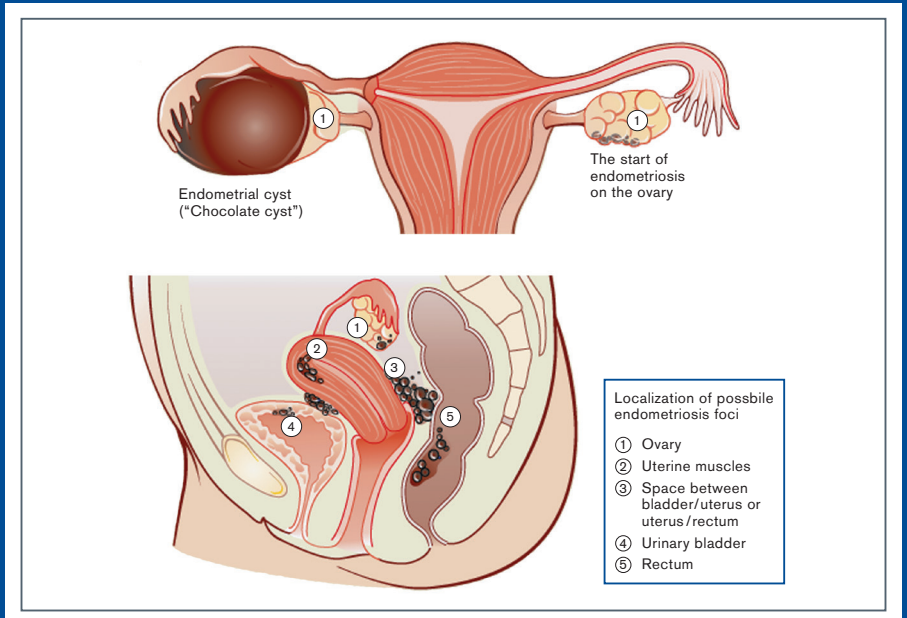
Sperm cell maturation in men

As in women, hormones coordinate and regulate reproduction in men. Here, too, the sex hormones FSH and LH are released into the bloodstream through the brain. Both hormones control processes in the testicles. FSH is responsible for the formation of sperm cells. From puberty onwards, millions of sperm cells are produced each day in the seminiferous tubules. They then move to neighboring reservoirs (epididymis), where they mature. During ejaculation, sperm are propelled through the vas deferens (sperm duct) and urethra by contracting muscles. Each ejaculation contains approximately 300 to 400 million sperm cells. This large number is necessary, as only a few hundred sperm reach the egg in the fallopian tube. A sperm cell consists of a head, body and tail. The sperm head contains the paternal genetic material which, among other factors, determines the sex of the child, should fertilization be successful.

At what point is involuntary infertility discussed?

Infertility or sterility may be discussed (or diagnosed) when pregnancy does not occur after one year of regular unprotected sexual intercourse.





Causes of Infertility in Women

Egg maturation disorders

Hormonal balance is crucial for the ability to conceive. Hormonal dysfunctions can lead to disorders in egg maturation, failure to ovulate and a lack of corpus luteum formation.

Infertility caused by fallopian tubes issues

A classic reason for involuntary infertility is complete or partial blockage of the fallopian tubes. This can be caused, for example, by inflammation (especially chlamydia infections), endometriosis or even ligation (i.e., sterilization).

Endometriosis

15-20% of all women with fertility problems suffer from endometriosis. Endometriosis is the growth of uterine lining tissue outside the uterine cavity, which can lead to chronic inflammation and adhesions. The exact cause of the disease is still not entirely clear.

If the ovaries are affected, cysts known as endometriosis cysts may form.

Changes in the uterus and cervix

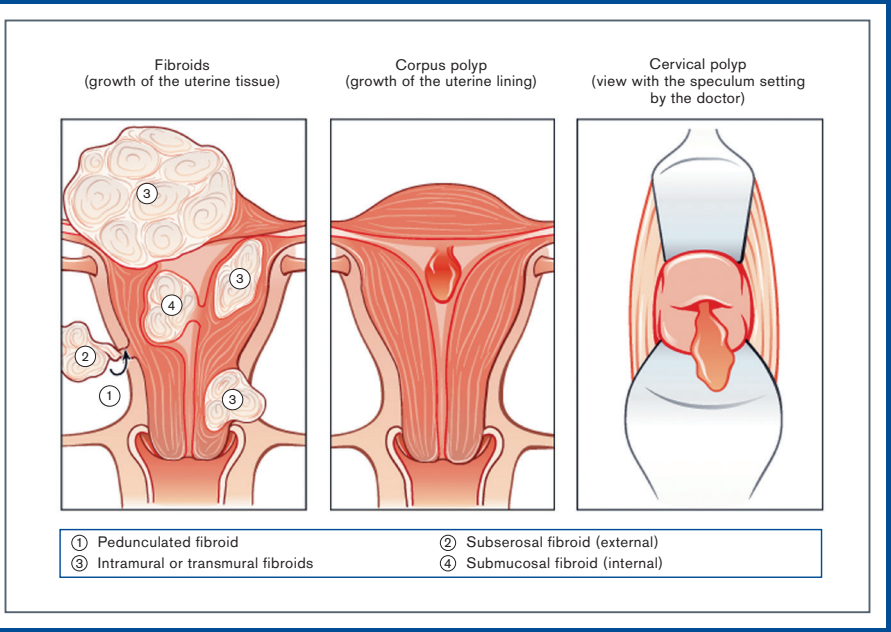
Similar to a bottleneck, the cervix is the narrowest point for sperm on their way to the egg. Scarring (e.g., from surgery), blockages or inflammation of the cervix can hinder reproduction.

