IJMPR 2021, 5(2), 105-110

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

INVITRO FERTILIZATION – ITS ROLE, IMPORTANCE AND RISK FACTORS

S. Sangeetha*

Lecturer, Department of Anatomy, Saveetha Dental College, Saveetha Institute of Medical sciences And Technology (SIMATS) Saveetha University, Chennai-600077.

Received on: 25/02/2021
Revised on: 15/03/2021
Accepted on: 05/04/2021

***Corresponding Author**
S. Sangeetha
Lecturer, Department of Anatomy, Saveetha Dental College, Saveetha Institute of Medical sciences And Technology (SIMATS) Saveetha University, Chennai-600077.

ABSTRACT

In vitro fertilisation (IVF) is a process of fertilisation where an egg is combined with sperm outside the body, in vitro ("in glass"). The process involves monitoring and stimulating a woman's ovulatory process, removing an ovum or ova (egg or eggs) from the woman's ovaries and letting sperm fertilise them in a liquid in a laboratory. After the fertilised egg (zygote) undergoes embryo culture for 2–6 days, it is implanted in the same or another woman's uterus, with the intention of establishing a successful pregnancy. IVF is a type of assisted reproductive technology used for infertility treatment and gestational surrogacy. A fertilised egg may be implanted into a surrogate's uterus, and the resulting child is genetically unrelated to the surrogate. Some countries have banned or otherwise regulate the availability of IVF treatment, giving rise to fertility tourism. Restrictions on the availability of IVF include costs and age, in order for a woman to carry a healthy pregnancy to term. IVF is generally not used until less invasive or expensive options have failed or been determined unlikely to work. This paper reviews the role, importance and complications of invitro fertilization.

KEYWORDS: Invitro, fertilization, embryo, culture, ovum, treatment.

INTRODUCTION

In vitro fertilization (IVF) is a complex series of procedures used to help with fertility or prevent genetic problems and assist with the conception of a child. During IVF, mature eggs are collected (retrieved) from ovaries and fertilized by sperm in a lab. Then the fertilized egg (embryo) or eggs (embryos) are transferred to a uterus. One full cycle of IVF takes about three weeks. Sometimes these steps are split into different parts and the process can take longer. IVF is the most effective form of assisted reproductive technology. The procedure can be done using your own eggs and your partner's sperm. Or IVF may involve eggs, sperm or embryos from a known or anonymous donor. In some cases, a gestational carrier — a woman who has an embryo implanted in her uterus — might be used.

Role of IVF

In vitro fertilization (IVF) is a treatment for infertility or genetic problems. If IVF is performed to treat infertility, you and your partner might be able to try less-invasive treatment options before attempting IVF, including fertility drugs to increase production of eggs or intrauterine insemination — a procedure in which sperm are placed directly in your uterus near the time of ovulation.

Sometimes, IVF is offered as a primary treatment for infertility in women over age 40. IVF can also be done if you have certain health conditions. For example, IVF may be an option if you or your partner has:

- **Fallopian tube damage or blockage.** Fallopian tube damage or blockage makes it difficult for an egg to be fertilized or for an embryo to travel to the uterus.
- **Ovulation disorders.** If ovulation is infrequent or absent, fewer eggs are available for fertilization.
- **Endometriosis.** Endometriosis occurs when the uterine tissue implants and grows outside of the uterus — often affecting the function of the ovaries, uterus and fallopian tubes.
- **Uterine fibroids.** Fibroids are benign tumors in the wall of the uterus and are common in women in their 30s and 40s. Fibroids can interfere with implantation of the fertilized egg.
- **Previous tubal sterilization or removal.** If you've had tubal ligation — a type of sterilization in which your fallopian tubes are cut or blocked to permanently prevent pregnancy — and want to conceive, IVF may be an alternative to tubal ligation reversal.
- **Impaired sperm production or function.** Below-average sperm concentration, weak movement of sperm (poor mobility), or abnormalities in sperm size and shape can make it difficult for sperm to fertilize an egg. If semen abnormalities are found, your partner might need to see a specialist to

determine if there are correctable problems or underlying health concerns.

