

# Progesterone and Pregnancy: What You Need to Know

## WHY PROGESTERONE IS IMPORTANT BEFORE AND DURING PREGNANCY

Before pregnancy, progesterone is essential in preparing the uterine lining (endometrium) for implantation of a fertilized egg. Progesterone continues to have a critical role throughout pregnancy, maintaining a nurturing environment for embryonic and fetal development. In fact, the word progesterone is derived from the Latin word *gestare*, meaning to bear or carry, and progesterone is often called "the pregnancy hormone."

Progesterone production begins in the ovaries during the luteal phase, which follows ovulation. A follicle in the ovaries releases an egg and then transforms into the corpus luteum, a temporary structure that produces a large amount of progesterone. The progesterone causes the endometrium to thicken, helping to prepare for a fertilized egg. If pregnancy does not occur, the corpus luteum shrivels and the falling progesterone levels trigger menstruation. The uterine lining is shed in preparation for the next cycle.

The luteal phase-when progesterone production by the corpus luteum begins-is as important in in vitro fertilization (IVF) cycles as natural ones. This is the time following egg retrieval when the fertilized egg, or embryo, is transferred into your uterus for implantation.

After about 8 weeks of pregnancy, levels of progesterone start rising again as the placenta takes over progesterone production from the ovaries. It is important to have a large and constant supply of progesterone to maintain a nurturing and supportive environment for embryonic and fetal development.

## PROGESTERONE DURING INFERTILITY TREATMENT

Women going through Assisted Reproductive Technology (ART) procedures, such as IVF, usually need some kind of progesterone supplementation. The medications you may use during these procedures, such as those that aid ovulation, can suppress your body's ability to produce progesterone. Certain procedures can even, inadvertently, remove progesterone-producing cells from the ovaries. Given the essential role of progesterone in achieving and maintaining pregnancy, progesterone supplementation is a common part of infertility treatment regimens.

Sometimes, there are physical considerations, such as little or no progesterone production from the ovaries, or poorly developed follicles that do not secrete enough progesterone to develop the uterine lining. When the ovaries can't function properly, replacement progesterone can help.

Supplemental and replacement progesterone have been proven safe and effective and are widely used. Your doctor can recommend the best treatment options for you.

## THE ROLE OF PROGESTERONE DURING PROCEDURES COMMONLY USED TO TREAT INFERTILITY

### Controlled ovarian stimulation

During this procedure, fertility medications such as clomiphene citrate (an oral medication) or gonadotropins (injectable medications) are used to stimulate the ovaries to produce more than one egg. Clomiphene citrate and medications used along with gonadotropins to help control ovulation can interfere with progesterone production and impact normal endometrial development.

Controlled ovarian stimulation may be performed in conjunction with intrauterine insemination (IUI), where sperm from the partner or a donor is placed directly into the uterus via a small tube. Controlled ovarian stimulation is also performed during many procedures using ART, the most common of which is IVF. During IVF, eggs are removed from the ovary through a hollow needle inserted through the top of the vagina and combined with sperm in a laboratory. Resulting embryos are then returned directly into the uterus via a small tube.

The timing and duration of progesterone administration during controlled ovarian stimulation depends on which fertility drugs are used and whether IUI or IVF is performed.

### Egg donation

Egg donation and IVF may be an option for women with premature ovarian failure, as well as women with intact ovarian function, such as women over 40 years old who have diminished ovarian reserve. Successful egg donation involves using fertility medications to synchronize endometrial development in the recipient with controlled ovarian stimulation in the donor and the resulting embryo transfer.

Progesterone is one of the fertility medications used to align a recipient's cycle with the donor's cycle. Progesterone is also needed for women with ovarian failure because they have insufficient levels of progesterone for normal uterine preparation. Women with functioning ovaries receive certain medications to ensure synchronized endometrial development. Because these medications can temporarily suppress progesterone production, progesterone is also given to women with functioning ovaries.

### Frozen embryo transfer

During a typical IVF cycle, a small number of embryos are transferred into the uterus, which can leave viable embryos unused. The unused embryos can be frozen and transferred in a future cycle. Frozen embryos can also be donated to couples who are unable to produce their own viable embryos.

As with egg donation, fertility medications are used in frozen embryo transfers to help ensure that endometrial development is in alignment with the timing of embryo transfer. Progesterone is used in (1) women with ovarian function undergoing frozen embryo transfer with their own or donated frozen embryos, and (2) in women with ovarian failure who receive donor embryos.

## IS PROGESTERONE SUPPORT NECESSARY DURING PREGNANCY, TOO?

Often, yes. In early pregnancy, progesterone helps maintain a supportive environment for the developing fetus. Eventually, when the placenta is more fully developed, it can produce its own supply of hormones, including progesterone, to support the rest of the pregnancy.

A woman undergoing IVF usually starts progesterone supplementation around the time of egg retrieval or embryo transfer and continues using it well into pregnancy. The dosing schedule for progesterone supplementation varies but, as an example, you might start its use on the evening of or the day following egg retrieval to begin to prepare the uterine lining prior to embryo transfer. You will probably be given supplemental progesterone until the first or second pregnancy test. Then, if you become pregnant, you may keep using progesterone as a supportive measure for up to 12 weeks, depending on your doctor's recommendation.

## HOW DO I KNOW WHICH PROGESTERONE SUPPLEMENT IS RIGHT FOR ME?

Your healthcare team will recommend the best way to manage your progesterone needs, depending on your situation. There are several types of progesterone formulations available, ranging from injections to capsules, suppositories, tablets, or a gel placed directly into the vagina. The information below will help you discuss the different options with your doctor.

