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Patient information: In vitro fertilization (IVF) (Beyond the Basics)

IN VITRO FERTILIZATION OVERVIEW

In vitro fertilization (IVF) is a treatment for infertility in which a woman's eggs (oocytes) are fertilized by sperm in a laboratory dish. One or more of the fertilized eggs (embryos) are then transferred into the woman's uterus, where it is hoped they will implant and produce a pregnancy.

This topic will discuss the reasons IVF might be recommended, the medications used to prepare for IVF, and the outcomes of treatment. Other topics that discuss infertility are available separately:

- Diagnosis and evaluation of infertility (see "Patient information: Evaluation of the infertile couple (Beyond the Basics)")
- Treatment of infertility (see "Patient information: Treatment of male infertility (Beyond the Basics)" and "Patient information: Ovulation induction with clomiphene (Beyond the Basics)" and "Patient information: Infertility treatment with gonadotropins (Beyond the Basics)").

WHO SHOULD CONSIDER IN VITRO FERTILIZATION?

IVF is usually considered by couples who have:

- Absent or blocked fallopian tubes
- Severe male factor infertility (sperm counts or sperm motility is low)
- Advanced reproductive age, as time to conception is critical and pregnancy rates with other therapies are low
- All other causes of infertility, after failing treatment with other therapies (eg, endometriosis, ovulation disorders, unexplained infertility)
- Ovarian failure, although donor eggs would be required in this case

Although IVF has a high rate of success in helping couples to become pregnant, it has some disadvantages as well, including high costs, potential risks from fertility medications and invasive procedures used, as well as an increased rate of multiple gestation (ie, twins or triplets). There may also be an increased risk of some pregnancy complications, such as preterm birth. Ectopic pregnancies can occur after IVF, although the risk is much lower than with other fertility therapies.

Women who are considering IVF should discuss the risks, benefits, and alternatives with their healthcare provider and partner before treatment begins. In most cases, several cycles of a less expensive and less invasive infertility treatment are recommended before considering IVF.

IN VITRO FERTILIZATION PROCEDURE

The IVF procedure consists of several steps that take place over a period of weeks:

- Education of the couple about the complex steps involved in IVF, its risks and benefits, and techniques for giving injections at home.
- Stimulation of the ovaries to produce several eggs
- Retrieval of the eggs from the ovaries and obtaining a semen sample
- Fertilization of the eggs with sperm and growth of the embryos in the laboratory
- Transfer of one or more embryos into the uterus

More than one cycle of IVF treatment is often necessary before pregnancy occurs. Unfortunately, some women will not become pregnant despite multiple IVF attempts.

Ovarian stimulation — The first step of the IVF procedure involves the use of fertility medications to increase the number of eggs (follicles) that develop in the ovaries and control the time of ovulation [1]. The stimulation regimen is selected based upon the woman's diagnosis and the physician's preferences. It is possible to perform IVF without ovarian stimulation. This is known as “natural cycle IVF” or “unstimulated IVF;” usually only one egg is retrieved. However, the vast majority of IVF cycles worldwide are performed with some type of ovarian stimulation.

The ovarian stimulation regimen described below is an example and may differ from that recommended by your doctor.

- Many clinicians will prescribe a birth control pill for the woman to take for one or more weeks before beginning IVF. The pill helps to prevent the woman's body from releasing hormones that could stimulate natural ovulation.
- The woman will start giving herself injections of a medication (a GnRH agonist) that helps to prevent the body from releasing hormones that could stimulate ovulation or allow premature ovulation. This medication is called leuprolide acetate or Lupron, and is started approximately one week after starting the birth control pill. The injection can be given under the skin in most cases and is not painful.
- Most programs ask that you call on the first or second day of menstrual bleeding to schedule an appointment for blood tests and an ultrasound. The first day of menstrual bleeding is considered day one of the cycle.
- On day three to five, you may be asked to have a pelvic ultrasound to evaluate your ovaries and blood testing to measure hormone levels. If these tests are OK, you will be given a date to start giving yourself injections with FSH to stimulate the growth of egg follicles.