- **Unexplained infertility.** Unexplained infertility means no cause of infertility has been found despite evaluation for common causes.
- **A genetic disorder.** If you or your partner is at risk of passing on a genetic disorder to your child, you may be candidates for preimplantation genetic testing — a procedure that involves IVF. After the eggs are harvested and fertilized, they're screened for certain genetic problems, although not all genetic problems can be found. Embryos that don't contain identified problems can be transferred to the uterus.
- **Fertility preservation for cancer or other health conditions.** If you're about to start cancer treatment — such as radiation or chemotherapy — that could harm your fertility, IVF for fertility preservation may be an option. Women can have eggs harvested from their ovaries and frozen in an unfertilized state for later use. Or the eggs can be fertilized and frozen as embryos for future use.

Women who don't have a functional uterus or for whom pregnancy poses a serious health risk might choose IVF using another person to carry the pregnancy (gestational carrier). In this case, the woman's eggs are fertilized with sperm, but the resulting embryos are placed in the gestational carrier's uterus.

Risks of IVF

- **Multiple births.** IVF increases the risk of multiple births if more than one embryo is transferred to your uterus. A pregnancy with multiple fetuses carries a higher risk of early labor and low birth weight than pregnancy with a single fetus does.
- **Premature delivery and low birth weight.** Research suggests that IVF slightly increases the risk that the baby will be born early or with a low birth weight.
- **Ovarian hyperstimulation syndrome.** Use of injectable fertility drugs, such as human chorionic gonadotropin (HCG), to induce ovulation can cause ovarian hyperstimulation syndrome, in which your ovaries become swollen and painful.

Symptoms typically last a week and include mild abdominal pain, bloating, nausea, vomiting and diarrhea. If you become pregnant, however, your symptoms might last several weeks. Rarely, it's possible to develop a more severe form of ovarian hyperstimulation syndrome that can also cause rapid weight gain and shortness of breath.

- **Miscarriage.** The rate of miscarriage for women who conceive using IVF with fresh embryos is similar to that of women who conceive naturally — about 15% to 25% — but the rate increases with maternal age.
- **Egg-retrieval procedure complications.** Use of an aspirating needle to collect eggs could possibly cause bleeding, infection or damage to the bowel, bladder or a blood vessel. Risks are also associated with sedation and general anesthesia, if used.
- **Ectopic pregnancy.** About 2% to 5% of women who use IVF will have an ectopic pregnancy — when the fertilized egg implants outside the uterus, usually in a fallopian tube. The fertilized egg can't survive outside the uterus, and there's no way to continue the pregnancy.
- **Birth defects.** The age of the mother is the primary risk factor in the development of birth defects, no matter how the child is conceived. More research is needed to determine whether babies conceived using IVF might be at increased risk of certain birth defects.
- **Cancer.** Although some early studies suggested there may be a link between certain medications used to stimulate egg growth and the development of a specific type of ovarian tumor, more-recent studies do not support these findings. There does not appear to be a significantly increased risk of breast, endometrial, cervical or ovarian cancer after IVF.
- **Stress.** Use of IVF can be financially, physically and emotionally draining. Support from counselors, family and friends can help you and your partner through the ups and downs of infertility treatment.

Preparation

Before beginning a cycle of IVF using your own eggs and sperm, you and your partner will likely need various screenings, including:

- **Ovarian reserve testing.** To determine the quantity and quality of your eggs, your doctor might test the concentration of follicle-stimulating hormone (FSH), estradiol (estrogen) and anti-mullerian hormone in your blood during the first few days of your menstrual cycle. Test results, often used together with an ultrasound of your ovaries, can help predict how your ovaries will respond to fertility medication.
- **Semen analysis.** If not done as part of your initial fertility evaluation, your doctor will conduct a semen analysis shortly before the start of an IVF treatment cycle.
- **Infectious disease screening.** You and your partner will both be screened for infectious diseases, including HIV.
- **Practice (mock) embryo transfer.** Your doctor might conduct a mock embryo transfer to determine the depth of your uterine cavity and the technique most likely to successfully place the embryos into your uterus.
- **Uterine exam.** Your doctor will examine the inside lining of the uterus before you start IVF. This might involve a sonohysterography — in which fluid is injected through the cervix into your uterus — and an ultrasound to create images of your uterine cavity. Or it might include a hysteroscopy — in which a thin, flexible, lighted telescope (hysteroscope) is inserted through your vagina and cervix into your uterus.