## PROGESTERONE SPECIALLY FORMULATED FOR VAGINAL ADMINISTRATION

This method involves placing progesterone (in a gel, tablet, or suppository) into the vagina. It helps minimize the amount of hormone circulating throughout the body which may cause side effects. Compared with other formulations, a vaginal method efficiently sends medication directly to the endometrium and helps avoid unpleasant effects, especially those associated with intramuscular injections. (See *details below*.)

Vaginal progesterone is available in several formulations as described here:

### Vaginal gel

The vaginal gel has been used for over a decade and its efficacy is well established through many clinical trials, with pregnancy rates comparable to other forms of progesterone, including injections. It has a unique delivery system and works by coating the vaginal walls for a slow, steady release of progesterone directly to the endometrium. As a result, it need only be used once a day. In fact, it is the only once-daily progesterone approved by the Food and Drug Administration (FDA) for ART for up to 12 weeks of pregnancy. It is also the only progesterone that the FDA approved for replacement in donor egg recipients and frozen embryo transfers.

Vaginal progesterone gel is available in pre-filled applicators, specially designed with a smooth rounded tip, similar to a tampon, for comfortable application of progesterone into the vagina. While there is little leakage with the gel, it is possible for residue to build up, which can easily be removed in the shower.

The gel formulation has been extensively used as part of ART treatments. When compared with other forms of supplemental progesterone, including other vaginal formulations, the majority of women preferred the gel for comfort and convenience.

### Vaginal suppositories

Pharmacies that specialize in dispensing fertility medications often make vaginal progesterone suppositories. These wax-based suppositories are relatively easy to insert into the vagina and, once in place, the warmth of the body melts the wax and releases the hormone. In a medical study of women undergoing IVF, many users complained of the amount of leakage with progesterone suppositories.

Although vaginal progesterone suppositories are considered safe and effective, the FDA has not approved the use of these suppositories for infertility treatment. Furthermore, the suppositories must be inserted two to three times a day. So, they are not always convenient and may interfere with daily activities.

### Vaginal inserts or tablets

Progesterone is contained in tablets that have been developed for vaginal use. The tablets are effervescent, and they dissolve in vaginal secretions. The tablets come with a disposable applicator to help insert the tablet into the vagina. This method has been approved by the FDA for women needing progesterone supplementation, but not for use in women needing progesterone replacement. Studies have shown efficacy in women under the age of 35; efficacy in women over 35 has not been established. The usual dose requires inserting a tablet two or three times a day, which can be inconvenient for some women.

## PROGESTERONE CAPSULES, USED VAGINALLY

Progesterone capsules, designed to be taken by mouth, can sometimes be prescribed for vaginal use. This helps avoid the unpredictable absorption and the side effects seen with oral administration. The FDA has not approved the use of oral progesterone capsules for vaginal administration, nor for use during infertility treatment. These progesterone capsules were not formulated for vaginal administration, and they must be inserted up to three times a day. This dosing schedule can be inconvenient. It can also be messy since vaginal use can result in a discharge that contains residue from the capsule as it melts.

## PROGESTERONE CAPSULES, TAKEN BY MOUTH

Originally, progesterone capsules for oral administration were developed for gynecological conditions. They have been used during infertility treatment with mixed results and are not often used by fertility specialists. Orally administered progesterone is processed by the liver, which can break down used by the progesterone. Medical studies have shown that successful implantations and pregnancies are less likely to occur in women using oral progesterone, compared with women using intramuscular injections or vaginally administered preparations. This method can also result in side effects such as drowsiness and irritability. However, oral progesterone is convenient and like vaginal forms, avoids daily intramuscular injections.

## PROGESTERONE INJECTIONS OR PROGESTERONE IN OIL (PIO)

Progesterone in an oil-based solution is injected directly into a muscle, usually in the buttocks, once a day. Unlike the small thin needles used for medications that stimulate ovulation, progesterone injections require a longer, thicker needle to help penetrate the layers of skin and fat to the muscle.

The use of PIO is the oldest method for progesterone delivery during infertility treatment. The efficacy of this approach is well established, and health care providers have considerable experience using this formulation.

However, you, like many women, may find there are significant downsides to the injections, besides the thick needles. For instance:

- It is common to get skin reactions, such as soreness and inflammation, at the injection site. You may find it uncomfortable to sit down.
- The injection area is small and difficult to reach, and you will probably need someone to help give the injections. This can be inconvenient and may interfere with daily schedules for both of you.
- The injection does not directly target the area where the progesterone is needed. Instead, progesterone is absorbed by other parts of the body, including the brain, and may cause some unwanted side effects, such as sleepiness and mood swings.

If your doctor suggests intramuscular progesterone in oil, you may want to ask if there are other formulations that might be more suitable instead. Remember, you may need to have a long-term daily injection for pregnancy support.

## WHICH PROGESTERONE IS RIGHT FOR YOU?

Progesterone is an important part of infertility treatment because it supports implantation and pregnancy. Your healthcare provider may prescribe progesterone to ensure that you have the best chance of becoming pregnant. Your healthcare provider may also have you continue with progesterone during the first trimester until the placenta starts producing enough progesterone to support the pregnancy.

Healthcare providers often have a preference for which form of progesterone they prescribe for infertility treatment. Their preference is generally based on their experience with the various methods. But patient convenience and request are also important considerations. Be sure to discuss the various delivery methods, including any preference or concerns you may have regarding a particular option, with your healthcare provider.