

## Infertility

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Infertility is a common medical condition affecting 1 in 7 couples. There are many different reasons to seek fertility services. Many, but not all, cases of infertility can be explained. The underlying causes of infertility can be broken down into several key factors: sperm, eggs, uterus, tubes, and hormones.



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### What is infertility?

Infertility is a medical condition where the ability to conceive (become pregnant) and then give birth to a child is limited or impaired in some way. While infertility can be socially isolating, it is very common. Infertility affects an estimated 1 in 7 couples. Recent data from the CDC report that 7.3 million women in the United States, or 12% of all reproductive age women aged 15-44, used some type of fertility service from 2011 to 2015. There is an even higher number of people who experience infertility, because some people don't seek help.

Infertility is often defined as the failure to conceive after one year. This is the definition because 85% of couples attempting to conceive will do so within one year, and only an additional 7% will successfully conceive in the year following. This metric is helpful in providing a general rule for when most couples should seek fertility services. However, there are important exceptions to this rule, which will be addressed here.

This definition leaves out many patients seeking fertility treatment, including single individuals wanting to become parents, same-sex couples, and patients who suffer from recurrent miscarriages even though they get pregnant easily. Plus, some patients may not want to get pregnant right away but rather want to get testing or treatment for fertility preservation. This means that the patient wants to get pregnant later in life, or they are going to have a medical or surgical treatment that could make it harder to get pregnant later.

Infertility has many causes. Some patients might be fertile in one sense but suffer from infertility in another sense. For example, a person may have normal eggs but not have a uterus (“uterine factor”) or functional fallopian tubes (“tubal factor”). A male partner may suffer from performance anxiety during intercourse, have problems with his sperm, or consistently be away during peak fertility of their partner’s menstrual cycle. Or, an individual may not have a male partner at all (all are “male factor”). Some patients can become pregnant easily, but then consistently lose those pregnancies early in the first trimester (“recurrent pregnancy loss”).

Other reasons for infertility include:

- problems related to ovaries, ovulation, or eggs, including a lack of eggs (“primary ovarian insufficiency”)
- abnormal menstrual cycles and excess of androgens (“polycystic ovary syndrome”)
- a lack of periods due to lack of hormone release from the brain (“hypothalamic amenorrhea”)

Sometimes, there is no clear reason. When there is no obvious reason for infertility, the term “unexplained infertility” is used. This happens about 15% of the time.

## Diagnosis and Treatment

In a very basic sense, natural fertility requires five basic components:

- capable sperm
- capable eggs
- proper hormone signaling
- a means and location (the fallopian tubes) for the egg and sperm to fertilize to create an embryo
- a place (the uterus) for the embryo to implant and grow into a baby

For an individual or couple seeking fertility services, the first step is to look at these key areas. These tests will determine which treatments are offered.

### Sperm

Sperm production normally begins with puberty and continues until death. However, many problems can occur. Some of these problems are lack of sperm production, destruction of sperm, or blockage of sperm transport. A test called a **semen analysis** looks at several components of the sperm:

- the total volume
- the concentration of sperm
- number of motile (swimming) sperm

## 🌱 the shape of the sperm

Semen analysis is not a perfect test, and there is a very large range of what is considered normal. However, given that male factor is a major contributor to the failure to conceive (present in 40% of heterosexual infertile couples), semen analysis is part of the first tests of infertility.

If the semen analysis is abnormal, it is often repeated to confirm the abnormal finding. If confirmed, the patient meets with a reproductive urologist. At this point, options are discussed including lifestyle changes, medications, and surgery. If these options to improve sperm quantity/quality are not available, feasible, or successful, **intrauterine insemination ("IUI")** and **in vitro fertilization ("IVF")** may be offered. IUI and IVF may also be offered if the patient does not have a male partner. A *sperm donor* can be used with IUI or IVF if a patient has very poor sperm quantity and/or quality. A sperm donor would also be used for patients who do not have a partner with testes.

**IUI** is a half-day process. Semen is collected from the male patient and then washed and prepared in the lab. Later that day, their female partner undergoes a pelvic exam in the office (like a pap smear) where a thin tube is passed through the cervix. The sperm is pushed through the tube into the inside of uterus. This brings the sperm closer to the fallopian tubes and ovaries, increasing the chance of pregnancy.