  In most cases, you will give yourself an injection of FSH once per day, generally in the evening. The injection can usually be given under the skin, rather than deep into the muscle.

- After a few days of injections, you will be asked to have a pelvic ultrasound to measure follicle growth, and a blood test to measure hormone levels. Depending upon the results of these tests,

the dose of FSH may be increased or decreased. Blood testing and pelvic ultrasound may be repeated several times during a cycle.

- In some cases, a class of medication called a GnRH antagonist (abarelix/Plenaxis, cetrorelix/Cetrotide, or ganirelix/Antagon) will be recommended instead of the GnRH agonist. In this case, stimulation with FSH is started immediately after stopping the birth control pill and the antagonist is added once the follicles have reached a certain size (often around 14 mm). This medication helps to prevent premature ovulation [2].
- The goal of stimulation is to have at least two follicles that are approximately 15 to 18 mm in size. The number of follicles that develops depends on the ovaries and hormone levels of the individual patient. In most cases, more than 2 follicles develop; in some cases, more than 20 may develop. When blood testing and ultrasound measurements show that the follicles are "ready", you will be instructed to give an injection of hCG to trigger ovulation. hCG stands for human chorionic gonadotropin, with brand names including Ovidrel, Pregnyl, and Novarel. hCG is usually injected under the skin at a particular time in the evening. This allows the follicles to be ready for egg retrieval during a window of time, approximately 36 hours later.

Side effects of treatment — FSH injections do not cause side effects directly. However, the ovaries become enlarged during treatment, which can cause abdominal swelling and discomfort, and in more severe cases, nausea or even vomiting.

Ovarian hyperstimulation syndrome (OHSS) is a condition in which the side effects of ovarian enlargement and abdominal swelling become extreme. The woman may develop severe abdominal pain, vomiting, and if untreated, blood clots in the legs or lungs and fluid imbalances in the blood. Mild forms of OHSS occur in 2 to 6 percent of women undergoing ovulation induction for IVF. Severe cases of OHSS occur in approximately 1 percent of cases, typically in association with the retrieval of more than 20 eggs.

The risk of OHSS can be reduced by canceling the IVF cycle when blood estrogen levels become too high or there are too many follicles seen on ultrasound. The IVF cycle may be cancelled before hCG is given or after the oocyte retrieval. If the cycle is cancelled after oocytes are retrieved, they are often fertilized and cryopreserved for use in a subsequent cycle. Because symptoms of OHSS peak approximately three to five days after egg retrieval, the decision to freeze all embryos may be delayed until this time. (See 'Storing unused embryos' below.)

Egg retrieval — Approximately 32 to 36 hours after injecting hCG, a procedure is performed to retrieve the eggs. The physician inserts an ultrasound probe into the vagina and then uses a needle to withdraw the egg from each follicle. The procedure takes approximately 15 to 30 minutes, depending upon how many follicles are present. This is generally done while the woman is sedated.

Serious complications of oocyte retrieval are uncommon, but side effects such as pelvic cramping, light bleeding, and vaginal discharge often occur. If these problems are persistent or become severe, it is important to call a healthcare provider as soon as possible. Abdominal swelling and discomfort may also be signs of early ovarian hyperstimulation syndrome (OHSS), so close contact with the healthcare provider(s) is a good idea.

Postprocedure care — After the retrieval, the patient will be monitored in a recovery area for a few hours and then allowed to go home. Due to the effects of the anesthesia, the patient should not drive or return to work for approximately 24 hours.

Fertilization — After the retrieval procedure, the eggs are combined with sperm in a laboratory dish so they will fertilize. In general, approximately 50 percent of oocytes become fertilized.

In cases of severe male factor infertility, fertilization is achieved by intracytoplasmic sperm injection (ICSI). ICSI is an option for all men with severe male factor infertility, regardless of their sperm count. Only mature oocytes can be injected. Fertilization rates with ICSI range from 50 to 70 percent [3].

