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Invitro Fertilization: Management for Infertility

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ABSTRACT

Infertility is the major problem faced by reproductive age people throughout the world. According to World Health Organization (WHO) estimates that approximately 8-10% of couples experience some form of infertility problems. On a worldwide scale, this means that 50-80 million people suffer from infertility. Since the birth of the first IVF (in vitro fertilized) Baby in 1978, the possibility of pregnancy and having a child through Assisted Reproductive Technology (ART) was provided for many infertile couples. Invitrofertilization has been a major advancement in infertility treatment over the last couple of decades. The procedure demands sophisticated technological equipment plus a high level of skill on the part of medical operators. The success rate of pregnancy associated with this treatment ranges between 15-30%. The world's first IVF baby, Louise Brown, was born in 1978 in England as a result of the pioneering efforts of Edwards and Steptoe. The case of Subhas Mukerji in Calcutta is well known. He reportedly produced India's first and the world's second test tube that born in 1978 October, just a few months after Louise Brown was born.

KEYWORDS :

INTRODUCTION

Reproduction is a device that has evolved for the survival of the living organisms of different species by producing continuous streams of new generation of the specific species. Production of a new human being begins with fertilization. The prevalence of infertility in India is between 10-20%. The World wide incidence of infertility is 15%. In Karnataka the prevalence rate is 15-20% and in Bangalore the incidence is 10-20%.[1]

Even in today's society, we tend to assume that individuals in committed relationships have the goal of procreation. Woman is often identified with their ability to give birth. Both men and women are supposed to pass on their genetic and generational legacies. It is more traumatic for women than men, because society had made child bearing and child rearing as an integral part of the women and they are considered as very essence of female role and identity. Fertility is associated with feminism, sexuality, body image and self esteem. Thus infertility leads to concrete feeling of physical and social inferiority that over shadows all other personal and social values[2]

In India infertility estimates one in five is childless, 20% of women who got married get pregnant in the first month and another 40% by the end of the six months, the remaining 40%, 25% get pregnant in two years time, while 15% remain childless and needing help[3]

The most common female infertility factor is an ovulation disorder. Other causes of female infertility such as blocked fallopian tubes, which can occur when a woman has had pelvic inflammatory disease or endometriosis, Congenital anomalies (birth defects) involving the structure of the uterus and uterine fibroids are associated with repeated miscarriages. Aging is also an important factor in female infertility. The ability for ovaries to produce eggs declines with age, especially after age 35[4]

There are several number of assissted reproductive technologies (ART) to increase the chance for a women to become pregnant, the methods are intrauterine insemination, invitrofertilization, embryo transfer, intracytoplasmic sperm injection, gamete intrafallopian transfer (GIFT). Among all these IVF is the most common method used and most of them accepted. IVF accounts for more than 95% success rate than other ART procedures[4]

INVITROFERTILIZATION

IVF is a method of assisted reproduction in which a man's sperm and a woman's eggs are combined outside of the body in a laboratory dish. One or more fertilized eggs (embryos) may be transferred into the woman's uterus, where they may implant in the uterine lining and develop[5]

Indications

- Tubal disease or block
- Endometriosis
- Cervical hostility
- Unexplained infertility
- Ovarian failure

Patient Selection

- Age of women(egg donor) less than 35years
- Presence of at least one functioning ovary
- Normal semenogram
- Couple negative for HIV& hepatitis

Steps in an InvitroFertilization

The basic steps in an IVF treatment cycle are ovarian stimulation, egg retrieval, fertilization and embryo culture, and embryo transfer.

Ovarian Stimulation

During ovarian stimulation, also known as ovulation induction, medications or "fertility drugs," are used to stimulate multiple eggs to grow in the ovaries rather than the single egg that normally develops each month (Table 1) (Please see the ASRM booklet titled, Medications for Inducing Ovulation for more detailed information). Multiple eggs are stimulated because some eggs will not fertilize or develop normally after fertilization[6]

Medications for Ovarian Stimulation

- human menopausal gonadotropin (hMG)
- follicle stimulating hormone (FSH)
- luteinizing hormone (LH) (used in conjunction with FSH)
- human chorionic gonadotropin (hCG)
- clomiphene citrate

Medications to Prevent Premature Ovulation

- Gonadatropin releasing hormone (GnRH) agonists
- GnRH antagonists

Clomiphene citrate and letrozole are administered orally while the other medications listed are given by injection. These oral medications are less potent than injectable medications and are not as commonly used in ART cycles. There is no evidence that one injectable medication is superior to any other.