Steps In IVF

IVF involves several steps — ovarian stimulation, egg retrieval, sperm retrieval, fertilization and embryo transfer. One cycle of IVF can take about two to three weeks, and more than one cycle may be required.

Ovulation induction[5]

If you're using your own eggs during IVF, at the start of a cycle you'll begin treatment with synthetic hormones to stimulate your ovaries to produce multiple eggs — rather than the single egg that normally develops each month. Multiple eggs are needed because some eggs won't fertilize or develop normally after fertilization.

You may need several different medications, such as:

- **Medications for ovarian stimulation.** To stimulate your ovaries, you might receive an injectable medication containing a follicle-stimulating hormone (FSH), a luteinizing hormone (LH) or a combination of both. These medications stimulate more than one egg to develop at a time.
- **Medications for oocyte maturation.** When the follicles are ready for egg retrieval — generally after eight to 14 days — you will take human chorionic gonadotropin (HCG) or other medications to help the eggs mature.
- **Medications to prevent premature ovulation.** These medications prevent your body from releasing the developing eggs too soon.
- **Medications to prepare the lining of your uterus.** On the day of egg retrieval or at the time of embryo transfer, your doctor might recommend that you begin taking progesterone supplements to make the lining of your uterus more receptive to implantation.

To determine when the eggs are ready for collection the following will be performed

- **Vaginal ultrasound,** an imaging exam of your ovaries to monitor the development of follicles — fluid-filled ovarian sacs where eggs mature
- **Blood tests,** to measure your response to ovarian stimulation medications — estrogen levels typically increase as follicles develop, and progesterone levels remain low until after ovulation

Sometimes IVF cycles need to be canceled before egg retrieval for one of these reasons:

- Inadequate number of follicles developing
- Premature ovulation
- Too many follicles developing, creating a risk of ovarian hyperstimulation syndrome
- Other medical issues

Egg retrieval[6]

Egg retrieval can be done in your doctor's office or a clinic 34 to 36 hours after the final injection and before ovulation.

- During egg retrieval, you'll be sedated and given pain medication.
- Transvaginal ultrasound aspiration is the usual retrieval method. An ultrasound probe is inserted into your vagina to identify follicles. Then a thin needle is inserted into an ultrasound guide to go through the vagina and into the follicles to retrieve the eggs.
- If your ovaries aren't accessible through transvaginal ultrasound, an abdominal ultrasound may be used to guide the needle.
- The eggs are removed from the follicles through a needle connected to a suction device. Multiple eggs can be removed in about 20 minutes.
- After egg retrieval, you may experience cramping and feelings of fullness or pressure.
- Mature eggs are placed in a nutritive liquid (culture medium) and incubated. Eggs that appear healthy and mature will be mixed with sperm to attempt to create embryos. However, not all eggs may be successfully fertilized.

Sperm retrieval[7]

If you're using your partner's sperm, he'll provide a semen sample at your doctor's office or a clinic through masturbation the morning of egg retrieval. Other methods, such as testicular aspiration — the use of a needle or surgical procedure to extract sperm directly from the testicle — are sometimes required. Donor sperm also can be used. Sperm are separated from the semen fluid in the lab.

Fertilization

Fertilization can be attempted using two common methods:

- **Conventional insemination.** During conventional insemination, healthy sperm and mature eggs are mixed and incubated overnight.
- **Intracytoplasmic sperm injection (ICSI).** In ICSI, a single healthy sperm is injected directly into each mature egg. ICSI is often used when semen quality or number is a problem or if fertilization attempts during prior IVF cycles failed.

In certain situations, your doctor may recommend other procedures before embryo transfer.

- **Assisted hatching.** About five to six days after fertilization, an embryo "hatches" from its surrounding membrane (zona pellucida), allowing it to implant into the lining of the uterus. If you're an older woman, or if you have had multiple failed IVF attempts, your doctor might recommend assisted hatching — a technique in which a hole is made in the zona pellucida just before transfer to help the embryo hatch and implant. Assisted hatching is also useful for eggs or embryos that have been previously frozen as the process can harden the zona pellucida.
- **Preimplantation genetic testing.** Embryos are allowed to develop in the incubator until they reach a stage where a small sample can be removed and tested for specific genetic diseases or the correct

number of chromosomes, typically after five to six days of development. Embryos that don't contain affected genes or chromosomes can be transferred to your uterus. While preimplantation genetic testing can reduce the likelihood that a parent will pass on a genetic problem, it can't eliminate the risk. Prenatal testing may still be recommended

Embryo transfer

Embryo transfer is done at your doctor's office or a clinic and usually takes place two to five days after egg retrieval.