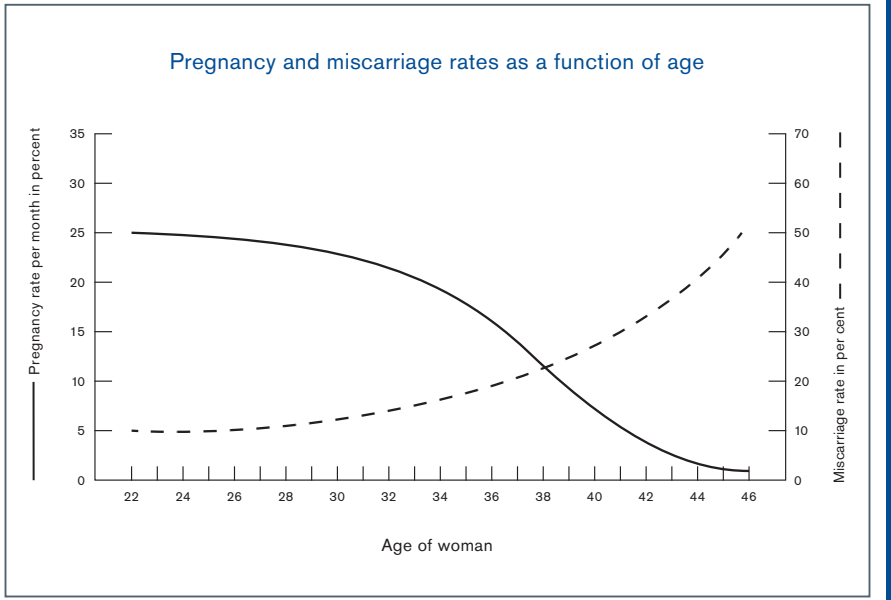
Myomas

Myomas are benign growths in the muscles of the uterus (uterine fibroids). They may not cause any symptoms, but they can lead to bleeding disorders, pressure and pain in the lower abdomen and inability to conceive. Whether fibroids can impede or prevent pregnancy depends on their location, number and size.

Malformations of the ovaries, fallopian tubes and uterus

Very rarely, congenital malformations of the reproductive organs are the cause of infertility.





Changes in the endometrium

Abnormal growths of the endometrium (polyps) can also prevent the implantation of the embryo in the uterine cavity after surgery (Asherman's Syndrom) or infections. It is assumed that in very rare cases, implantation can also be prevented by an overreaction or misreaction of the immune system. The exact connections are still unclear.

Age

A woman's fertility steadily decreases with age. A 30-year-old woman, for example, has about a 22% chance of becoming pregnant each month, while at 40, this drops to just under 5%. This decline is due to irreversible age-related genetic changes in the egg cells.

Causes of Infertility in Men

Sperm maturation disorders

The most common disorder of male fertility is insufficient production of normal, motile sperm in the testicular ducts. Male semen is considered normal if its sperm count is above 15 million per millimeter. Of this, at least 4% should be normally shaped, and 40% should be motile. If these values are not met, the man's fertility may be compromised.

Sperm transport disorders

In 4% of cases, sufficient semen is produced, but it cannot enter the woman's body during ejaculation due to blockages in vas deferens. This can be caused by a previous sterilization, or by underdeveloped or blocked epididymal ducts.

Causes of Infertility in Both Partners

In 15–30% of couples affected, both partners have contributing factors for involuntary infertility. In 5–10% of cases, no organic cause for infertility can be found in the man or the woman. This is referred to as unexplained infertility.

Lifestyle factors

Nicotine consumption reduces fertility in both men and women and lowers the chances of success in fertility treatments.

While the harmful effects of alcohol during pregnancy are well-established, sporadic alcohol consumption does not appear to have a significantly negative impact on fertility. However, daily alcohol consumption significantly reduces fertility in both partners.

Excessive caffeine consumption should also be avoided during pregnancy, and it is recommended to limit intake to no more than two cups of coffee per day.

Use of cannabis can reduce both sperm count and sperm functionality. It also has a negative impact on pregnancy and on the child's health.

Being extremely underweight or overweight can also reduce the chances of pregnancy. We recommend working to achieve a more balanced weight before undergoing fertility treatments.

