planning a pregnancy

Take every opportunity –
strong partners will help you

MERCK

contents

1 How does a pregnancy come about?

Infertility is a topic that affects many couples, giving rise to questions, fears and doubts. But it shouldn't be cause for resignation.

There is hope. Thanks to modern medicine, today over 70 percent of couples dealing with infertility can be helped.

The journey to parenthood takes time, understanding, and patience. This brochure aims to help you understand the wide range of reasons for infertility. In addition to describing causes, treatment options, opportunities and risks, it also presents useful addresses and links.

Be hopeful. Regain your confidence. By reading this brochure, you are taking the first step.

In order to understand the reasons for not becoming pregnant, it is important to understand the significance of the reproductive organs and the processes that lead to fertilizing the egg cell and to pregnancy.

The female reproductive system

The reproductive organs include both the external and internal genitalia. In women, the area containing the external genitalia is called the vulva. The vulva includes the fleshy “lips” around the vagina (labia majora and labia minora), the clitoris and the mons, a mound of fatty tissue above the pubic symphysis. The female internal genitalia include the vagina, the uterus, the fallopian tubes and the ovaries. The ovaries are also known as the female gonads.

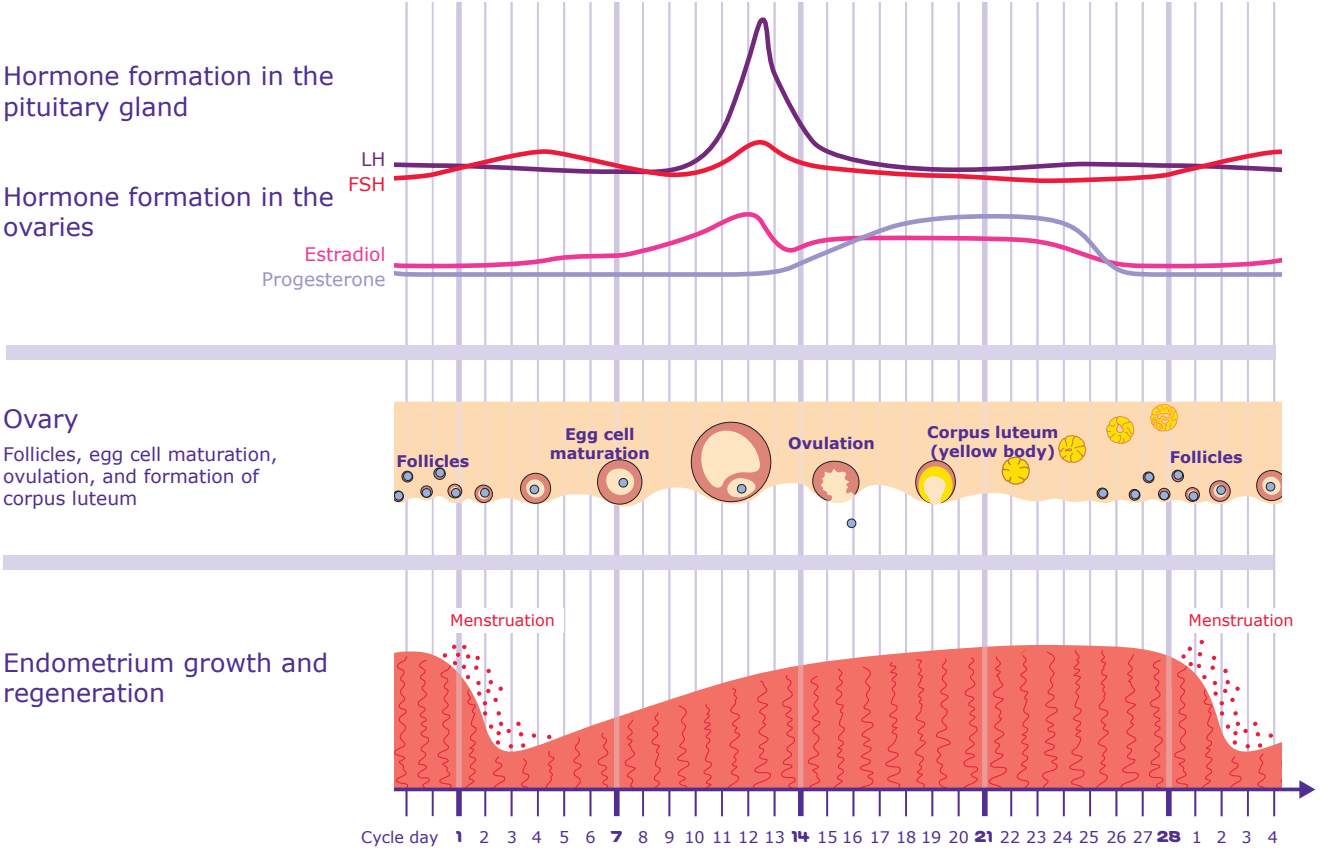
The menstrual cycle

The menstrual cycle is a periodically recurring process that establishes the conditions for reproduction. In the course of each cycle, a fertilizable egg cell matures and the uterine lining changes. During each menstrual cycle, the uterus prepares itself for a potentially fertilized egg cell.

As with other biological processes, with reproduction, our brain plays a highly significant role. The brain receives and processes all internal and external stimuli, for instance, controlling our emotions such as love, arousal, and desire. At the same time, it controls the menstrual cycle by excreting hormones.

The gonadotropin-releasing hormone (GnRH) is the most important hormone in this process. The excretion of GnRH in the brain causes the pituitary gland to release the two hormones FSH (follicle-stimulating hormone) and LH (luteinizing hormone). Both of these hormones act on the ovaries via the blood.

The Menstrual Cycle



The Male Reproductive System

The male external genital organs consist of the penis and the scrotum. The internal genital organs include the testes (testicles), the epididymis, the seminal vesicle, the vas deferens and the prostate gland.

Sperm Cell Maturation in Men

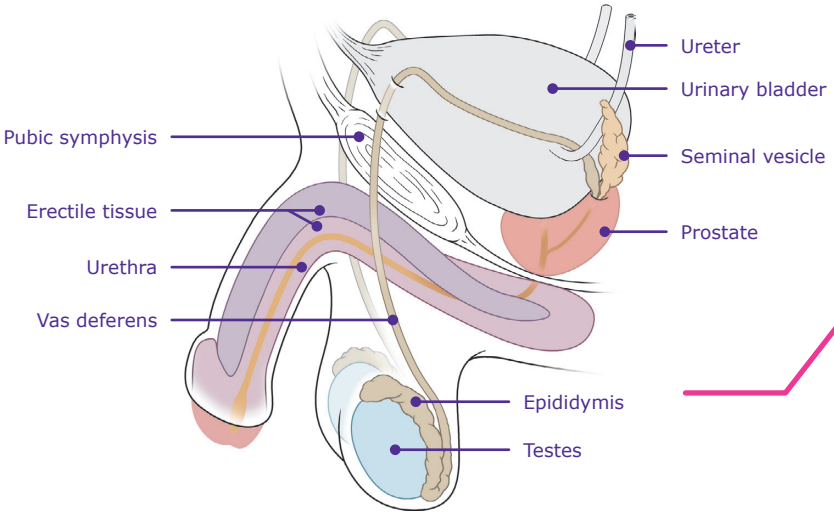
As in women, the reproductive processes in men are also regulated by hormones. Here too, the release hormone GnRH controls the release of the sex hormones FSH and LH into the blood. The two sex hormones regulate the processes in the testes: FSH plays a key role in forming sperm cells, millions of which develop in the seminiferous tubules every day. From there, they move to the epididymis, where they develop to full maturity.

During ejaculation, the contraction of various muscles causes sperm cells to be expelled from the reproductive tract through the vas deferens and urethra with a high level of force. Each ejaculation contains three to four hundred million sperm cells, of which only several hundred actually reach the egg cell.

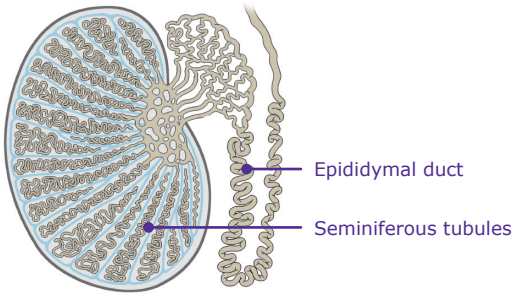
A sperm cell consists of a head, a midpiece, and a tail. The head contains the paternal DNA, which, in the event of successful fertilization, determines the sex of the baby among other things. The midpiece is responsible for the sperm cell's energy, and the tail is responsible for its whip-like forward movement.

Anatomy and physiology of the male reproductive system

A Male reproductive organs

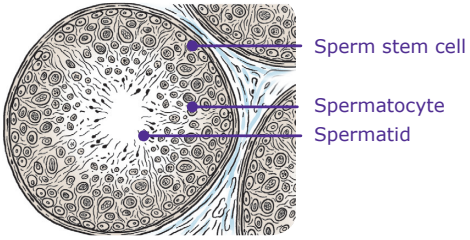


B Seminiferous tubules and epididymis



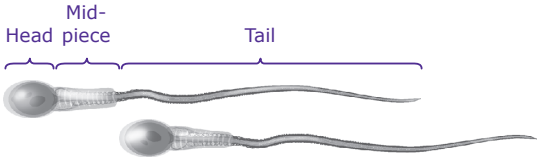
C Cross-section of a seminiferous tubule

(magnified approximately 180 times)



D Mature spermatozoa

(magnified approximately 2600 times)



How does a pregnancy come about?

1. In the first half of the menstrual cycle, the hormone FSH usually stimulates the growth and development of only one follicle in one of the ovaries. The egg cell then matures in the follicle. The estrogen formed by the follicles in the ovary stimulates the growth of the endometrium.

2. Once an egg cell has fully matured, a sudden increase in the hormone LH triggers ovulation. In a regular 28-day menstrual cycle, ovulation occurs on around the 14th to 16th day of the cycle. The follicle bursts and the fertilizable egg cell migrates into the fallopian tube. The corpus luteum is formed from the follicle cells left behind; it excretes progesterone. The progesterone prepares the uterus for a potential pregnancy.