**IVF** is a roughly month-long process. In IVF, the female partner's eggs are stimulated using special medications called *gonadotropins* and monitored closely with ultrasound. During this time, ovulation is prevented until the eggs are ready to be collected. Once ready, eggs are collected using a needle attached to an ultrasound probe placed in the vagina. The patient is asleep during this procedure. Then the eggs are fertilized in the lab to make embryos. The resulting embryos are transferred directly to the uterus through a tube. The process is similar to IUI, except the embryo, not sperm, is put into the uterus.

## Eggs

Unlike sperm production, a person with ovaries is born with all the eggs they will ever have. The number of eggs goes down with time until there are no eggs left.

**"Egg quantity"** (also known as the ovarian reserve) is the number of eggs that a person has. One common measure of egg quantity is anti-mullerian hormone (AMH), a simple blood test. AMH is often used (and marketed) as a way for patients *without known infertility* to predict future fertility. However, recent studies have shown that AMH doesn't work very well at predicting which patients will go on to conceive a child. In other words, many patients may get pregnant easily even if they have a low AMH. For this reason, AMH should not be routinely used

as a screening test or to predict future fertility *in the general population*. This test can be useful in patients with known infertility to predict their response to treatment, particularly IVF.

**“Egg quality”** is different from egg quantity. It refers to whether eggs have the normal number of chromosomes. Egg quality is closely related to patient age. As patients age, both the quality and quantity of eggs go down. This starts off gradually but then drops off dramatically as one approaches age 40. For this reason, many clinics recommend a test called PGS (preimplantation genetic screening) for patients over the age of 37 who are undergoing IVF. In PGS, embryos are biopsied and checked to see if they have the correct number of chromosomes.

Patients with lower egg quality or quantity are often “fast tracked” to IVF treatment, as it has the best chance for success, especially when there is concern for rapidly diminishing fertility. For patients with advanced age or very poor egg quantity and egg quality, or for patients who lack ovaries or a partner with ovaries, an *egg donor* can be used in IVF.

Another condition that can have an effect on the ovaries is **endometriosis**. Endometriosis occurs when the uterine lining (called endometrium) moves outside of the uterus. It is very common, affecting an estimated 10% of reproductive aged women. Diagnosis and treatment of endometriosis often requires surgery. It is a complex disease and treatment will depend on how severe it is and what the patient’s goals are.

## Hormones

In order for eggs to mature and for **ovulation** (the release of the egg from the ovary) to happen, special hormone centers in the brain send messages to the ovaries. These centers are known as the hypothalamus and pituitary gland. A doctor will get a complete menstrual history from the patient in order to see if the hormonal process is happening normally.



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A patient may have good egg quantity and quality but still be infertile if ovulation is not taking place. Without ovulation, an egg cannot be found and fertilized by a sperm. This is what happens for most PCOS (“polycystic ovary syndrome”) patients. People with PCOS have plenty of eggs but are not able to get pregnant because they do not have consistent ovulation. In this case, medications can help. The most common medications are *clomiphene citrate* (Clomid) and *letrozole* (Femara). These

medications act in different ways to do the same thing. Both methods stimulate the release of *follicle-stimulating hormone*, or FSH. These medications can also be given with IUI or IVF, though this is not required.

## Tubes

If both fallopian tubes are blocked or missing, an egg cannot be fertilized by sperm or move into the uterus. **Tubal blockage** (also called occlusion) can be caused by pelvic infections (usually chlamydia or gonorrhea) or any other severe pelvic inflammation (such as a history of ruptured appendicitis or endometriosis).

One of the first tests done for infertility is an **HSG (hysterosalpingogram)**. In an HSG, contrast dye is injected into the uterus and X-rays are taken. If there is a blockage, no dye will be seen spilling out the end of the fallopian tube. HSG is also able to detect other problems, including some polyps and fibroids that change the shape of the uterus.

A person can still get pregnant if there is one tube that is working normally. Depending on what is wrong with the tubes, surgery may be offered to some patients to fix the tube. For patients who have had a tubal sterilization procedure (tubal ligation, or getting one's "tubes tied") in the past but now desire to have a baby, reversal surgery is sometimes possible.

If surgery is not available or recommended, IVF is required to get pregnant. In many patients with fallopian tubes that don't work normally, removal of the tubes before IVF improves pregnancy rates. For this reason, patients having surgery to fix their tubes might get their tubes removed if the surgery doesn't work.