Understanding the Reasons of Infertility

The process begins with a detailed discussion, during which you will be asked various questions, and your personal medical history will be recorded. Based on your medical history and any potential concerns, a set of tests will be determined, and more or fewer tests may be needed.

Clarifications for Women

Hormone determinations

Hormone levels in the blood at the beginning and second half of the cycle provide insights into any egg maturation disorders, thyroid disorders and corpus luteum deficiency.

Ultrasound examinations

A transvaginal ultrasound allows for the assessment of the uterus, uterine lining, ovaries and follicular growth.

Post-coital test

In the post-coital test, the quality of cervical mucus and motility of sperm cells within it are assessed at the time of ovulation, following sexual intercourse.

Clarification through fallopian tube tests

Fallopian tube tests using contrast ultrasound (hysterosalpingo contrast sonography) or X-ray (hysterosalpingography) allow for visualization of the fallopian tubes and uterus. A contrast agent or sugar-based contrast agent foam is introduced into the uterine cavity through the cervix, after which the condition of the uterine cavity and the patency of the fallopian tubes are assessed using ultrasound or X-ray.

Laparoscopy

A laparoscopy can provide additional insight into cases of unclear fallopian tube conditions, cysts, pain and previous surgeries. During a laparoscopy, under anesthesia, an optical device is inserted through the navel into the abdominal cavity. The images transmitted by the camera serve as a valuable tool for making a diagnosis.

Uteroscopy/Hysteroscopy

During a hysteroscopy, a fine camera is inserted into the uterus through the vagina to detect uterine malformations, fibroids or changes to the uterine lining.

Clarifications for men

Spermiogramm

The spermiogram is the first step in assessing the state of male fertility. After a period of sexual abstinence of 2 to 5 days, the ejaculate is obtained through masturbation. Ejaculate volume, sperm count, motility, sperm appearance and infection parameters are assessed.

Urological/andrological examinations

An examination by a urologist and/or an andrologist (specialist in men's health) helps diagnose conditions such as anatomical anomalies, hormonal disorders, tumors, and others. In some cases, genetic testing may also provide insight into the cause of infertility.

Treatment options for women

Hormone stimulation

In cases of egg maturation disorders, the ovaries can be stimulated to produce follicles using oral tablets or daily hormone injections.

Insemination (IUI = Intrauterine Insemination)

In homologous insemination, the partner's washed and concentrated sperm is injected through the cervix into the uterine cavity using a fine catheter. This shortens the sperm's journey to the egg. The procedure is typically painless and takes only a few minutes.

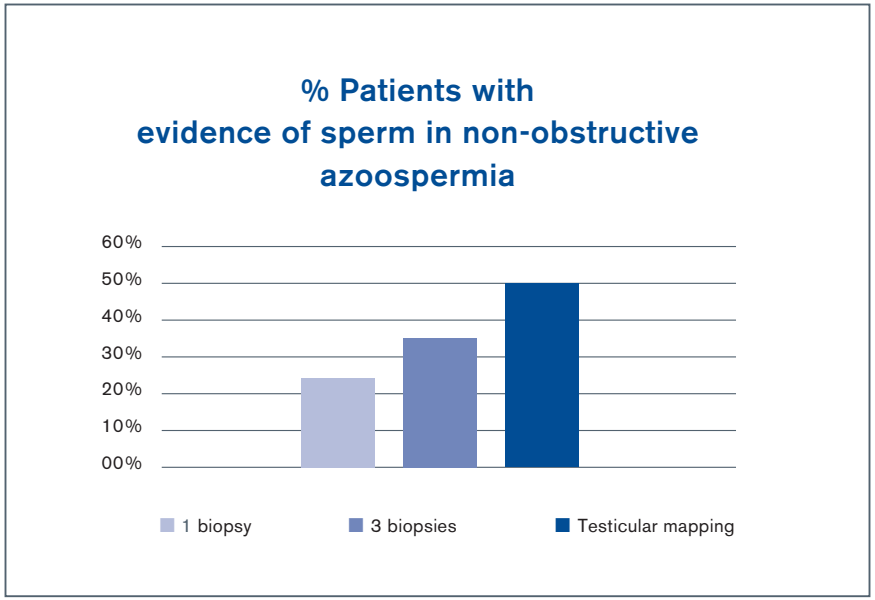
Restoration of the fallopian tubes in cases of tubal infertility

Before performing any microsurgical procedure on the fallopian tubes, other factors contributing to infertility should be clarified to accurately determine the prognosis after the operation. Restoring the fallopian tube after ligation is more likely to lead to pregnancy than after an infection has passed.

Surgical removal of fibroids

Submucosal fibroids are removed via hysteroscopy (surgical hysteroscopy), which is typically a minor outpatient procedure. If only one or two subserosal or intramural fibroids are present, they can be removed through laparoscopy. However, if there are three or more fibroids or transmural fibroids, removal through abdominal incision is preferred, as this allows for optimal restoration of the uterine wall.