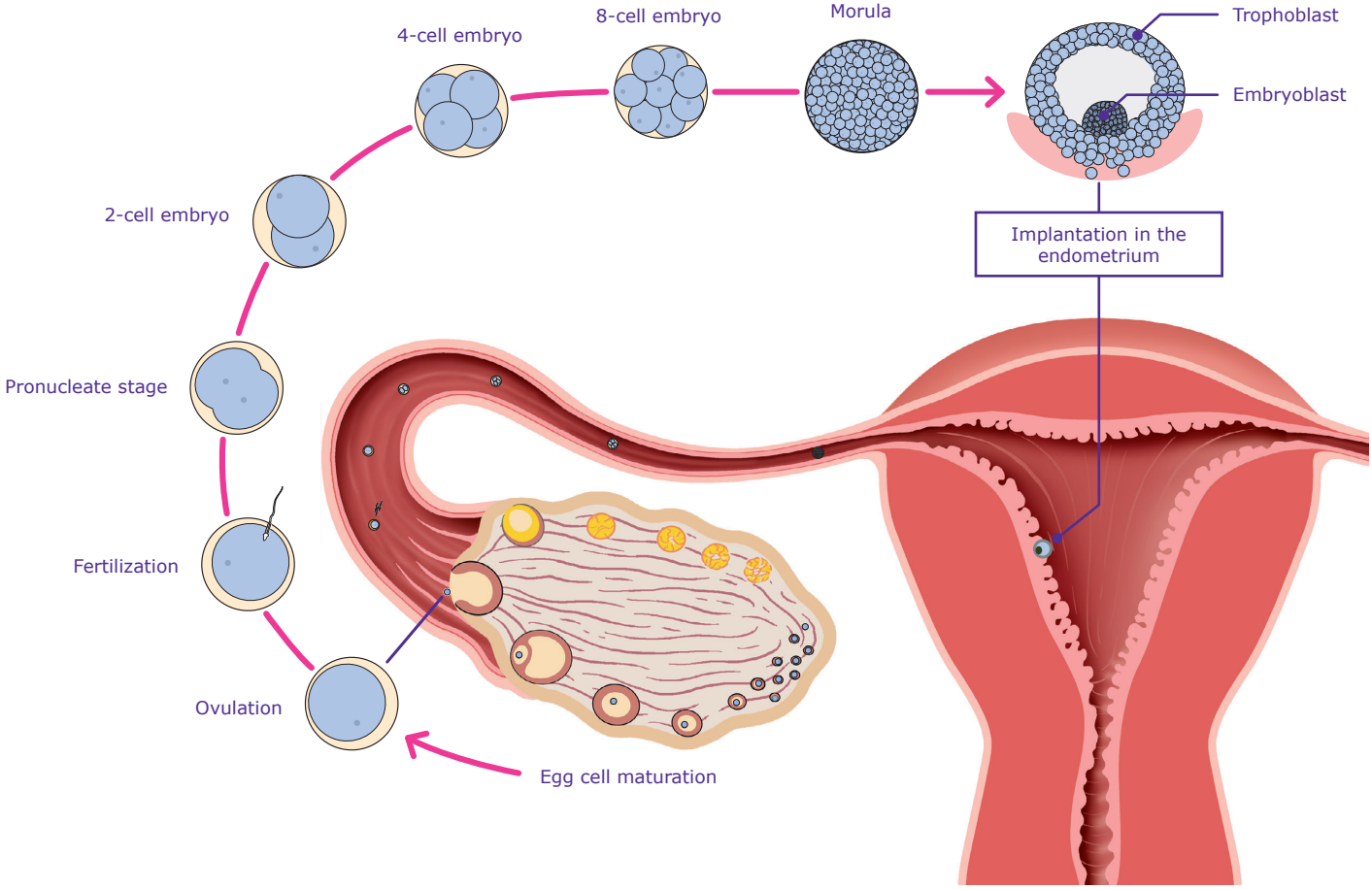
3. On its way through the fallopian tube to the uterus, the egg cell can be fertilized. Among the multitude of sperm cells that reach this point, only one of them manages to penetrate the protective shell of the egg cell. This act launches the process of combining the paternal and maternal DNA. An embryo has been created and new life has begun.

4. In the course of the first cell divisions, the embryo migrates ever further toward the uterus, where it must still hatch from the shell just before implantation.

5. At six days after fertilization at the earliest, the process of implantation in the endometrium begins.

At the implantation site, the placenta is formed. It serves to exchange nutrients and gas between the mother and the embryo and produces hormones required to maintain the pregnancy. If the egg is not fertilized or if the embryo is unable to become implanted for other reasons, the endometrium is expelled, menstruation begins and the cycle starts over.

How a pregnancy begins



2 Diagnosis and causes of infertility

When is the term "infertility" used?

The term refers to the inability to carry out a pregnancy successfully. The term is also used synonymously with the term sterility, i.e. the inability to become pregnant or to procreate. The term infertility is used when a couple has regular unprotected intercourse for over a year but does not become pregnant.

In most cases, infertility is not a congenital condition but rather an acquired one; for example, it may be caused by infection-related fallopian tube obstruction.

Age also plays a key role: As early as age 30, and more frequently from the age of 35 to 40, female fertility decreases. In men, sperm production and functionality slowly declines starting from around the age of 40. The shift of family planning to later life phases has also substantially contributed to the issue of infertility. For example, today 25 percent of couples are over the age of 30 when their first child is born, while in 1970 some 90 percent of women and men were below the age of 30 at the birth of their first child.

In around a third of cases, the cause of infertility involves only the woman, in around a third of cases, the cause of infertility involves only the man, and in a third of the cases, both the male and female partners are involved.

Basic information

In all cases, both partners should be tested, since infertility is equally common in men and women. In addition, the diagnosis influences treatment in a complex manner. In order for appropriate and promising fertility treatment to be initiated, all of the underlying causes have to be diagnosed.

It may be helpful for you to write down any questions you may wish to ask your doctor before you meet for the first time. If there is anything you didn't understand, you should be sure to ask for clarification. It's also important to take along any records of previous examinations and/or surgical reports you may have.

To get an idea of the prior history of your infertility, your doctor may ask you questions such as those listed below:

- How long have you been trying to get pregnant?
- Have you ever had medical treatment for infertility?
- Do you have any explanation for your infertility?
- How difficult is it for the two of you to deal with your infertility?
- What aspects of your life have changed since you started dealing with infertility issues (partnership, career, self-esteem)?

In addition to a consultation with the doctor, diagnostics include a physical examination and laboratory tests. Diagnosing the reasons for infertility requires a special, step-by-step procedure that takes a fair amount of time and requires your patience.
But if you do it together, you'll make it!

Male infertility causes

The most common male fertility disorder involves a low sperm count and low sperm motility. There are a number of potential reasons for this, and in many cases, the cause cannot be conclusively identified.

- Mumps during childhood
- Varicose veins in the testes
- Undescended testicles
- Hormone disorders
- Diabetes
- Tumors that have been surgically removed
- Genetic defects
- Stress
- Infections
- Exposure to environmental toxins
- Heavy smoking and/or drinking

Less frequently, male infertility is caused by sperm transport blockage. In this case, while enough sperm cells are formed, they are unable to enter the woman's body because the vas deferens is blocked in some way. This is often caused by underdeveloped epididymal ducts or adhesions there.

Testing Male Infertility

Palpation and Ultrasound

Men seeking treatment for infertility will see a urologist or andrologist (specialist for disorders of the male reproductive system). The examination begins with the physician performing palpation, during which he or she will look for abnormalities in the testes and epididymis. The prostate is palpated through the rectum. A thorough examination also includes an ultrasound of the testes and prostate.

Semen Analysis

Male fertility can be tested through microscopic semen analysis. The sperm cells obtained through masturbation are examined under a microscope for their form and motility. Since sperm quality can fluctuate widely, testing is performed twice at an interval of at least three months. If no sperm cells or an insufficient number of intact sperm cells are found in the ejaculate, it may be necessary to take a tissue sample from the testes. The sample is used to determine whether the sperm cell production is impaired.

Hormone Level Evaluation

Deficient sperm production can be caused by a hormone disorder. To rule out this kind of disorder, blood tests are performed to determine the hormone levels. However, hormone disorders are much less common in men than in women.

Genetic Testing

Testing for genetic abnormalities is another way to diagnose the reasons for a low sperm count. This can be carried out with a simple blood sample that is tested in a lab.

Female infertility causes

Egg cell maturation disorders

The most common reason for impaired egg cell maturation, a common reason for female infertility, is abnormal hormone function in the ovaries. If the hormones are imbalanced, this can negatively impact the egg cell maturation and ovulation or the formation of the corpus luteum.

Fallopian tube-related infertility

The fallopian tubes are the conduits through which the sperm cells reach the egg cell. They are also like a “conveyer belt” transporting the egg cells to the uterine cavity. If the fallopian tubes are closed due to adhesions or other reasons, this can complicate or even completely prevent egg cell transport. The causes may include inflammation or previous ectopic pregnancies as well as surgical procedures or a spontaneous proliferation of the uterine lining outside the uterus (endometriosis).

Abnormalities of the uterus and cervix

For the sperm cells, the cervix is the narrowest opening on their way to the egg cell. Scarring (for example, after surgery), blockages or inflammation can prevent the egg cell from being fertilized. Uterine fibroids (benign muscle tumors) are sometimes the reason for long-term infertility or miscarriage.

Defects of the ovaries, fallopian tubes or uterus

In very rare cases, reproductive organ defects, most of them congenital, are responsible for infertility.