## Uterus

The uterus is an organ with two layers. There is a muscular layer ("myometrium") that can change size and shape when a person is pregnant. And there is an inner layer ("endometrium") that builds up every month and is released during a person's period. The fallopian tubes and the cervix are part of the uterus. A simple pelvic ultrasound can detect many common problems with the uterus that can lead to infertility.

One common cause of infertility is having a type of growth in the myometrium known as **fibroids**. Fibroids can affect fertility by changing the shape of the uterus. This can stop a fertilized egg from attaching to the wall of the uterus. Fibroids also can cause a miscarriage. Surgical removal of fibroids is called myomectomy. Myomectomy is often done in a minimally invasive procedure. It can be done either by instruments passed through tiny incisions in the abdomen (laparoscopy) or through the vagina and cervix (hysteroscopy). Sometimes the surgery is done through large abdominal incisions (laparotomy). The type of surgery is based on



the location, size, and number of the fibroids. Not all fibroids need to be removed, and not all fibroids cause infertility.

The endometrial layer of the uterus can also be the site of growths known as endometrial **polyps**. Polyps can prevent a fertilized egg from attaching to the wall of the uterus. Polyps are removed through a hysteroscopic procedure (through the vagina and cervix).

The uterus can have other structural problems, including an irregular shape. Or, the uterus might have a uterine septum, a band of tissue that divides the inside of the cavity in two. These problems can often, but not always, be corrected surgically. Several causes of “unexplained infertility” are probably due to problems with the uterus.

Another potential cause of unexplained infertility is a problem with the cervix. Both IUI or IVF can help in this case.

Some people are born without a uterus. Some people have their uterus removed during emergencies such as severe hemorrhage, for early stage cancer, or because they are born with a deformed uterus. For these patients with “**absolute uterine factor**” infertility, the only options to have a genetically related child is to use a gestational carrier (which is not legal in many countries and states) or receive a uterus transplant. Uterus transplant is experimental, but there have been over a dozen babies born worldwide. There are at least three active ongoing research trials in United States.

## When to seek help

**Heterosexual couples** who have vaginal intercourse on a regular basis, should talk to a doctor if they don't get pregnant after 1 year. If the female partner doesn't have a uterus or regular periods, they should seek fertility services as soon as possible. In addition, they should seek care as soon as possible if:

- the female partner has had pelvic infections
- if either person has had sexually transmitted diseases
- if the female partner has had uterine polyps or fibroids
- if either person has had problems with infertility in the past with previous partners, or
- if the female partner is over 40 years old



If the female partner is 35 years old or older, they should seek fertility services after 6 months of trying to conceive instead of 1 year.

**Same-sex couples** should talk to a doctor as soon as possible.

**People with recurrent pregnancy loss** should talk to a doctor about fertility testing after having 2 miscarriages.

**If a person wants to freeze their eggs** to delay childbearing, they should talk to a doctor about it as soon as possible. It's best to do it before the age of 35, because as a person gets older their egg quality and quantity go down. Once eggs are frozen, they can be stored almost indefinitely. The egg freezing procedure takes at least 2-3 weeks.

**People with cancer who want to have a baby in the future** should talk to a doctor about this before starting chemotherapy or any surgery that may harm the reproductive system. The preferred method of fertility preservation is freezing of embryos or eggs. However, these methods require advance planning and weeks of treatment, which may not be feasible or realistic for many patients.

**The most important step is learning as much as you can about your own fertility.** We recommend you seek consultation with a fertility specialist if you have any questions or concerns.

## Take Home Points

- ✦ Infertility is relatively common, affecting 1 in 7 couples in the United States.
- ✦ Infertility has many causes, related to eggs, sperm, hormonal signaling, and structure and function of the reproductive organs.
- ✦ There are many options available for people suffering from infertility
- ✦ IUI and IVF can be very effective
- ✦ New and exciting technologies are being developed, such as uterus transplant, in vitro maturation, tissue regeneration, better preimplantation testing of embryos, and new therapeutics
- ✦ There has never been a more hopeful time for people who suffer from infertility!

## Reference

<https://www.cdc.gov/nchs/fastats/infertility.htm>

## About the Author

Elliott G. Richards, M.D. is a fellow in Reproductive Endocrinology and Infertility at the Cleveland Clinic. His interests include endometriosis, reproductive surgery, in vitro fertilization, and uterus transplantation.

No conflicts of interest to declare.