These patients often have a predisposition to fibroid formation. The aim of the surgery is to remove all fibroids, even the very small ones. This helps extend the window of opportunity for achieving pregnancy



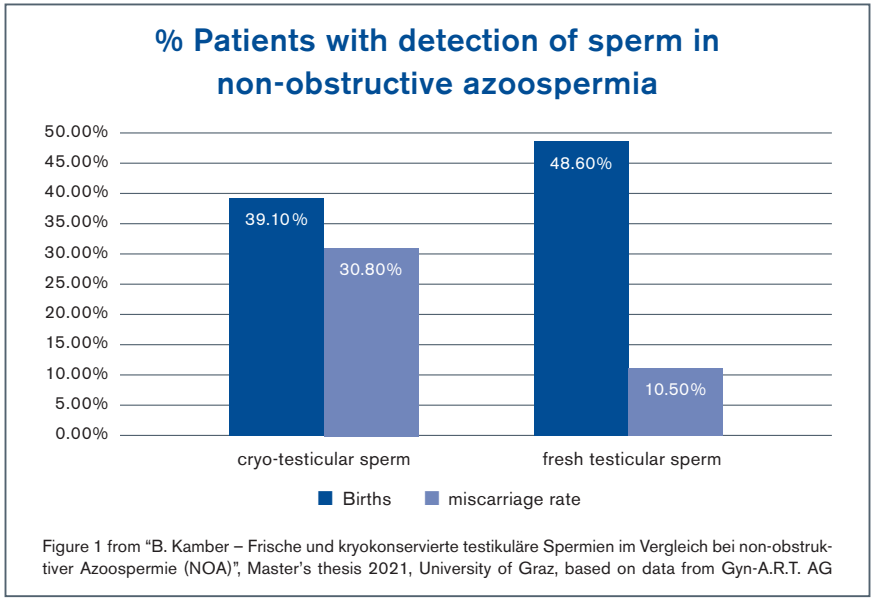


Figure 1 from "B. Kamber – Frische und kryokonservierte testikuläre Spermien im Vergleich bei non-obstruktiver Azoospermie (NOA)", Master's thesis 2021, University of Graz, based on data from Gyn-A.R.T. AG

Treatment Options for Men

Azoospermie/fehlende Spermien im Ejakulat

If no sperm cells are present in the ejaculate (i.e., azoospermia), this may be due to a blockage in the transport pathways (**obstructive azoospermia**) or an issue with sperm production in the testicles (**non-obstructive azoospermia**). It is estimated that approximately 10% of male fertility problems are due to **azoospermia**. To establish a reliable diagnosis, two spermiograms with ultracentrifugation must be performed at a specific interval. The following procedures are available for the treatment of **azoospermia**:

Restoring the vas deferens after ligation through microsurgical vasovasostomy

If the vas deferens is blocked and the conditions are favorable, restoring the vas deferens is recommended. This microsurgical operation is best performed under general anesthesia and typically takes 1.5 to 3 hours, depending on the circumstances. If no sperm can be detected at the site of ligation, it may be possible to connect the vas deferens to the epididymis (vasoepididymostomy), provided that sperm can be found here.

Surgical sperm extraction from the testicles (TESE: Testicular Sperm Extraction)

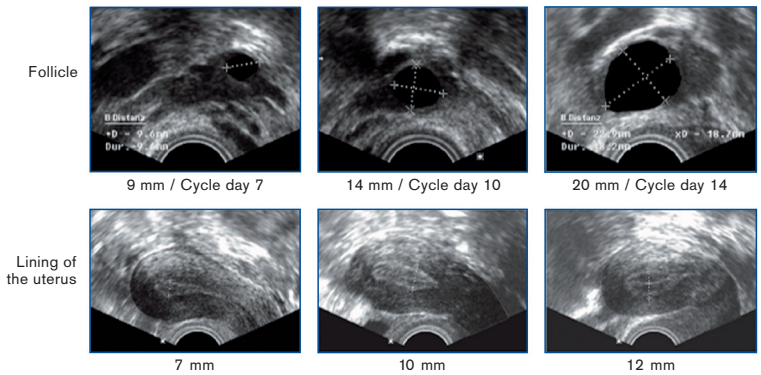
If there is a disorder in sperm production in the testicles, a testicular biopsy can be performed. This is the only method to precisely classify the sperm production issue.