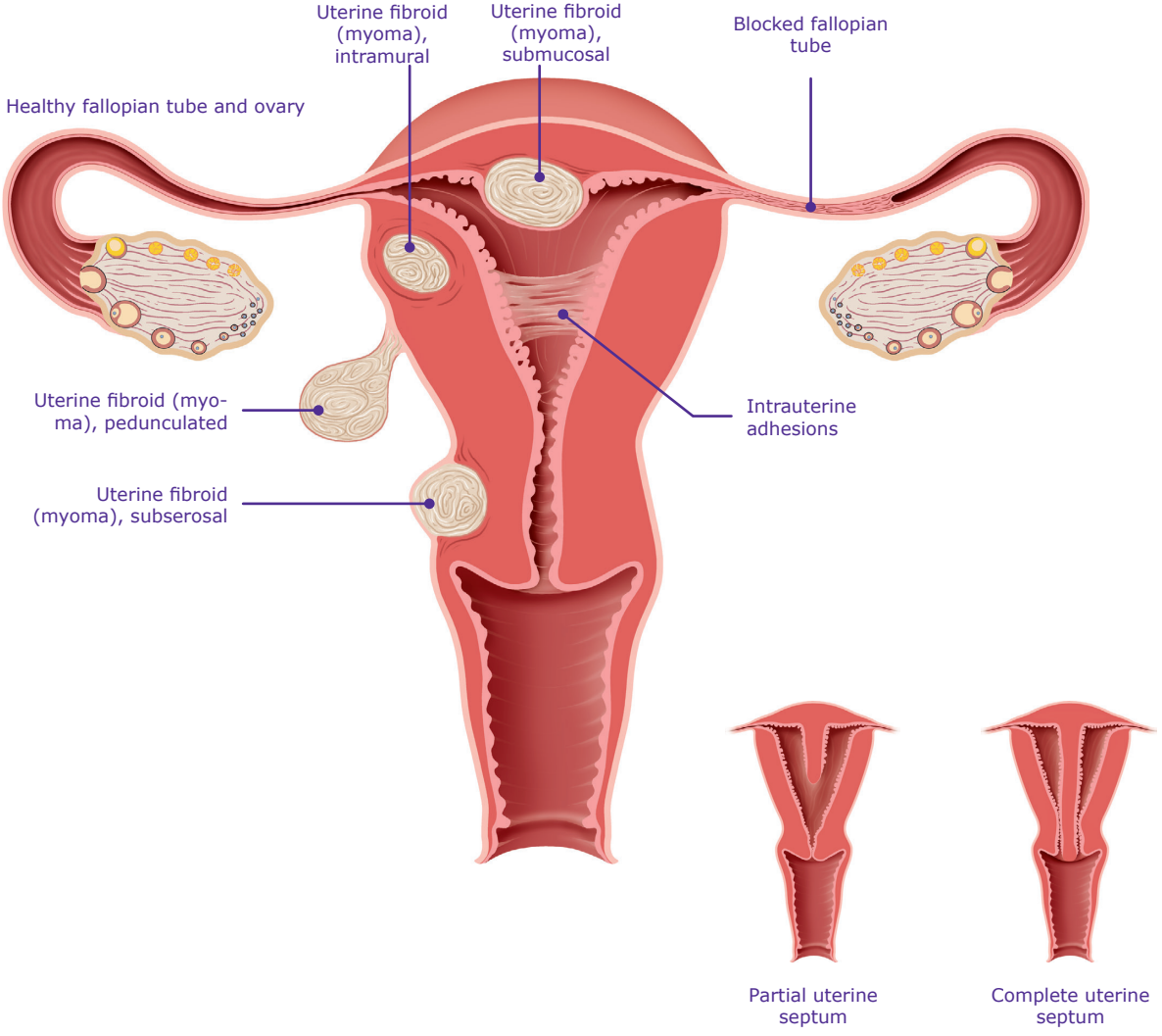
Immune disorders

Another very rare cause of female infertility is impaired immune response. In patients with this disorder, the body's own immune system perceives the egg cell or sperm cell as a foreign body and attacks it as an "intruder".

Lifestyle

Another factor influencing infertility is lifestyle, which affects men and women equally. Obesity, an unhealthy diet, as well as excessive consumption of alcohol, coffee or nicotine can also play a role. In some cases, the increasing exposure to environmental toxins or a high level of stress can also have a negative impact on fertility. In five to ten percent of couples, no medical reasons for infertility can be identified.

Abnormalities of the female reproductive system



secondary conditions affecting fertility

Sometimes infertility is the result of an illness that also affects other areas of life.

Endometriosis

Endometriosis involves the benign growth of the uterine lining outside the uterus, for example, in the fallopian tubes or ovaries, or even the bladder or bowel. During the menstrual cycle, the endometrium in these places undergoes the same changes as the tissue in the uterus itself. However, it is unable to exit the body during menstruation and therefore often causes severe menstruation-related symptoms. Little is known about the causes of endometriosis. It is known, however, that women with endometriosis have lower fertility levels. In many cases, the endometriosis lesions can be surgically removed.

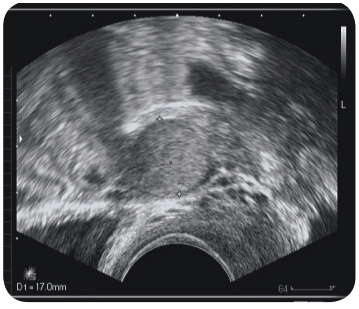
polycystic ovary syndrome (PCOS)

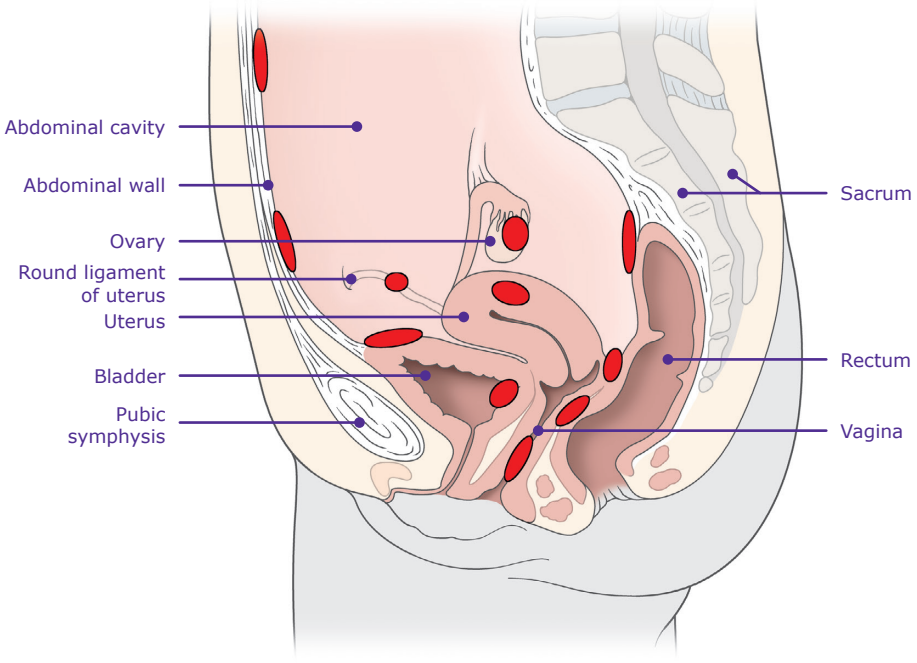
As suggested by the name, this syndrome is characterized by numerous small cysts in the ovaries. The women affected also often have irregular menstrual cycles and high levels of male hormones. Their risk of diabetes and obesity is elevated, and fertility is reduced. Today, PCO syndrome can be treated relatively effectively with drugs.

Thyroid disorders

Both hypothyroidism and hyperthyroidism can reduce fertility in women. At the same time, thyroid function plays an important role in the course of a pregnancy. In men, hypothyroidism can reduce sex drive and lead to impotence.

Endometriosis





Possible endometrial tissue sites outside the uterus (endometriosis)

Testing female infertility

Palpation

During the gynecological exam, the physician uses palpation to detect abnormalities of the reproductive organs or other changes to the body that may be responsible for infertility.

Ultrasound

In the next step, the physician uses an ultrasound device for a more precise examination of the reproductive organs. This painless and harmless exam is performed through the vagina, which allows the best view of the ovaries, fallopian tubes, and uterus.

Hormone level evaluation

In order to rule out an egg cell maturation disorder, the hormone levels are determined in the blood on certain days of the menstrual cycle. At the beginning of the cycle, estrogen, LH, FSH, androgen and prolactin levels are determined, among others. The thyroid hormone TSH is also checked, since major variations in TSH levels can negatively impact fertility. During the second half of the cycle, progesterone and estrogen levels may be measured.

Laparoscopy

A laparoscopy is performed under general anesthesia. First, a tube-shaped instrument (laparoscope) is introduced into the abdominal cavity through a tiny abdominal incision

below the navel. This instrument is connected through a camera to a monitor, which allows a very precise image of the reproductive organs to be viewed by the physician. Where necessary cysts, adhesions or endometriotic tissue can be removed via the laparoscope.

Complications resulting from the procedure are rare. The main complications include damage to internal organs or infections. Anesthesia-related problems are also very rare.

Hysteroscopy

To detect deformities, uterine fibroids (myomas) or lesions in the uterine lining, a very fine probe is inserted in the uterus through the vagina. This method allows the physician to obtain a precise view of the uterine cavity and fallopian tubes by means of a camera fitted in the probe – and even perform minor surgeries as needed.

Examining the fallopian tubes

If there is suspected damage to the fallopian tubes, imaging or surgical examination may be used. Imaging procedures involve the use of X-ray (with contrast media) or ultrasound to determine the function and condition of the uterine cavity and fallopian tubes. The procedures can be performed on an outpatient basis and without general anesthesia. For precise diagnosis, it may be a good idea to undergo laparoscopy, which may require brief hospitalization.

3 Impacts on fertility

Modern medicine has now identified several factors that play a role in fertility. Some of them, such as diet or excessive alcohol or caffeine consumption, can be controlled. Others, such as age, cannot be influenced.

The age factor

There is a clear association between age and the likelihood of pregnancy, not only under natural conditions, but also for fertility treatments. As early as age 30, female fertility declines. Starting from the age of 35, this trend becomes particularly obvious. The probability of becoming pregnant is around 66 percent at the age of 20, 30 percent at the age of 30 and only 4 percent at the age of 40.

Body weight and BMI

A balanced diet and a healthy body weight can increase the chances of becoming pregnant. Being either overweight or underweight can reduce fertility. In women, obesity can cause disruptions of the menstrual cycle that reduce fertility and increase the risk of miscarriage. In men, being overweight can slow or reduce the production of sperm and restrict fertility.

Several studies have shown that women who are overweight (BMI > 25 kg/m^2) or underweight (BMI < 17 kg/m^2) are more likely to experience fertility problems than women of a normal weight (BMI 20 – 24.9 kg/m^2).

In overweight women, losing even 5 to 10 percent of the starting weight dramatically increased the spontaneous pregnancy rate without any additional invasive treatment. However, weight loss should occur slowly, since crash dieting can also negatively impact fertility. In case of doubt, you should talk to your doctor and find out which weight loss method is right for you.

Nicotine, alcohol, and caffeine

Moderate amounts of caffeine do not affect fertility. However, large amounts of coffee or tea can reduce fertility.

There are indications that excessive alcohol consumption reduces both male and female fertility. Nicotine can also have a negative impact: Female smokers can have a much harder time becoming pregnant. In male smokers, sperm quality may be reduced.

Diet

You should eat plenty of fresh fruit and vegetables. By so doing, you will automatically reduce your calorie intake and increase the consumption of important nutrients that your body particularly needs right now.
If you have an eating disorder (bulimia or anorexia), you must consult your doctor.

Grodstein F. et al, “Body mass index and ovulatory infertility.” Epidemiology, 5(2), 1994:247–50

What role does the mind play?

Saying “yes” to having a baby together is an unambiguous expression of deep affection and trust between two individuals. This “yes” also means that both partners wish to take responsibility for a new person that is part of the two of them.

If a couple is unable to have children, this can easily burden the relationship, because a shared goal appears to be in jeopardy. In many cases, this makes talking about infertility taboo. Not talking about it, however, also means dealing with the stress that can result from infertility alone. In many cases, this sets off a vicious circle in which in response to unexpressed accusations or the feeling of failure the body “refuses” to become pregnant. In this kind of situation, it can be very helpful to consult a therapist. Professional psychological support can help restore communication between partners. A sex life “on a schedule”, all too often characterized by frustration rather than desire, can be steered back to satisfaction. To get a better idea of your attitude toward becoming pregnant, you and your partner could ask the following questions during therapy:

- Why do we actually want to have a baby right now?
- What does a baby mean for our partnership?
- What has changed in our relationship since it hasn’t “worked”?
- How do we experience our sexuality?
- How might our life look without children?
- How do we feel about adoption or taking on a foster child?