- You might be given a mild sedative. The procedure is usually painless, although you might experience mild cramping.
- The doctor will insert a long, thin, flexible tube called a catheter into your vagina, through your cervix and into your uterus.
- A syringe containing one or more embryos suspended in a small amount of fluid is attached to the end of the catheter.
- Using the syringe, the doctor places the embryo or embryos into your uterus.
- If successful, an embryo will implant in the lining of your uterus about six to 10 days after egg retrieval.

After the procedure

After the embryo transfer, you can resume normal daily activities. However, your ovaries may still be enlarged. Consider avoiding vigorous activity, which could cause discomfort.

Typical side effects include

- Passing a small amount of clear or bloody fluid shortly after the procedure — due to the swabbing of the cervix before the embryo transfer
- Breast tenderness due to high estrogen levels
- Mild bloating
- Mild cramping
- Constipation

The chances of giving birth to a healthy baby after using IVF depend on various factors, including:

- **Maternal age.** The younger you are, the more likely you are to get pregnant and give birth to a healthy baby using your own eggs during IVF. Women age 41 and older are often counseled to consider using donor eggs during IVF to increase the chances of success.[1]
- **Embryo status.** Transfer of embryos that are more developed is associated with higher pregnancy rates compared with less-developed embryos (day two or three). However, not all embryos survive the development process. Talk with your doctor or other care provider about your specific situation.
- **Reproductive history.** Women who've previously given birth are more likely to be able to get pregnant using IVF than are women who've never given birth. Success rates are lower for women who've previously used IVF multiple times but didn't get pregnant.
- **Cause of infertility.** Having a normal supply of eggs increases your chances of being able to get pregnant using IVF. Women who have severe endometriosis are less likely to be able to get pregnant using IVF than are women who have unexplained infertility.
- **Lifestyle factors.** Women who smoke typically have fewer eggs retrieved during IVF and may miscarry more often. Smoking can lower a woman's chance of success using IVF by 50%. Obesity can decrease your chances of getting pregnant and having a baby. Use of alcohol, recreational drugs, excessive caffeine and certain medications also can be harmful.

Embryo Culture

The main durations of embryo culture are until cleavage stage (day two to four after co-incubation) or the blastocyst stage (day five or six after co-incubation).[13] Embryo culture until the blastocyst stage confers a significant increase in live birth rate per embryo transfer, but also confers a decreased number of embryos available for transfer and embryo cryopreservation, so the cumulative clinical pregnancy rates are increased with cleavage stage transfer. Transfer day two instead of day three after fertilisation has no differences in live birth rate. There are significantly higher odds of preterm birth (odds ratio 1.3) and congenital anomalies (odds ratio 1.3) among births having from embryos cultured until the blastocyst stage compared with cleavage stage.[13]

Embryo Selection

Laboratories have developed grading methods to judge oocyte and embryo quality. In order to optimise pregnancy rates, there is significant evidence that a morphological scoring system is the best strategy for the selection of embryos.[2] Since 2009 where the first time-lapse microscopy system for IVF was approved for clinical use,[3] morphokinetic scoring systems has shown to improve to pregnancy rates further.[4] However, when all different types of time-lapse embryo imaging devices, with or without morphokinetic scoring systems, are compared against conventional embryo assessment for IVF, there is insufficient evidence of a difference in live-birth, pregnancy, stillbirth or miscarriage to choose between them.[5] Active efforts to develop a more accurate embryo selection analysis based on Artificial Intelligence and Deep Learning are underway. Embryo Ranking Intelligent Classification Assistant (ERICA)[6] is a clear example. This Deep Learning software substitutes manual classifications with a ranking system based on an individual embryo's predicted genetic status in a non-invasive fashion.[7] Studies on this area are still pending and current feasibility studies support its potential.[8]