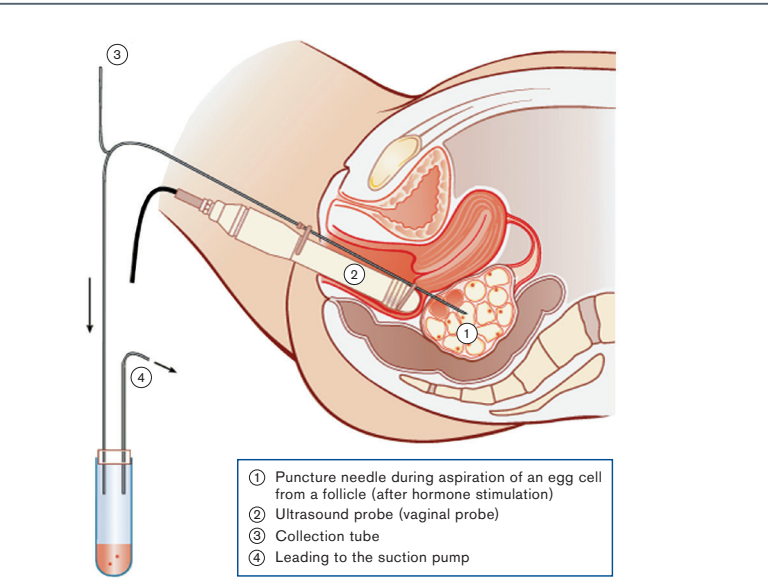
Testicular mapping

In cases of non-obstructive azoospermia, an open testicular biopsy involving cutting and exposing the testicles provides limited information, as it is difficult to predict where sperm production may still be preserved. With a single biopsy, sporadic sperm is found in 25% of patients with non-obstructive azoospermia; if three biopsies are taken, the detection rate increases to 35%.

It is important to obtain a complete picture of sperm production in the testicles of patients with non-obstructive azoospermia. To find these sperm production sites, we perform systematic fine needle punctures (testicular mapping). This allows us to detect sperm in 50% of all patients. The fine needle puncture can be performed on an outpatient basis and is painless due to local anesthesia.

After successful detection of sperm, they can be removed from the production site using fine needle aspiration for in-vitro treatment using ICSI.





In-Vitro Fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI)

If there is no prospect of achieving pregnancy using the methods described so far, in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) may be considered. These methods are used in cases such as damaged fallopian tubes, endometriosis, severe sperm quality issues, or unexplained sterility. In both IVF and ICSI, the egg is fertilized outside the body.

IVF and ICSI procedure:

Preparation phase

An IVF/ICSI cycle must be carefully planned, at least 6 to 8 weeks in advance. The couple receives a written protocol with a schedule, which includes the week for follicle puncture and embryo transfer. In the cycle before hormonal stimulation, the woman takes hormone tablets for 2 to 3 weeks. Menstruation occurs again after stopping the hormone tablets, and the actual stimulation cycle can then begin during or after this menstruation.

Ovarian stimulation

After menstruation, the ovaries are stimulated with fertility hormones, such as follicle- stimulating hormone (FSH), to mature multiple eggs. The hormones must be injected subcutaneously (under the skin) daily, preferably at the same time each day, by the patient herself. The growth of the follicles is monitored regularly using ultrasound and, occasionally, through blood hormone tests.

Stimulation methods

As multiple eggs mature simultaneously, premature ovulation must be prevented during ovarian stimulation (downregulation). There are various strategies for this. The ovaries can either be immobilized with injections before stimulation begins —during the preparation phase (also known as the long or agonist protocol)—or ovulation can be inhibited during the course of stimulation (short protocol or antagonist protocol).

Triggering ovulation

Once the growing follicles reach the ideal size (usually after 10 to 14 days of stimulation), ovulation is triggered (ovulation induction). The timing of this injection—typically at 10 p.m. or as prescribed by a doctor—is crucial! This makes the eggs capable of fertilization, and the follicular puncture appointment is scheduled 36 to 38 hours later.

Egg retrieval (follicular puncture)

What happens in the operating room

The ovaries have enlarged as a result of stimulation and are now located in the pelvis, directly next to the vagina. This makes the follicles easily accessible for egg retrieval.

On the day of egg retrieval, the patient must arrive at the scheduled appointment time on an empty stomach. The eggs are retrieved through the vagina using ultrasound and a fine needle. This outpatient procedure is performed in the operating room at our practice and typically takes around 10 to 15 minutes.

During the procedure, a highly effective painkiller is administered through an infusion. The patient remains awake and responsive but experiences no pain.

After egg retrieval, the patient remains in the practice for 1 to 2 hours for outpatient monitoring.

What happens in the laboratory

Sperm preparation

On the day of the follicular puncture, the partner's sperm is required between 7 and 11 a.m. The sample is then analyzed and prepared using an appropriate procedure.

Egg cells

The eggs are identified under the microscope, washed and transferred to a culture medium. After these steps in the laboratory, the couple is informed of the number of eggs retrieved, typically within 10 to 20 minutes.

The eggs, sperm, zygotes and embryos are carefully handled in our IVF laboratory, from the time of egg retrieval and sperm collection to embryo transfer.

Using an electronic witness system, all cells in the laboratory are tracked, ensuring cells, sperm and embryos are precisely assigned to the correct person or couple.