You can also contact the association Verein Wunschkind e.V., which is also happy to provide support (see the Web and postal address in the annex to this brochure). The internet portal www.calimera4you.de offers additional detailed information on all aspects of pregnancy and fertility.

Give your emotional side all the attention it deserves!

Take advantage of professional support. In Germany, there are around 120 specialized fertility centers. The only way to identify the medical reasons for your infertility and find the best solution for you is to undergo in-depth testing.

Of course, there is no guarantee that treatment will be successful. Human nature is not something mechanical but rather involves the complex interaction of mind and body. But you'll see: modern medicine has made huge strides. Many couples dealing with infertility can be helped today.

4 options for treating infertility

Before treatment is initiated, the reason for infertility must be identified. The first step always involves a consultation with your doctor. As with all medical examinations, your doctor will start by asking you about pre-existing conditions and past illnesses. Based on your answers, your doctor will put together your history, which includes all of your important medical landmarks.

Contrary to a consultation for regular illnesses, however, for fertility treatment, your doctor will need to ask you questions that may be personal or affect your emotions. For this reason, it is good to know that doctors specializing in fertility treatment are aware of these special problems and are used to dealing with them. They will take seriously any requests, concerns or uncertainties on the part of you or your partner.

what to expect at the fertility center

A fertility treatment center is a larger practice with physicians specialized in reproductive medicine. These physicians and their staff members are experts in diagnosing and treating fertility disorders. A fertility treatment center also has all the facilities required for treatment, such as its own laboratory and operating room.

On your first visit, you usually need to fill out a questionnaire on your medical history and list your current medications. During your initial consultation, the doctor will then discuss possible reasons for infertility with you. In many cases, the doctor will already explain potential treatments during the consultation.

The doctor will then perform a gynecological exam to look for possible organic reasons for infertility. It may also be necessary to perform additional tests, such as an ultrasound, blood tests or – in rare cases – a laparoscopy.

In men, testing sperm quality is very important. A semen sample is collected through masturbation either at home or at the fertility center. Fertility centers provide a special room for this in which the man will not be disturbed. Once the sample has been collected, it is placed in a pass-through door to the laboratory. Semen analysis is then performed under a microscope. A biologist with special training as an embryologist will then evaluate the number, motility and appearance of the sperm cells.

Depending on the reason for infertility, various treatment methods are available. After a diagnosis has been made based on the test results, the physician draws up an individual treatment plan in consultation with the couple seeking treatment.

Once the doctor has given you the treatment plan, you should apply for reimbursement from your statutory health insurer. For married couples within the legally specified age range (both women and men must be over 25, the woman must be under 40 and the man must be under 50 years old), statutory health insurance providers in Germany generally cover 50 percent of the treatment costs. Some health insurers offer additional voluntary services. The treatment costs and prerequisites may vary depending on the health insurer. This means that the share of the treatment costs (medical care, laboratory costs, drugs) that is not reimbursed by the health insurance providers must be financed by the couples themselves undergoing fertility treatment. Some German federal states also provide subsidies for the treatment costs by means of financial assistance programs.

What treatment options are available?

There are a number of methods available for treating infertility. Depending on the causes and the conditions, various treatment paths are selected.

Hormone therapy in Men and Women

A hormone disorder may be responsible for both male and female infertility. For example, if an FSH or LH deficiency in a man has caused hypogonadism (impaired growth of the testicles), the doctor may prescribe hormone replacement.

If the reason for infertility is due to an “accompanying” hormone disorder in the woman, drugs with a specific action may be used.
If, despite normal hormone levels, the function of the ovaries is reduced, prescribing clomiphene tablets or injecting follicle-stimulating hormone (FSH) and possibly luteinizing hormone (LH) may be used to simulate the natural cycle. It is possible to trigger ovulation with the administration of the pregnancy hormone human chorionic gonadotropin (hCG). Hormone therapy in women, therefore, aims to stimulate egg cell maturation or ovulation.

The hormone therapy is used to counteract a hormone imbalance, a disorder in egg cell maturation or in ovulation, or a disorder of the hormonal testicular function.

Assisted reproductive technology

The term “artificial insemination” used in the past has now been replaced by the term “assisted reproductive technology.” This new term clearly refers to methods in which fertilization is only assisted. The success of this method, i.e. the fusion of the egg and sperm cell, still continues to be an individual and natural process, however. A whole range of methods is available that are used according to the prerequisites and medical history.

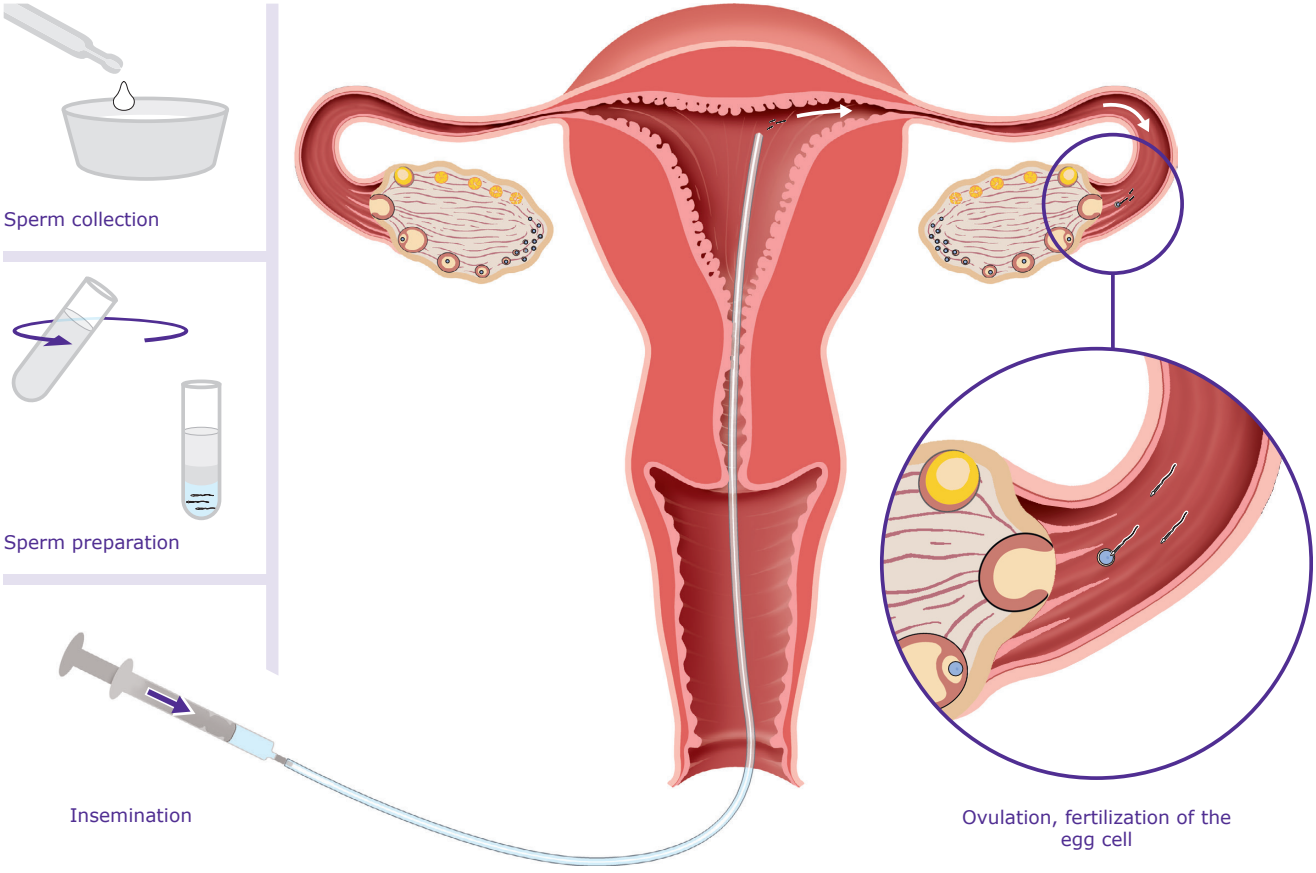
For patients with hormone disorders, hormone replacement therapy can help.

Intrauterine insemination (IUI)

This method is particularly suitable for treating the male partner's low sperm count or weak sperm motility. Before insemination can be initiated, egg cell maturation can be promoted by administering drugs, generally FSH, and ovulation is triggered by administering hCG.

Semen is collected through masturbation, after which it is washed and selected in the laboratory. A thin, flexible catheter is used to place the sperm sample into the uterus.