Embryo transfer — Approximately two to five days after the retrieval, one or more eggs that have been fertilized (embryos) are placed in the woman's uterus using a thin, flexible catheter inserted through the cervix. Most commonly, embryo transfer is performed on day 3 after egg retrieval. The catheter is inserted as gently as possible to minimize uterine cramping; traumatic transfer procedures are associated with lower success rates. Anesthesia is not usually needed for this procedure.

Following the transfer procedure, the woman is generally encouraged to rest at home for several hours. Although studies do not show that rest increases the chance of pregnancy, many women prefer not to resume their normal activities immediately.

Most clinicians will prescribe a progesterone medication to improve the chances that the embryo will implant inside the uterus. This medication is started either on the day of retrieval or the day of transfer. There are several ways to administer progesterone, with the most common being a vaginal gel or suppository, or an injection given into a muscle.

How many embryos to transfer? — The number of embryos transferred depends upon the woman or couple's preferences, the previous history of pregnancy and miscarriage, the woman's age, and the quality of the embryos. Younger women (under age 35) in their first cycle of IVF are often encouraged to have only one or two embryos transferred. If multiple attempts of IVF are not successful in achieving pregnancy, a physician may recommend transferring more than one or two embryos to increase the chances of pregnancy. However, this may also increase the risk of multiple gestation (twins, triplets).

The rate of implantation is lower among women over age 40 years; as a result, more embryos (eg, up to five) are often transferred in these women. However, older women who are receiving eggs from younger donors (eg, donor eggs) have a rate of implantation similar to that of younger women, and are generally advised to transfer no more than one or two embryos (table 1).

Storing unused embryos — Embryos that are not transferred may be stored by freezing them (called cryopreservation). Because some embryos do not survive the thawing process, the chances of a successful pregnancy using frozen embryos is usually lower than that when using fresh embryos.

The embryos may be cryopreserved for an unlimited period of time. However, most couples are encouraged to choose one of the following options [4]:

- Transfer the embryos at a later date
- Donate them for research or for use by another couple
- Dispose of the embryos

TESTING FOR PREGNANCY AFTER IN VITRO FERTILIZATION

Blood testing — Approximately two weeks after the embryo transfer, a blood or urine test for hCG, the hormone that signifies pregnancy, can be done. Home urine pregnancy testing is not as sensitive for detecting an early pregnancy as blood testing.

- If the first blood hCG level is <5 IU/L, the woman is not pregnant.
- If the first hCG level is >10 IU/L, the test is usually repeated 48 hours later to confirm that the levels are increasing. The hCG level should approximately double every 48 hours during the first 21 days after embryo transfer.
- If the second hCG level does not double or decreases, the blood test may be repeated again 48 hours later. Depending upon the situation, there is a possibility that the pregnancy is not viable. hCG levels do not increase or begin to decline when the pregnancy is not progressing normally. (See 'When in vitro fertilization is not successful' below.)

Ultrasound — If the hCG levels increase as expected, a pelvic ultrasound may be done three to four weeks after the transfer. At this time, it is usually possible to see a gestational sac inside the uterus. The gestational sac is a fluid-filled sac containing the embryo (image 1).

At five to six weeks of pregnancy (four to five weeks after the transfer), the yolk sac is usually visible. The yolk sac provides nourishment to the embryo early in development. A heart beat is usually visible by 6 to 6.5 weeks of pregnancy (4 to 4.5 weeks after the transfer).

Pregnancy care — In most cases, prenatal care begins at 6 to 10 weeks of pregnancy. At this time, the woman will begin to see her obstetrical physician or nurse on a regular basis. These visits allow the obstetrical provider to monitor the woman and baby's health and to answer any questions.

WHEN IN VITRO FERTILIZATION IS NOT SUCCESSFUL

In vitro fertilization has a reasonable rate of success in most cases. Overall, approximately 27 percent of IVF cycles will end in a live birth, and the cumulative chances of success are higher when more than one cycle of IVF is done [5].