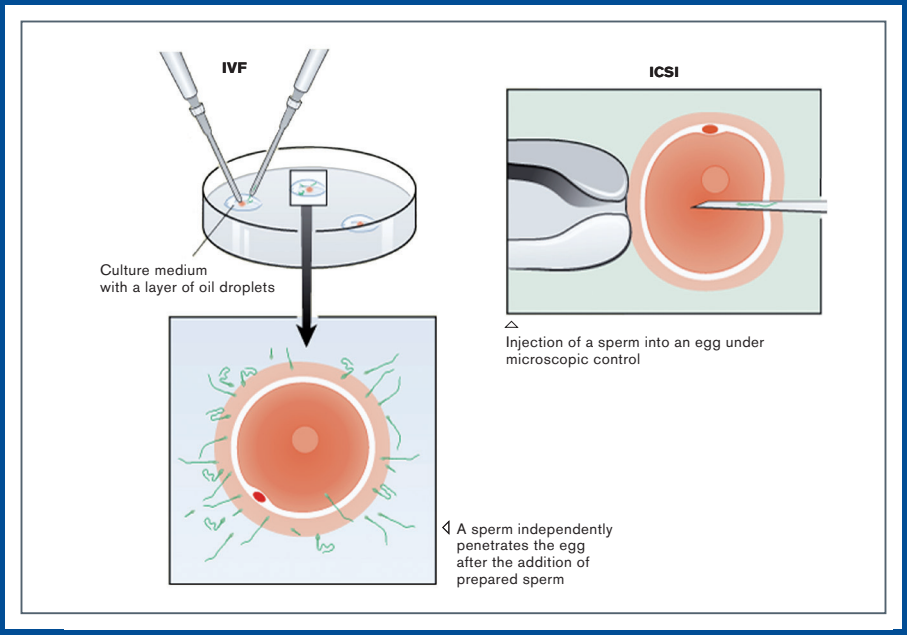
Egg cell fertilization

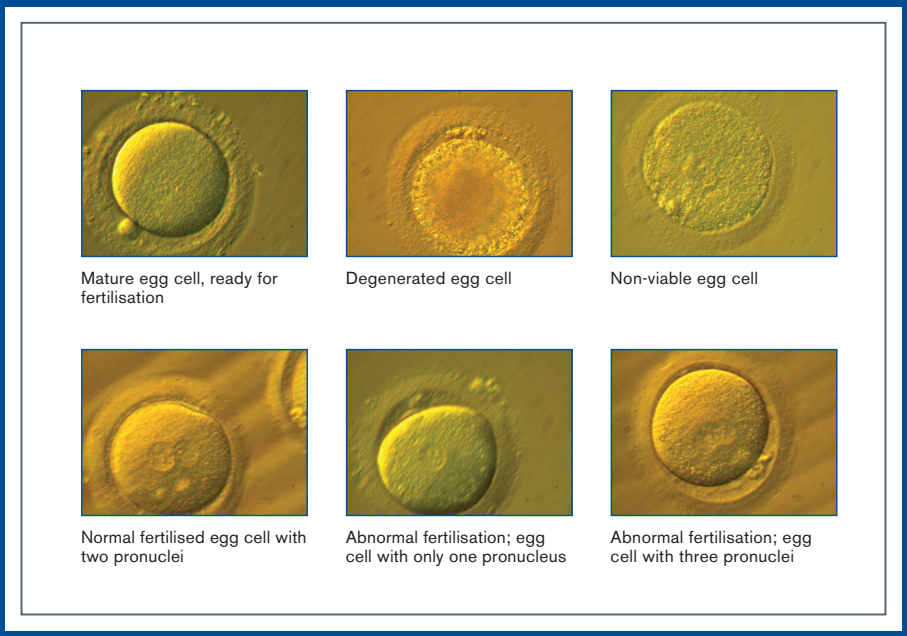
Classic in-vitro fertilization (IVF)

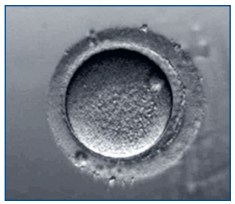
Between 1 and 6 hours after egg retrieval, sufficiently motile and normally shaped sperm are added to the egg cells. Fertilization occurs naturally between the eggs and sperm.

Intracytoplasmic sperm injection (ICSI)

Approximately 2 hours after the follicular puncture, the oocytes are separated from the surrounding cells (cumulus and corona cells) and assessed for their fertilization potential. A single sperm is then injected directly into each mature egg 3 to 6 hours after retrieval using a microneedle.