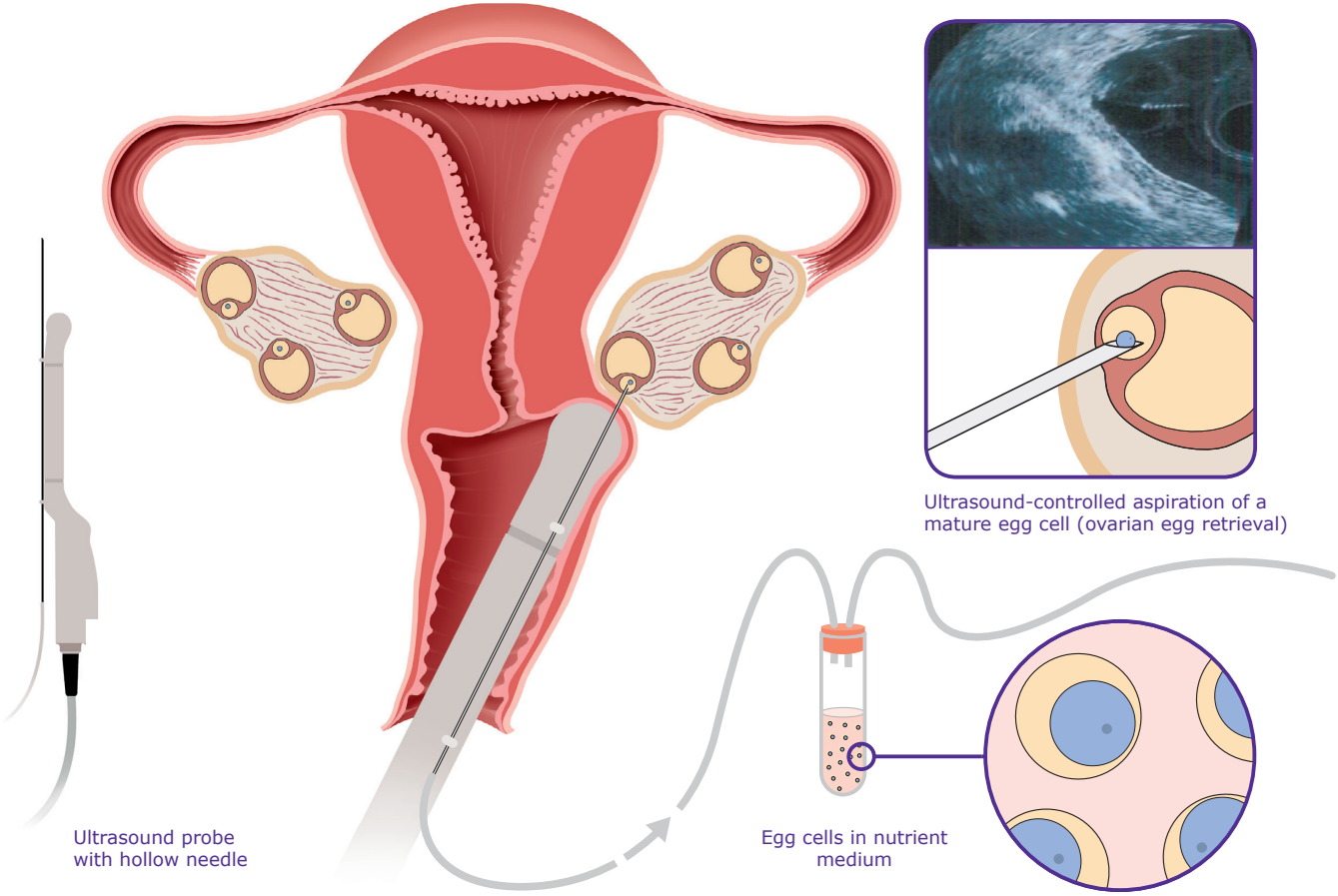
The advantage of this method is that a large number of sperm cells reach the egg cell at very close proximity. The method is used primarily when there is limited sperm function or an immune reaction to the sperm cells. It is also used if there is narrowing of the cervix and for unexplained infertility.


Sperm collection
Sperm preparation
Insemination
Ovulation, fertilization of the egg cell

In vitro fertilization (IVF)

In vitro (Latin) stands for “in glass (test tube)” and refers to methods performed under laboratory conditions. IVF therefore refers to a fertilization method outside the body. IVF too is always initiated by stimulation of egg cell maturation using FSH. However, in contrast to conventional stimulation, several egg cells are brought to maturation simultaneously by means of an appropriately adapted dose of hormones and are retrieved for insemination.

With the patient under general anesthesia or using a mild sedative, a hollow needle is used to remove the egg cells from the mature follicle. The egg cells are then brought together with the sperm in a glass dish. After 24 hours in an incubator, the sample is checked under a microscope to see whether the egg and sperm cells have become combined. If this is the case, after two or three days, a maximum of three embryos are transferred to the woman.



Ultrasound-controlled aspiration of a mature egg cell (ovarian egg retrieval)

The preparatory and stimulation phase

The first treatment step serves to optimally prepare the body for hormone stimulation.

Hormone therapy in men and women

Normally, hormones are used to set the woman's cycle to allow the time of ovulation and egg cell retrieval to be controlled externally. To do this, medications are used that inhibit the production of FSH and LH, the body's own fertility hormones. This is referred to as "downregulation". The medications given in this phase (e.g. GnRH agonists) affect the part of the brain that releases the fertility hormones.

To suppress the body's own hormone production, GnRH antagonists are also available. The GnRH antagonists also have the advantage that they are not applied until during the stimulation phase. This shortens the overall treatment time and prevents potential hormone withdrawal symptoms.

Ovarian stimulation aims to make several egg cells develop simultaneously. This is necessary because not every egg cell can be fertilized and not every embryo becomes implanted in the uterus.

The hormonal stimulation is closely monitored by means of ultrasound examinations and by testing the hormone levels in the blood. Regular monitoring facilitates observation of the number and size of the follicles and the thickness of the uterine lining. This is the only way to determine the ideal time to trigger ovulation and perform the egg retrieval. This monitoring can also reduce the risk of overstimulation.

What Medications are used?

Certain preparations, such as clomiphene tablets, stimulate the brain to increase the release of fertility hormones. To deliberately stimulate egg cell maturation and prepare for ovulation, medications are used that correspond to the natural function of the fertility hormones:

FSH (follicle-stimulating hormone)

Follicle-stimulating hormone (FSH) can be manufactured in various ways, either from the urine of menopausal women or by means of biotechnology in a laboratory. FSH therapy generally starts 14 days after downregulation or in the first three days of the cycle (first day of the cycle = first day of menstruation). The treatment lasts between 11 and 13 days. During this period, a certain amount of the hormone is injected under the skin every day, ideally at around the same time of the day. If your doctor prescribes a GnRH antagonist to suppress your body's own hormone production, it will be administered additionally from the fifth to the seventh day of stimulation.

LH (luteinizing hormone)

LH (luteinizing hormone) as a pure substance is also manufactured biotechnologically today. LH is additionally administered in women with an LH deficiency. With the first pure, biotechnologically manufactured LH, an individual combined option of FSH plus LH can be selected.

Egg cell Maturation and egg retrieval

Once the egg cells have reached full maturity in the follicles, the administration of FSH is discontinued. A further hormone, hCG (human chorionic gonadotropin) now serves to prepare the follicle for ovulation.

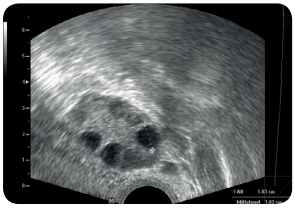
For obtaining hCG too, modern biotechnological methods are in more frequent use in order to guarantee the highest possible level of purity of the preparation. hCG assumes the role of LH in the natural cycle, stimulating ovulation. Around 36 hours after hCG has been administered – just before ovulation – a cannula is used to retrieve the egg cells from the follicles (egg retrieval).

The eggs must be removed prior to ovulation; otherwise, the egg cells would disappear into the fallopian tube and be irretrievable. The procedure is performed through the vagina under ultrasound control.

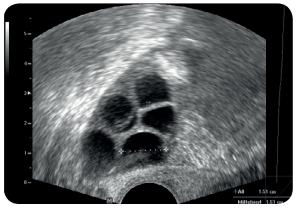
You will be given a pain reliever or sedative or light general anesthesia. After the egg retrieval, you may experience minor pain and spotting.

ovarian stimulation

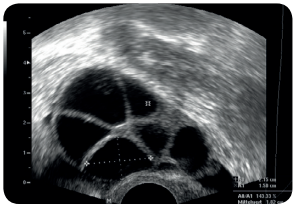
Ultrasound



1st ultrasound



2nd ultrasound



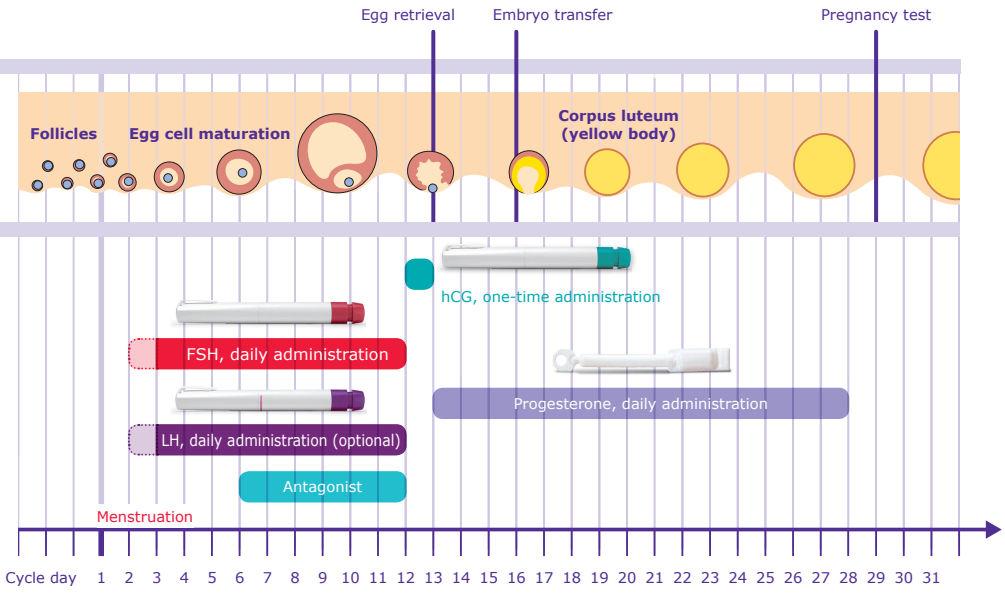
3rd ultrasound

Egg retrieval, embryo transfer, pregnancy test

Ovary

Follicle, egg cell maturation, corpus luteum formation

Hormone stimulation



collecting and preparing the sperm sample

In order to fertilize the egg, sperm cells freshly collected from the partner on the same day are needed. The sperm cells are usually collected through masturbation. However, since masturbation is not always possible "on command", it is important to address the problem of sperm collection early on. This will allow you, your partner and your fertility center to work together to find a good solution.

For example, you can collect the ejaculate at home and bring it with you to the center. It is important, however, that no more than two hours elapse between the time the semen sample is collected and delivery to the center. To keep from the semen from cooling, you should transport it next to your body.

The ejaculate must be collected under hygienic conditions. Before masturbation, you should carefully wash both your hands and your penis with soap and water and thoroughly rinse off the soap. To collect the semen sample, be sure to use special containers supplied by the fertility center. You should not use a condom to collect the semen, because condoms are usually coated with a spermicide.

At the fertility center, the ejaculate is specially prepared, a process that lasts from around 1 to 3 hours. During preparation, the most vital sperm cells are isolated, concentrated and activated, and bacteria and other undesirable components of the ejaculate (e.g. prostaglandins) are removed.