However, an individual's chance of success depends on several factors, including the woman's age, cause of infertility, and treatment approach. For example, in the United States, the live birth rate for each IVF cycle started is approximately 30 to 35 percent for women under age 35; 25 percent for women ages 35 to 37; 15 to 20 percent for women ages 38 to 40; and 6 to 10 percent for women over 40. The success rates of individual infertility clinics in the United States is published on the internet at the Society for Assisted Reproductive Technology (www.sart.org/).

It can be difficult to deal with the emotional highs and lows of infertility treatment. This is especially true if the woman (and her partner) have been trying to conceive for a long time, if treatment is not covered by insurance, or if there are any underlying problems in the couple's life (eg, medical, family or partner, job, financial).

Support groups and counseling services are available at many infertility treatment centers, as well as on the internet. (See 'Where to get more information' below.) To find a reputable group, talk to your healthcare provider.

COSTS OF IN VITRO FERTILIZATION TREATMENT

The costs of IVF treatments can be high, depending upon what tests are required, the type and dose of medication(s) used, and the number of cycles required to become pregnant. The average cost of an IVF cycle in the United States is more than $10,000. Insurance policies cover the costs of infertility treatment in some states, although this varies by location and individual insurance policy. Less than half of the states within the US have laws requiring insurers to cover infertility treatment.

More information about a state's laws can be obtained by calling your state Insurance Commissioner's office. Information can also be found by visiting the website for the American Society of Reproductive Medicine (http://www.asrm.org/insurance.aspx).

WHERE TO GET MORE INFORMATION

Your healthcare provider is the best source of information for questions and concerns related to your medical problem.

This article will be updated as needed on our web site (www.uptodate.com/patients). Related topics for patients, as well as selected articles written for healthcare professionals, are also available. Some of the most relevant are listed below.

Patient level information — UpToDate offers two types of patient education materials.

The Basics — The Basics patient education pieces answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials.

Patient information: Infertility in women (The Basics)
Patient information: Infertility in men (The Basics)
Patient information: Infertility in couples (The Basics)
Patient information: Endometriosis (The Basics)
Patient information: Ectopic pregnancy (The Basics)
Patient information: Turner syndrome (The Basics)

Beyond the Basics — Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are best for patients who want in-depth information and are comfortable with some medical jargon.

Patient information: Evaluation of the infertile couple (Beyond the Basics)
Patient information: Treatment of male infertility (Beyond the Basics)
Patient information: Ovulation induction with clomiphene (Beyond the Basics)
Patient information: Infertility treatment with gonadotropins (Beyond the Basics)

Professional level information — Professional level articles are designed to keep doctors and other health professionals up-to-date on the latest medical findings. These articles are thorough, long, and complex, and they contain multiple references to the research on which they are based. Professional level articles are best for people who are comfortable with a lot of medical terminology and who want to read the same materials their doctors are reading.

Effect of advanced age on fertility and pregnancy in women
Epidemiology, clinical manifestations, diagnosis, and natural history of uterine leiomyomas

(fibroids)
Evaluation of male infertility
Surrogate pregnancy
In vitro fertilization
Intracytoplasmic sperm injection
Oocyte donation for assisted reproduction
Overview of treatment of female infertility
Pathogenesis and treatment of infertility in women with endometriosis
Pregnancy outcome after assisted reproductive technology
Preimplantation genetic diagnosis
Psychological stress and infertility
Reproductive issues in women with uterine leiomyomas (fibroids)
Strategies to control the rate of high order multiple gestation
Techniques for preimplantation sex selection
Treatment of male infertility
Use of assisted reproduction in HIV and hepatitis infected couples

The following organizations also provide reliable health information.

- National Library of Medicine

(www.nlm.nih.gov/medlineplus/healthtopics.html)

- American Society for Reproductive Medicine

(www.asrm.org)

- Resolve: The National Infertility Association

(www.resolve.org)

- The International Council on Infertility Information Dissemination

(www.inciid.com)

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References

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