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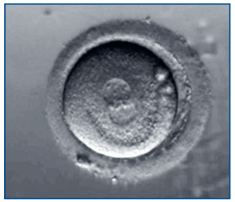

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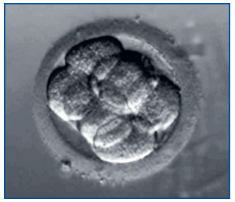

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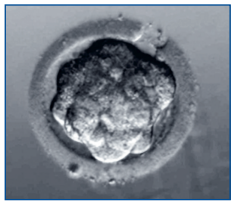

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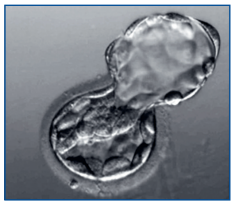


⑤

① Unfertilized egg cell
② 2PN fertilized egg (zygote)"
③ **Day 3:** Embryo (8 cells)
④ **Day 4:** Embryo (morula)
⑤ **Day 5:** Embryo (hatched blastocyst)

The day after egg retrieval

16 to 18 hours after the eggs and sperm have been united, the eggs are checked for signs of successful fertilization. The couple is informed of the result by telephone, and the date for transfer (2 to 5 days after follicular puncture) is agreed upon. Unfortunately, due to changes in the eggs, sperm or both, not all eggs may be fertilized. For the same reasons, not every fertilized egg cell will develop into a blastocyst.

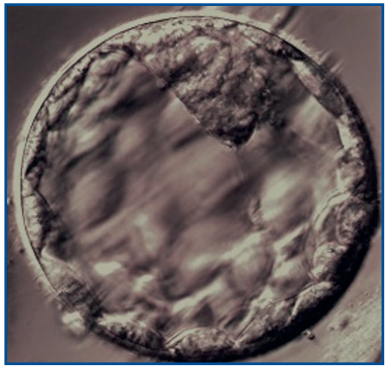
According to Swiss legislation, a maximum of twelve fertilized eggs may be developed into embryos at the same time. If additional fertilized eggs are available, they are cryopreserved (frozen) for later use in the zygote stage (imprinted eggs).

Cryopreservation

The method for cryopreserving fertilized eggs is vitrification. During vitrification, cells are frozen at an extremely high cooling rate (–23,000 °C/min.) without the formation of ice crystals.

Vitrification is successfully used to preserve unfertilized and fertilized eggs and embryos. Survival rates of over 90% are possible with this method. Comparable pregnancy rates can be achieved with vitrified and thawed embryos as with "fresh" embryos.

Sperm can also be cryopreserved if necessary (in this case, it may result in loss of quality).



Embryo day 5

Embryo transfer

The goal of the treatment is to achieve a low-risk singleton pregnancy.

Although Swiss law permits the transfer of up to three embryos, this practice is no longer considered current. Since a multiple pregnancy carries a significantly increased risk for both the mother and the children, only one embryo is typically transferred per cycle.

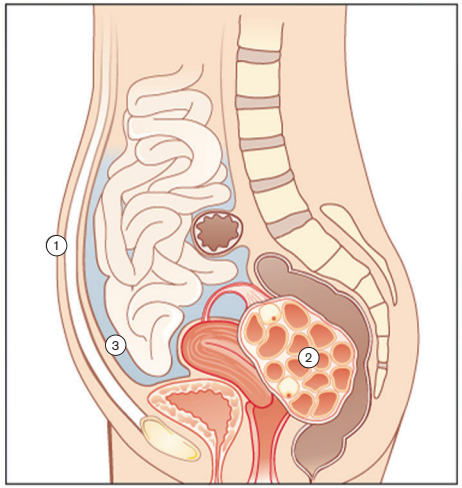
During the transfer, the embryo is placed into the uterine cavity using a fine, soft catheter. The ideal positioning of the embryo is monitored with ultrasound.

The bladder should be filled during the transfer. The transfer is typically performed on the fifth day of embryonic development and is usually pain-free.

Corpus luteum phase

For many, this marks the most challenging phase of treatment. Optimism and tension, along with fear and anxiety, often alternate. We recommend that you lead as normal a life as possible and take it easy physically. Avoid hot baths, saunas and intense physical activity.

The second half of the cycle is supported with medication, either through injections or vaginally inserted progesterone suppositories. Two weeks after the embryo transfer, a blood pregnancy test can be performed. If the test is positive, the medication is continued, and an ultrasound scan is scheduled for two weeks later.



Symptoms of OHSS:

- Increase in abdominal girth and body weight
- Feeling of tension in the abdomen ①
- Stomach pressure, nausea, vomiting
- Enlarged ovaries and luteal cysts ②
- Possible fluid accumulation in the abdomen ③
- Possible breathing difficulties
- Possible reduction in urine volume
- Possible "thickening" of the blood and increased risk of thrombosis

Risks and Complications of IVF/ICSI

Ovarian hyperstimulation syndrome (OHSS), infections, postoperative bleeding and ovarian torsions

The most common complication after IVF/ICSI is ovarian hyperstimulation syndrome (OHSS), which can affect any patient undergoing hormonal stimulation for these treatments. Most affected patients experience a mild or moderate form of ovarian hyperstimulation. The symptoms typically begin 4 to 5 days after the follicular puncture and may include abdominal swelling, pressure or mild pain.

These symptoms typically disappear within a few days, unless the embryo transfer is successful, and a pregnancy occurs. In that case, the symptoms may return later.

Very rare complications include infections, secondary bleeding in the abdominal cavity and ovarian torsion. The latter may require laparoscopy.