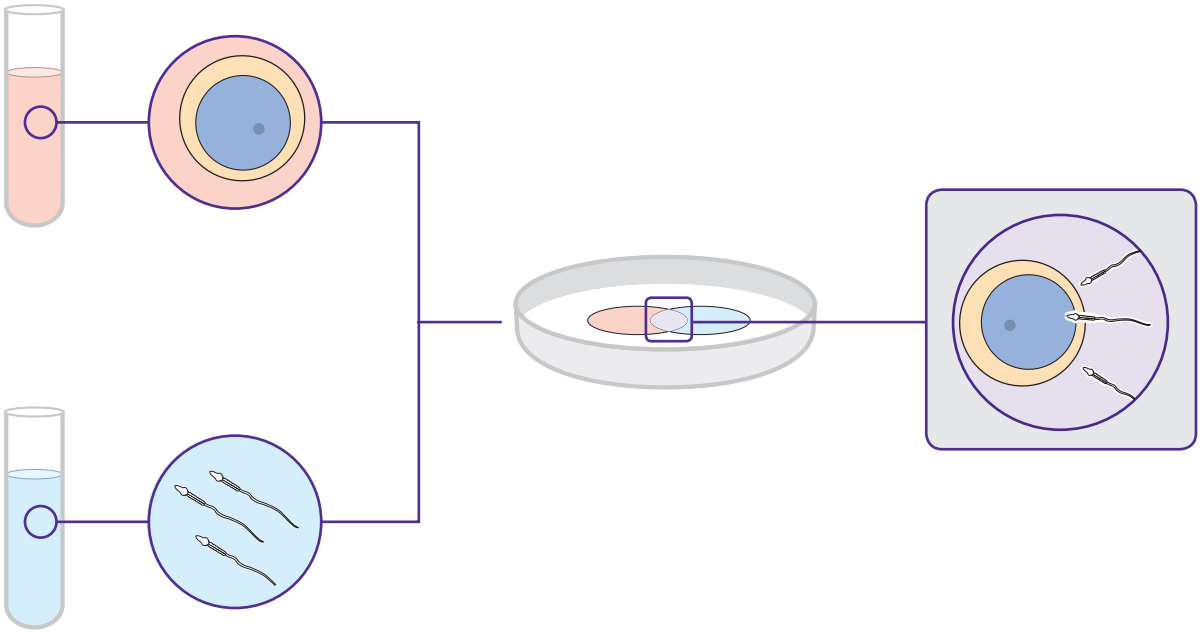
when there are no sperm cells in the ejaculate

If the semen contains no sperm or no moving sperm cells, for instance, if the vas deferens is blocked, it is often still possible to collect sperm cells. To do this, sperm cells can be obtained from the epididymis (microsurgical epididymal sperm aspiration = MESA) or from the testes (testicular sperm extraction = TESE).

Fertilization and embryo transfer

The seminal fluid is first prepared in a laboratory in order to make the sperm cells as fertilizable as possible. Only then are the egg and sperm cell mixed in a laboratory dish in a nutrient medium and cultivated in an incubator for 24 hours.

No more than three fertilized egg cells are then allowed to continue maturing in an incubator for two to three days (embryo transfer) or for five to six days (blastocyst transfer). Excess fertilized egg cells remaining after the embryo transfer but still in the pronucleate stage can be frozen for fertilization in later cycles (cryopreservation).



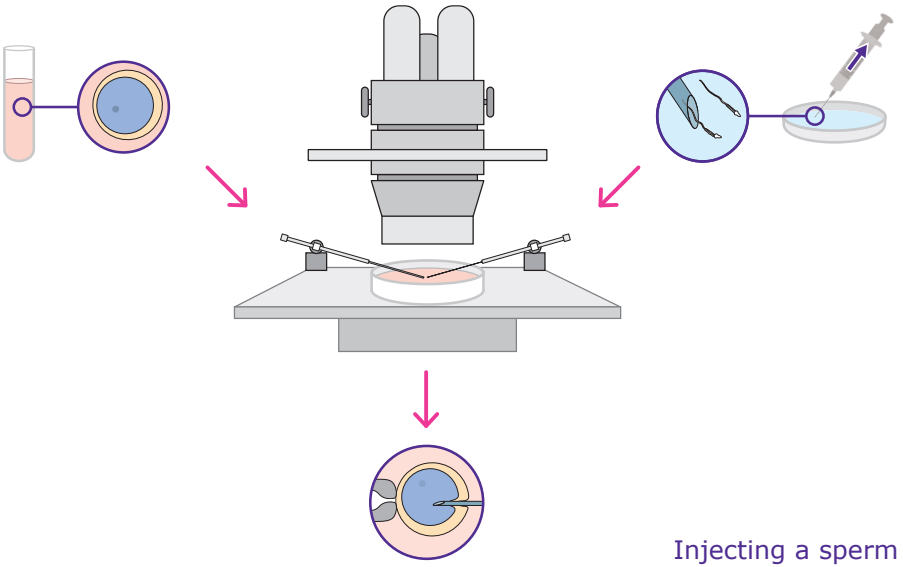
In vitro fertilization

When too few sperm cells are viable

If there is a pronounced sperm weakness, meaning that the number of fully viable sperm cells is too low, in vitro fertilization is not promising. In this case, ICSI is used instead.

Intracytoplasmic sperm injection (ICSI)

Similar to IVF, prior to ICSI, egg cells must be collected by means of hormone stimulation and egg retrieval. Under a special microscope, gentle suction is used to aspirate a single sperm into a fine hollow glass needle. It is then injected directly into the egg cell (into the cell plasma = intracytoplasmically).
This microinjection therefore imitates the natural process of a sperm cell penetrating an egg cell. Similarly to IVF, once the egg has been fertilized and cell division has occurred, after two to three days a maximum of three embryos are placed in the uterus.

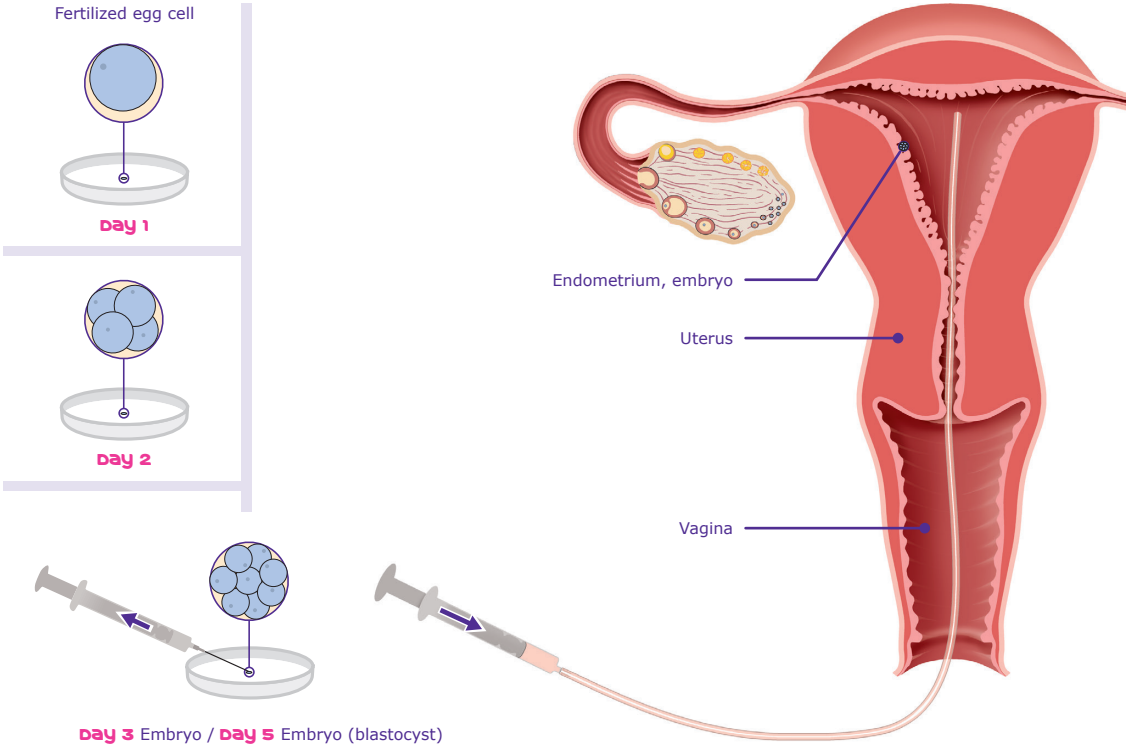


Injecting a sperm cell into an egg cell

Embryo transfer

A thin, flexible plastic tube is inserted through the vagina into the uterus to transfer a maximum of three embryos into the uterine cavity. The procedure is not painful.

The more embryos are placed in the uterus, the higher the probability of multiple births. This is why it is standard practice for one or two embryos to be transferred.



Embryo transfer

What prerequisites have to be met for IVF?

The first prerequisite for IVF treatment is that the infertility cannot be resolved with any other method. Furthermore, generally only egg and sperm cells from the husband or wife can be used. Both partners are legally required to have an HIV test (blood test to rule out an AIDS infection) and a test to rule out hepatitis, a contagious liver infection.

Special prerequisites for men

The most important prerequisite for men is proof of production of sufficiently viable sperm. If a sperm-production disorder has been diagnosed, genetic testing is recommended before further treatment methods can be used.

Special prerequisites for women

The female partner should be below the age of 40 if possible. She should have at least one intact ovary and an intact uterus. In Germany, physicians offering IVF treatment must comply with the Embryo Protection Act, which regulates a number of aspects related to assisted reproductive techniques.

If you become pregnant

The first pregnancy test is performed around two weeks after the embryo transfer. However, at this point the further course of the pregnancy cannot yet be assessed.

Important: You should take it easy on yourself and your body. Despite the suspense and tension, you need to try to relax and stay calm. However, you should still go about your daily business, both at work and at home.

To be on the safe side, your gynecologist or reproductive specialist will perform several follow-up examinations. As early as the second half of the cycle, or if you are pregnant, longer than this, you may be advised to take progesterone to foster proper implantation of the embryo or to maintain the pregnancy. The medical term for this is luteal phase support.

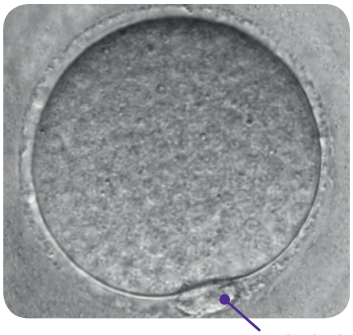
5 Additional Methods used during fertility treatment

Embryo assessment

When in vitro fertilization is performed, the embryos that have been fertilized in this manner must first mature on a nutrient medium in glass dishes in an incubator. Their development is monitored by an embryologist.

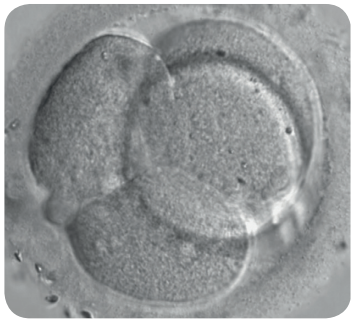
A successful pregnancy is dependent on a number of factors. One of the most important factors involves identifying the most viable embryos. To do this, the glass dishes with the embryos are usually removed from the incubator and are evaluated under the microscope based on their appearance.

However, more and more technologies are becoming available to aid the embryologist in evaluating an embryo. For example, embryos can mature in incubators equipped with cameras. This enables the embryo's development to be continuously monitored without having to remove it from the environment that facilitates its growth.