Embryo Transfer

The number to be transferred depends on the number available, the age of the woman and other health and diagnostic factors. In countries such as Canada, the UK, Australia and New Zealand, a maximum of two embryos are transferred except in unusual circumstances. In the UK and according to HFEA regulations, a woman over 40 may have up to three embryos transferred, whereas in the US, there is no legal limit on the number of embryos which may be transferred, although medical associations have provided practice guidelines. Most clinics and country regulatory bodies seek to minimise the risk of multiple pregnancy, as it is not uncommon for multiple embryos to implant if multiple embryos are transferred. Embryos are transferred to the patient's uterus through a thin, plastic catheter, which goes through her vagina and cervix. Several embryos may be passed into the uterus to improve chances of implantation and pregnancy.[9]

Expansions

Cryopreservation

Cryopreservation can be performed as oocyte cryopreservation before fertilisation, or as embryo cryopreservation after fertilisation.

The Rand Consulting Group has estimated there to be 400,000 frozen embryos in the United States in 2006.[10] The advantage is that patients who fail to conceive may become pregnant using such embryos without having to go through a full IVF cycle. Or, if pregnancy occurred, they could return later for another pregnancy. Spare oocytes or embryos resulting from fertility treatments may be used for oocyte donation or embryo donation to another woman or couple, and embryos may be created, frozen and stored specifically for transfer and donation by using donor eggs and sperm. Also, oocyte cryopreservation can be used for women who are likely to lose their ovarian reserve due to undergoing chemotherapy.[11]

By 2017, many centers have adopted embryo cryopreservation as their primary IVF therapy, and perform few or no fresh embryo transfers. The two main reasons for this have been better endometrial receptivity when embryos are transferred in cycles without exposure to ovarian stimulation and also the ability to store the embryos while awaiting the results of pre-implantation genetic testing.

The outcome from using cryopreserved embryos has uniformly been positive with no increase in birth defects or development abnormalities.[12]

Other Expansions

- Intracytoplasmic sperm injection (ICSI) is where a single sperm is injected directly into an egg. Its main usage as an expansion of IVF is to overcome male infertility problems, although it may also be used where eggs cannot easily be penetrated by sperm, and occasionally in conjunction with sperm donation. It can be used in teratozoospermia, since once the egg is fertilised abnormal sperm morphology does not appear to influence blastocyst development or blastocyst morphology.[14]
- Additional methods of embryo profiling. For example, methods are emerging in making comprehensive analyses of up to entire genomes, transcriptomes, proteomes and metabolomes which may be used to score embryos by comparing the patterns with ones that have previously been found among embryos in successful versus unsuccessful pregnancies.[15]
- Assisted zona hatching (AZH) can be performed shortly before the embryo is transferred to the uterus. A small opening is made in the outer layer surrounding the egg in order to help the embryo hatch out and aid in the implantation process of the growing embryo.
- In egg donation and embryo donation, the resultant embryo after fertilisation is inserted in another woman than the one providing the eggs. These are resources for women with no eggs due to surgery, chemotherapy, or genetic causes; or with poor egg quality, previously unsuccessful IVF cycles or advanced maternal age. In the egg donor process, eggs are retrieved from a donor's ovaries, fertilised in the laboratory with the sperm from the recipient's partner, and the resulting healthy embryos are returned to the recipient's uterus.
- In oocyte selection, the oocytes with optimal chances of live birth can be chosen. It can also be used as a means of preimplantation genetic screening.
- Embryo splitting can be used for twinning to increase the number of available embryos.[16]
- Cytoplasmic transfer is where the cytoplasm from a donor egg is injected into an egg with compromised mitochondria. The resulting egg is then fertilised with sperm and implanted in a womb, usually that of the woman who provided the recipient egg and nuclear DNA. Cytoplasmic transfer was created to aid women who experience infertility due to deficient or damaged mitochondria, contained within an egg's cytoplasm.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest

REFERENCE

1. "In vitro fertilization (IVF) Results – Mayo Clinic". www.mayoclinic.org. Retrieved, 5 November, 2015.
2. Rebmann V, Switala M, Eue I, Grosse-Wilde H (July). "Soluble HLA-G is an independent factor for the prediction of pregnancy outcome after ART: a German multi-centre study". Human Reproduction, 2010; 25(7): 1691–8. doi:10.1093/humrep/deq120. PMID 20488801.