Thawing Cycle

The thaw transfer can be performed within a lightly stimulated cycle. Ovulation timing is determined by using ultrasound and blood sampling and is triggered with an HCG injection. This enables the precise calculation of the thawing and transfer day. The luteal phase is also supported with medication.

In women with ovulation problems, the uterine lining can be artificially built using estrogen tablets. As soon as the ultrasound shows a well-developed endometrium, the corpus luteum phase can be initiated with vaginal progesterone suppositories alongside the estrogen tablets.

Chances of Success

If the cause of infertility is an isolated egg maturation disorder, the prognosis is very good. In cases of hormonal issues, pregnancy rates of 60–90% can be achieved with therapy after six cycles. For couples with unexplained infertility or minor restrictions, the pregnancy rate with insemination is 10–15% after three cycles.

With in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), the pregnancy rate per transfer across all age groups is approximately 30–40%.

For women under 35, the pregnancy rate per transfer is 55%, while for women over 43, the pregnancy rate drops significantly to 5–15%. For women over 43, pregnancies are extremely rare.

The chances of success are highly individual and depend on factors such as age, cause of infertility and egg and sperm quality. We will discuss the optimal fertility treatment and its chances with you personally.

Preimplantation Genetic Diagnosis

Preimplantation genetic testing (PGT) allows for a genetic analysis of the embryo before its transfer into the uterus. In cases of severe familial genetic disorders, PGT-M (Preimplantation genetic testing for monogenetic disorders) can be used to prevent the transmission of these conditions.

The provisions for performing preimplantation genetic diagnosis are clearly outlined in the Reproductive Medicine Act and are subject to strict conditions. Before PGT-M can be performed, both a consultation with a geneticist and a decision by an ethics board are required.

In cases of advanced maternal age or recurrent miscarriages, we can perform an analysis for chromosomal abnormalities in the embryo, known as PGT-A (Preimplantation genetic testing for aneuploidy). This can prevent the transfer of non-viable embryos and reduce the risk of miscarriage. ICSI treatment is always required for this procedure. PGT-M is often combined with PGT-A.

For both tests, a sample is taken from the embryo on day 5 or 6 of embryonic development, during the blastocyst stage. This involves removing a few cells from the future placenta (trophoblast) of the embryo for analysis in our partner laboratory. The results are available after 2–3 weeks. After the sample is taken, the embryo is cryopreserved and stored in our laboratory. Once we have discussed the genetic results with you, we will plan the next treatment steps. If abnormal findings are detected, we will arrange genetic counseling.

Biopsy of a blastocyst

Cryopreservation of Eggs and Sperm

Eggs and sperm can be frozen to preserve fertility. This can be done, for example, before planned chemotherapy or due to life circumstances. Sperm can be cryopreserved after ejaculation.

The egg freezing process follows the same steps as in-vitro treatment until egg retrieval. The mature eggs are then vitrified. If the eggs are to be used later, an intracytoplasmic sperm injection is necessary for fertilization.

We would be happy to provide you with personalized medical advice.

Costs

The costs of infertility investigations are covered by health insurance.

Hormone stimulations are reviewed by the health insurance company on a case-by-case basis and are typically approved for up to 12 cycles, after deductible is applied. Prior cost approval from the health insurance company is required.

Health insurance companies will cover up **to three inseminations**, based on individual assessment.

Microsurgical **refertilization** after ligation in women is not a mandatory benefit provided by health insurance. The costs range from CHF 7,000 to CHF 10,000.

The cost of repairing the v**as deferens** after ligation (microsurgical **vasovasostomy** or vasoepididymostomy) is approximately CHF 5000 to CHF 6000 and is not covered by health insurance.

The costs for in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), ranging from CHF 7,500 to CHF 10,000, are not covered by Swiss health insurance companies. Additionally, the medication for hormone stimulation is not covered.

Surgical sperm extraction from the testicles (TESE = testicular sperm extraction, or TESA = testicular sperm aspiration) is not covered by health insurance. The cost of TESA is CHF 1,300. The costs for TESE with cryopreservation of testicular tissue vary depending on the urologist performing the procedure.

Testicular mapping is a covered service by health insurance if a testicular biopsy has not yet been performed.

Prices are subject to change.

Legal Basis

Since the first successful IVF treatment in England in 1978, discussions about the legal framework have continued in Switzerland. The law on reproductive medicine has been in force in Switzerland since 2001. The law and the corresponding ordinance were partially revised in 2017. This law outlines the conditions under which medically assisted reproduction procedures may be used in humans. It protects human dignity, the individual and the family, while prohibiting the misuse of biotechnology and genetic engineering. In addition, a national ethics commission has been established. Among others, egg and embryo donation, surrogate motherhood and cloning are prohibited.

Design: Adriano Ackermann, Zurich

GYN – A.R.T. AG
Center for Gynecology, Reproductive Medicine, Microsurgery and Minimally Invasive Surgery
Hardturmstrasse 130 · 8005 Zurich · Phone: 044 446 60 60 · praxis@gynart.ch · www.gynart.ch