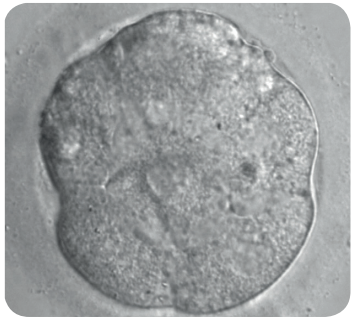
Day 0 **Egg cell**

Day 1 **Pronucleate stage**

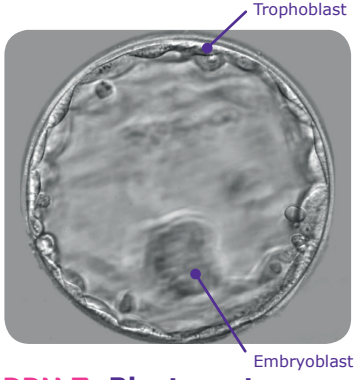


Day 2 **4-cell embryo**

Day 3 **8-cell embryo**



Day 4 **Morula**



Day 5 **Blastocyst**

Normal development of an embryo after in vitro fertilization

Images provided by Dr. Martin Greuner, IVF SAAR Saarbrücken-Kaiserslautern

Assisted hatching

Under certain conditions (for example, after several failed attempts at embryonic transfer), an attempt is made to increase the chances of pregnancy by helping the embryo hatch from the egg's shell. To this end, a laser is used to slice a tiny opening in the outer shell of the embryo before it is placed in the uterus.

Cryopreservation

It is possible to store cells in the pronucleate state by freezing them. The term "pronucleate stage" means that while fertilization has taken place, the genetic material of the two cells has not yet fused. Cryopreservation is usually only possible if at least three excess high-quality fertilized egg cells exist; it enables them to be used as alternatives in case an egg cell dies after thawing. The advantage of cryopreservation: If pregnancy has not occurred after a cycle of treatment and treatment needs to be repeated, hormone stimulation and egg retrieval do not have to be carried out again.
For this reason, prior to undergoing IVF treatment, it is important for you to talk with your doctor about whether excess egg cells in the pronucleate stage should be frozen.

One modern method of cryopreservation is vitrification, which is when the egg cells are "flash-frozen" within several seconds.
This facilitates a survival rate of over 90 % when the egg cells are thawed[1].

1. Golakov et al. Arch Gynecol Obstet. 2018; 297:529–537

Cryopreservation of egg cells

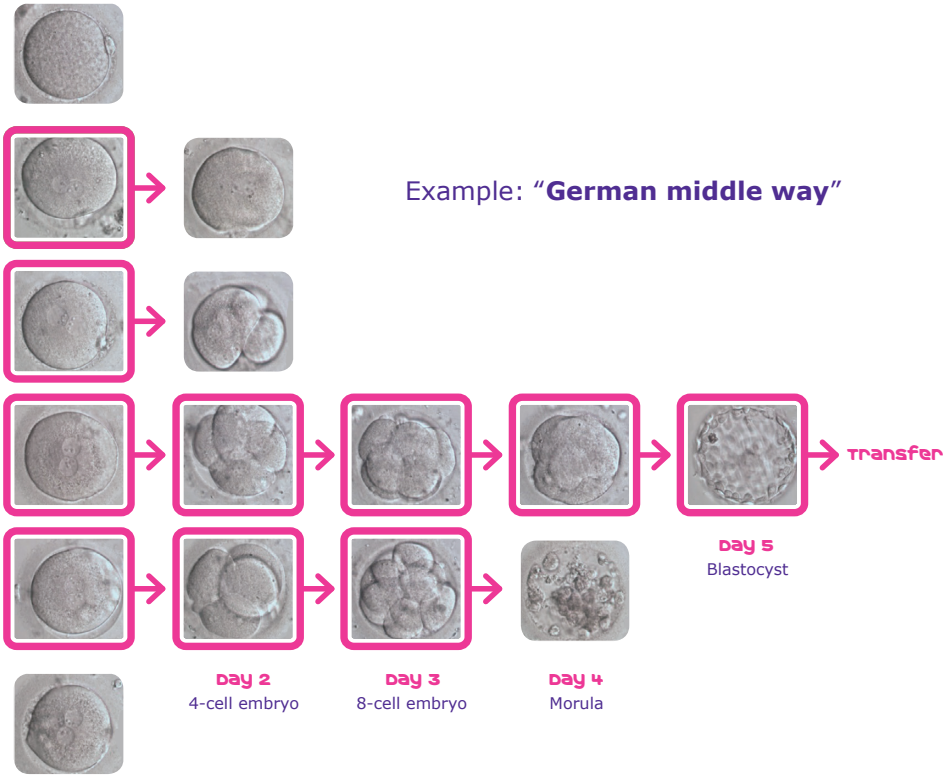


Image source: Adamson, G. D., et al., "Improved implantation rates using the time-lapse-enabled Eeva™ test as an adjunct to morphology for day 3 transfer." Fertility and Sterility 102.3 (2014): e18.

6 opportunities and risks of assisted fertility treatment

opportunities

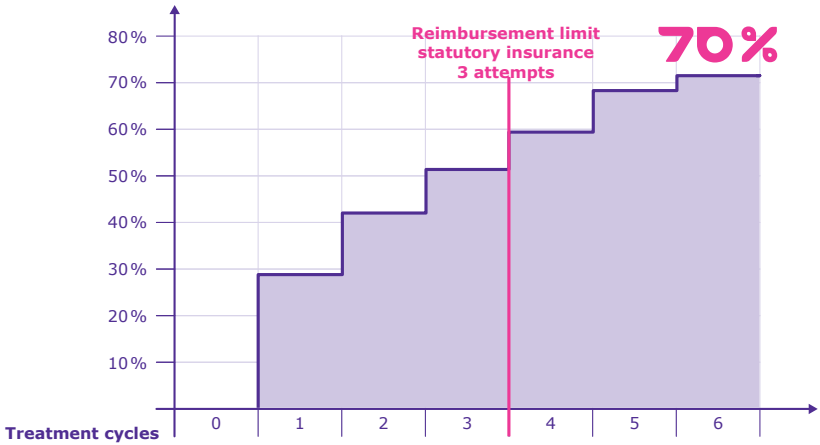
A number of factors play an important role in the success of treatment measures. For instance, apart from the nature and duration of the infertility disorder, as was mentioned above, the woman's age plays a key role. However, during a straightforward in vitro treatment course, the methods used today can achieve at least the same success per cycle as natural conception in a healthy couple.

the probability of becoming pregnant within a cycle is as follows:

- For a healthy, young couple: approx. 25 percent[1]
- Insemination: 12 to 15 percent[2]
- In vitro fertilization (IVF/ICSI): 20 to 45 percent (depending on age)[3]

The cumulative pregnancy rate, which allows conclusions to be drawn about the success of fertility treatment, proves that with the number of attempts, the chances of becoming pregnant increase. Considering that after two completed treatment cycles an average of around 40 percent of women become pregnant, this

Cumulative birth rate increases to 70 % by the 6th attempt



J. Reproduktionsmed. Endokrinol 2011; 8 (Supplementum 2)

1. H Carcio, Management of the Infertile Woman; M Rosenthal, Carcio and The Fertility Sourcebook.
2. Diedrich, Ludwig, Griesinger, Reproduktionsmedizin, 2013.
3. DIR Jahrbuch, 2016.

means that after the third treatment cycle, one out of two women can look forward to becoming pregnant, since the rate rises to 50 percent. The probability of a live birth reaches 72 percent after six treatment cycles and for women under 35, the rate is as high as 86 percent.

Risks

Like all medical treatments, fertility treatment can also be associated with risks and side effects. Fortunately, however, these risks are rare. Some of these risks are presented below.

Overstimulation

Due to the potential risk of overstimulation, the consulting physician carefully monitors the hormone treatment. When overstimulation occurs, the ovaries produce a high number of follicles that in turn release increased levels of hormones.
This hyperfunction can lead to nausea and edema with abdominal pain. If you experience increasing abdominal pain, you must notify your doctor immediately. If the overstimulation is too severe, hospitalization may be required.
Fortunately, with regular monitoring, the risk of severe overstimulation can be reduced to one to two percent. Here, your active participation is required, so please keep all of your examination appointments as scheduled.

Multiple births

With IVF, the probability of multiple births is always elevated (20 to 30 percent). This is because to ensure success, several (but no more than three, according to the Embryo Protection Act) embryos can be placed in the uterus.

Miscarriage

With increasing age and as a result of “subfertility” (limited ability to procreate or conceive), the risk of miscarriage increases slightly.

Surgical complications

In rare cases, surgical procedures associated with IVF lead to complications. In rare cases (<1:1,000), there may be abdominal bleeding, but this may also very rarely occur during spontaneous ovulation, too. In other very rare cases, infection may occur during egg retrieval.

Emotional stress

Fertility treatment requires a great deal of time, a whole range of appointments, and in some cases, more complex examinations. For this reason, it calls for an inordinate amount of patience on the part of both partners. The couples experience a period characterized by strong emotions and in some cases, wildly fluctuating feelings ranging from hope and fear, joy and disappointment. It is easy for emotional stress to crop up. It’s important to keep talking. Let others know how you are feeling – both mentally and physically. Talk with your partner. Talk with your friends, in a support group, if you prefer, and especially, talk to your physician.

Limits of fertility treatment

The limits of fertility treatment are determined both biologically and legally. For instance, in a 45-year-old patient, the probability of pregnancy following IVF or ICSI is less than 3 percent. The Embryo Protection Law in Germany also sets additional limits.
In Germany, egg donation is prohibited, for example. This means that if you read reports about a pregnant woman who is significantly older than 50, the pregnancy is very likely the result of an egg donation from a much younger woman.*

* Egg donation is prohibited in Germany.

7 Reimbursement/ financial assistance

statutory health insurance providers

The maximum number of treatment cycles supported by statutory health insurance providers is usually three. If a pregnancy occurs, a couple wishing to plan another pregnancy is entitled to up to three treatment attempts.

In accordance with the legal provisions, the statutory health insurance providers in Germany reimburse 50 percent of the treatment costs for three cycles. However, statutory health insurance providers are permitted to reimburse more than the legally stipulated 50 percent with additional voluntary optional benefits. At present, around 50 of the approx. 125 statutory health insurance providers in Germany offer optional benefits for fertility treatment. Some statutory health insurance providers even cover 100 percent of the treatment costs with their optional benefits. You should be able to obtain an overview of the current optional benefits offered by the statutory health insurance providers from your physician. However, you can also contact your statutory health insurance provider directly for more information about the relevant optional benefits.