3. "Unisense FertiliTech A/S Receives CE Mark of Approval for EmbryoScope(TM) Embryo Monitoring System".
4. Meseguer M, Rubio I, Cruz M, Basile N, Marcos J, Requena A (December). "Embryo incubation and selection in a time-lapse monitoring system improves pregnancy outcome compared with a standard incubator: a retrospective cohort study". Fertility and Sterility, 2012; 98(6): 1481–9. e10. doi:10.1016/j.fertnstert. 2012.08.016. PMID 22975113.
5. Armstrong, S; Bhide, P; Jordan, V; Pacey, A; Marjoribanks, J; Farquhar, C (29 May). "Time-lapse systems for embryo incubation and assessment in assisted reproduction". The Cochrane Database of Systematic Reviews, 2019; 5: CD011320. doi:10.1002/14651858.CD011320.pub4. PMC 6539 473. PMID 31140578.
6. "ERICA Embryo Ranking | Artificial Intelligence for Assisted Reproduction".
7. Chavez-Badiola, Alejandro; Flores-Saiffe Farias, Adolfo; Mendizabal-Ruiz, Gerardo; Drakeley, Andrew J.; Garcia-Sánchez, Rodolfo; Zhang, John J. "Artificial vision and machine learning designed to predict PGT-A results". Fertility and Sterility, 2019; 112(3):e231. doi:10.1016/j.fertnstert.2019.07. 715.
8. Chavez-Badiola, Alejandro; Flores-Saiffe Farias, Adolfo; Mendizabal-Ruiz, Gerardo; Garcia-Sanchez, Rodolfo; Drakeley, Andrew J.; Garcia-Sandoval, Juan Paulo (10 March). "Predicting pregnancy test results after embryo transfer by image feature extraction and analysis using machine learning". Scientific Reports, 2020; 10(1): 4394. Bibcode:2020NatSR..10.4394C. doi:10.1038/s41598 -020-61357-9. PMC 7064494. PMID 32157183.
9. Timeva, Tanya; Shterev, Atanas; Kyurkchiev, Stanimir "Recurrent Implantation Failure: The Role of the Endometrium". Journal of Reproduction & Infertility, 2014; 15(4): 173–183. ISSN 2228-5482. PMC 4227974. PMID 25473625.
10. Mundy, Liza (July–August). "Souls On Ice: America's Embryo Glut and the Wasted Promise of Stem Cell Research". Motherjones.com, 2006.
11. Porcu E, Fabbri R, Damiano G, Fratto R, Giunchi S, Venturoli S (April). "Oocyte cryopreservation in oncological patients". European Journal of Obstetrics, Gynecology, and Reproductive Biology, 2004; 113 Suppl 1: S14–6. doi:10.1016/j.ejogrb. 2003.11.004. PMID 15041124.
12. "Genetics & IVF Institute". Givf.com. Archived from the original on 21 May 2009. Retrieved, 2 November 2016.
13. Dar S, Lazer T, Shah PS, Librach CL "Neonatal outcomes among singleton births after blastocyst versus cleavage stage embryo transfer: a systematic review and meta-analysis". Human Reproduction Update, 2014; 20(3): 439–48.
14. French DB, Sabanegh ES, Goldfarb J, Desai N (March). "Does severe teratozoospermia affect blastocyst formation, live birth rate, and other clinical outcome parameters in ICSI cycles?". Fertility and Sterility, 2010; 93(4): 1097–103. doi:10.1016/j.fertnstert.2008.10.051. PMID 192 00957.
15. Fauser BC, Diedrich K, Bouchard P, Domínguez F, Matzuk M, Franks S, Hamamah S, Simón C, Devroey P, Ezcurra D, Howles CM "Contemporary genetic technologies and female reproduction". Human Reproduction Update, 2011; 17(6): 829–47. doi:10.1093/humupd /dmr033. PMC 3191938. PMID 21896560.
16. Illmensee K, Levanduski M, Vidali A, Husami N, Goudas VT (February). "Human embryo twinning with applications in reproductive medicine". Fertility and Sterility, 2010; 93(2): 423–7.