Keep in mind that it pays to compare.

private health insurance providers

Private health insurance providers generally cover a higher percentage of costs than the statutory health insurance providers. In most cases, private health insurance providers do not limit the number of attempts at in vitro fertilization. Moreover, unmarried partners are not excluded from coverage and there is no age limit. However, in order for the costs to be reimbursed by the private health insurance provider, the chances of a successful pregnancy must be at least 15 percent. If the partner responsible for infertility is privately insured, all costs for fertility treatment are always covered. This “principle of the responsible party” also means that the costs for treating a “non-responsible” partner insured with a statutory health insurance provider are also covered by the private health insurance (as of February 2018).

The specific benefits to which the insured party is entitled from his or her private health insurance are not regulated by legal provisions but rather by the individually selected insurance agreement. The insurance policy states the benefits provided by the private health insurance.

Financial subsidies provided by the federal states

In cooperation with the German Ministry for Family Affairs, some German federal states have set up assistance programs and cover part of the costs for fertility treatment. In most cases, these assistance programs cover 50 percent of the high co-pay amounts borne by the couple planning a pregnancy. Currently (as of June 2017), the federal states of Berlin, Mecklenburg-Western Pomerania, Lower Saxony, Saxony, Saxony-Anhalt and Thuringia offer these types of assistance programs.

8 safety, data privacy and IVF Registry

safety

At the IVF laboratory, all efforts humanly possible are made to prevent mix-ups or medical problems from occurring. Working in a sterile environment is a given at an IVF lab, as is unequivocal labeling and the identification of all samples and embryos. Consistent application of the cross-check principle ensures additional security. In order to prevent mix-ups, the employees also need information from you. This information goes beyond the data provided on your health ID card. For example, a copy of your personal identity card is made to ensure proper identification. The fertility center will also require your photograph. This photo is displayed in all data concerning you on the computer, which eliminates the chances of a mix-up. In addition, your signature is required before certain treatment steps are carried out.

Data privacy

At the fertility centers, your data privacy is top priority. Many fertility centers therefore have their own IT officer, who is responsible for protecting the sensitive patient data.

IVF Registry

The German IVF Registry (DIR) is tasked with providing the research community and the general public with information and transparency in the highly sensitive area of human reproductive medicine. It therefore serves both the general public and couples wishing to become pregnant, since its findings also help counsel these couples and ultimately inform their decision-making. Fulfilling these extensive tasks is the core objective and core competency of the German IVF Registry. Since 1992, nearly all reproductive medicine institutions in Germany have supplied data to the Registry.

9 Addresses and further information

The name Merck is associated with in-depth knowledge on all aspects of fertility. Its close cooperation with leading scientists keeps Merck on the cutting edge at all times.

To help you benefit from our knowledge beyond what is offered in this brochure, we have set up a toll-free hotline. A trained team is available to assist you on the telephone. Your questions will be answered immediately if possible, or your call will be returned with the appropriate information based on the team's research.

Service Center Toll-free Hotline: 0800-046-6253

Our website www.calimera4you.de features a wide range of up-to-date information and services.

The extensive information site: www.calimera4you.de

In addition to getting medical and psychological counseling, participating in a support group can often be very helpful. In the group, you can communicate with other individuals about your experiences and concerns. The nonprofit association for issues related to infertility – Wunschkind e.V. – will be happy to provide the address of a support group near you. The association's website also provides useful information on the topic.

Wunschkind e.V.

Association of support groups for issues concerning infertility
Fehrbelliner Straße 92, 10119 Berlin, Germany Tel.: +49-180-500-2166, Fax: +49-30-6904-0838,
Hotline: Tuesdays from 7 p.m. to 9 p.m., E-Mail: wunschkind@directbox.com
www.wunschkind.de

Bundesverband Reproduktionsmedizinischer Zentren Deutschlands e.V. (Federal Association of Reproductive Medicine Centers in Germany)

Dudweilerstraße 58, 66111 Saarbrücken, Germany, Tel.: +49-681-373-551,
Fax: +49-681-373-539, E-Mail: brz@repromed.de, www.repromed.de

pro familia Federal Association

Stresemannallee 3, 60596 Frankfurt, Telephone: +49-69-639-002, Fax: +49-69-639-852,
E-Mail: info@profamilia.de, www.profamilia.de

Would you like psychotherapeutic support? The Counseling Network for Infertility Germany (Beratungsnetzwerk Kinderwunsch Deutschland; German Society for Fertility Counseling) has published an extensive address list on its website: www.bkid.de.

In special cases, heterologous insemination – fertilization with donor sperm, also referred to as donogenous insemination – may be a treatment option. You can find an extensive address list online at www.donogene-insemination.de.

10 Glossary

Technical terms made simple

So that you can always understand what we are talking about, we have compiled a list of medical terms and their explanations for you.

Androgens
Male sex hormones.

Assisted hatching
Slitting the external shell of the embryo, for instance, with a laser, in order to facilitate implantation of the embryo in the uterine lining.

Chromosomes
Components of the cell nucleus and carriers of genetic information. Chromosomes consist primarily of DNA (deoxyribonucleic acid), the actual genetic material. During cell division, it is reproduced in the daughter cells. Humans have 23 pairs of chromosomes (i.e. 46 chromosomes altogether). 22 of the chromosome pairs are not involved in determining the baby's sex. The 23rd pair, the sex chromosome, is formed differently in men and women. Women have two X chromosomes per nucleus and men have one X chromosome and one Y chromosome per nucleus. The chromosome of the sperm cell fertilizing the egg determines the baby's sex.

Corpus luteum (yellow body)
What is left of the follicle after ovulation; takes on a yellow color after forming the secondary follicle ("yellow body").

Cryopreservation
Greek: kryo = cold, icy. With cryopreservation, egg cells in the “pronucleate stage” can be frozen and stored.

Downregulation
Using drugs to reduce the body’s own hormone excretion.

Ectopic pregnancy
Implantation of the embryo in one of the fallopian tubes instead of the uterine cavity.

Egg retrieval
Removing the fluid in the follicle with a very fine hollow needle in order to retrieve the egg cell.

Embryo
Once the DNA from the sperm and egg cells has merged, the term “embryo” is used. From the 13th week of gestation on, the developing baby is referred to as a “fetus”.

Embryo transfer
Transfer of an egg cell into the uterus after fertilization outside the body.

Endometriosis
From the Greek for “within” (endon) the “uterus” (metra). Frequent cause of infertility. Endometriosis is a disorder in which the tissue of the uterine lining grows outside the uterus, where it can cause scarring.

Endometrium
Well-vascularized mucous membrane periodically formed by the uterus.
The embryo implants itself in the endometrium.

Estrogen
Latin: oestrus = female animal's readiness to mate, gen = create. Estrogen is a female sex hormone formed in the ovaries and which is responsible for the buildup of the endometrium.

Fallopian tubes
Funnel-shaped "conveyer belt" in which the sperm cells are guided to the egg cell and the fertilized eggs are guided into the uterine cavity.

Follicles
Liquid-filled group of egg cells. Follicles mature in the ovaries.

FSH
Follicle-stimulating hormone; promotes the growth and development of the egg cells.

Gametes
Term used for both female and male sex cells that have only a simple set of chromosomes prior to fertilization.

GnRH
Gonadotropin-releasing hormone. From the Greek and English:
"producing" (gonos) and "effect on" (trop). Hormone effecting the excretion of LH and FSH.

GnRH agonist
Drug that inhibits the excretion of LH and FSH (after initial release of these hormones).

GnRH antagonist
From the Greek for “against” (anti). Drug preventing the excretion of the fertility hormones LH and FSH.

Gonadotropins
Collective term for gonadotropic hormones of the front lobe of the pituitary gland, the placenta or the endometrium that promote and control the growth of the gonads (sex glands in which the gametes develop).

Gonadotropic
Affecting the gametes, especially those of hormones.

HIV infection
Human immunodeficiency virus (HIV) infection that can lead to AIDS.

Hormones
The body’s own carriers of information between various organs.

Human chorionic gonadotropin (hCG) Outpatient
Latin: chorion = membrane surrounding the fetus, gonaden = sex glands, trop = affect.
Hormone used as a drug for triggering ovulation.
hCG is obtained from the urine of pregnant women or is manufactured through biotechnology.

Human menopausal gonadotropin (hMG)
hMG is obtained from the urine of post-menopausal women and is used for ovarian stimulation.

Infertility
When a couple has regular unprotected sexual intercourse for over a year but does not become pregnant, infertility is assumed. However, this does not have to be a final condition.

Intracytoplasmic sperm injection (ICSI)
Latin: intra = in, into, cytoplasma = cell contents.
Method of assisted fertilization in which a hollow needle is used to inject a single sperm cell into an egg cell.

Intrauterine insemination (IUI)
Insemination refers to the transfer of sperm cells into the vagina or uterus by means of technical assistance. With IUI, the sperm cell is introduced into the uterus as close as possible to the egg cell.

In vitro fertilization (IVF)
Latin: in vitro = in glass (test tube). IVF refers to fertilization outside the body.

Laparoscopy
Endoscopy of the abdominal cavity and organs. Used to explore the position, size, and condition of the abdominal organs.

Luteinizing hormone (LH)
Hormone triggering ovulation.

Outpatient
Treatment without admission to the hospital (opposite of inpatient).

Ovaries
Paired walnut-sized female organs in which the fertilizable egg cells are produced. The ovaries form the hormones estrogen and gestagen (gestatio = pregnancy, gen = create).

Ovulation
The egg cell leaves the ovary and enters the fallopian tube.

Placenta
Organ supplying nutrients to the developing fetus. After the birth, the placenta detaches from the uterine wall and is expelled as the “afterbirth”.

Polycystic ovary (PCO)
From the Greek for “cyst” (kytis) and “many” (poly). Ovary with many small cysts.

Progesterone
Latin: pro = for, gestatio = pregnancy. Progesterone is secreted by the corpus luteum and prepares the endometrium for implantation of the embryo.

Prolactin
Latin: lactis = milk. Hormone formed in the brain. Prolactin stimulates lactation.

TESE / MESA
If there is a complete absence of sperm in the ejaculate, it is possible to obtain sperm cells directly from the testes (TESE = testicular sperm extraction) or the epididymis (MESA = microsurgical epididymal sperm aspiration).

Uterine fibroid (myoma)
Benign tumor in the uterus consisting of muscle tissue. Uterine fibroids are sometimes the reason for long-term infertility or miscarriage.

Uterus
Pear-shaped organ in which the baby is carried. The uterus consists of the cervix, the neck of the uterus, and the uterine cavity. The two fallopian tubes are connected to the uterus.

Merck Service Center

Toll-free hotline:

0800-046-6253

The patient information website:

www.calimera4you.de

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https://www.merckgroup.com/d-de/company/who-we-are/healthcare.html

MyCalimera

The innovative online program for valuable expert information and emotional support.

Further information available at
www.mycalimera.de

Calimera Magazin

The Merck fertility treatment magazine

W.82343.0 | DE/NONF/0718/0037 | Published 07/2018

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