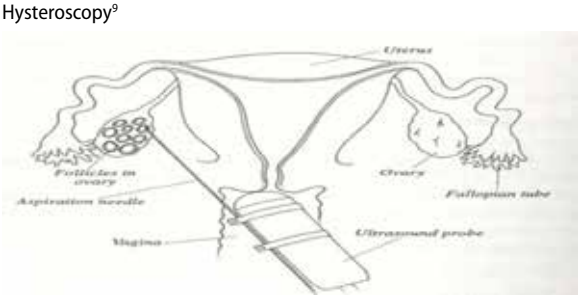
Timing is crucial in an IVF cycle. The ovaries are evaluated during treatment with vaginal ultrasound examinations to monitor the development of ovarian follicles (Figure 2). Blood samples are drawn to measure the response to ovarian stimulation medications. Normally, estrogen levels increase as the follicles develop, and progesterone levels are low until after ovulation[7]

Using ultrasound examinations and blood testing, the physician can determine when the follicles are ready for egg retrieval. Generally, eight to 14 days of stimulation is required. When the follicles are ready, hCG or other medications are given. The hCG replaces the woman's natural LH surge and causes the final stage of egg maturation so the eggs are capable of being fertilized. The eggs are retrieved before ovulation occurs, usually 34 to 36 hours after the hCG injection is given.Up to 20% of cycles may be cancelled prior to egg retrieval. IVF cycles may be cancelled for a variety of reasons, usually due to an inadequate number of follicles developing. Cancellation rates due to low response to the ovulation drugs increase with a woman's age, especially after age 35. When cycles are cancelled due to a poor response, alternate drug strategies may be helpful to promote a better response in a future attempt. Occasionally, a cycle may be cancelled to reduce the risk of ovarian hyperstimulation syndrome (OHSS). Treatment with a GnRH agonist or antagonist reduces the possibility of premature LH surges from the pituitary gland, and thereby reduces the risk of premature ovulation. However, LH surges and ovulation occur prematurely in a small percentage of ART cycles despite the use of these drugs. When this occurs, since it is unknown when the LH surges began and eggs will mature, the cycle is usually cancelled. Collection of eggs from the peritoneal cavity after ovulation is not efficient[8]

Egg Retrieval

Egg retrieval is usually accomplished by transvaginal ultrasound aspiration, a minor surgical procedure that can be performed in the physician's office or an outpatient center. Some form of pain medication is generally administered. An ultrasound probe is inserted into the vagina to identify the follicles, and a needle is guided through the vagina and into the follicles. The eggs are aspirated (removed) from the follicles through the needle connected to a suction device. Removal of multiple eggs can usually be completed in less than 30 minutes. Some women experience cramping on the day of the retrieval, but this sensation usually subsides by the next day. Feelings of fullness and/or pressure may last for several weeks following the procedure because the ovaries remain enlarged. In some circumstances, one or both ovaries may not be accessible by transvaginal ultrasound[9]

Laparoscopy may then be used to retrieve the eggs using a small telescope placed in the umbilicus. For more information on laparoscopy, consult the ASRM patient information booklet titled, Laparoscopy and Hysteroscopy[9]



Fertilization and Embryo Culture

After the eggs are retrieved, they are examined in the laboratory for maturity and quality. Mature egg are placed in an IVF culture medium and transferred to an incubator to await fertilization by the sperm. Sperm is separated from semen usually obtained by masturbation or in a special condom used during intercourse. Alternatively, sperm may be obtained from the testicle, epididymis, or vas deferens from men whose semen is void of sperm either due to an obstruction or lack of production[10]

Fertilization may be accomplished by insemination, where motile sperm are placed together with the oocytes and incubated overnight or by intracytoplasmic sperm injection (ICSI), where a single sperm is directly injected into each mature egg In the United States, ICSI is performed in approximately 60% of ART cycles. ICSI is usually performed when there is a likelihood of reduced fertilization, e.g., poor semen quality, history of failed fertilization in a prior IVF cycle. Overall, pregnancy and delivery rates with ICSI are similar to the rates seen with traditional IVF. Genetic counseling is advisable before ICSI if inherited abnormalities are identified that may be passed from father to son. For more information, see the ASRM fact sheet titled, Intracytoplasmic Sperm Injection[10]

Visualization of two pronuclei the following day confirms fertilization of the egg. One pronucleus is derived from the egg and one from the sperm. Usually 65% to 75% of mature eggs will fertilize after insemination or ICSI. Lower rates may occur if the sperm and/or egg quality are poor. Occasionally, fertilization does not occur at all, even if ICSI was used. Two days after the egg retrieval, the fertilized egg has divided to become a 2- to 4-cell embryo[10]

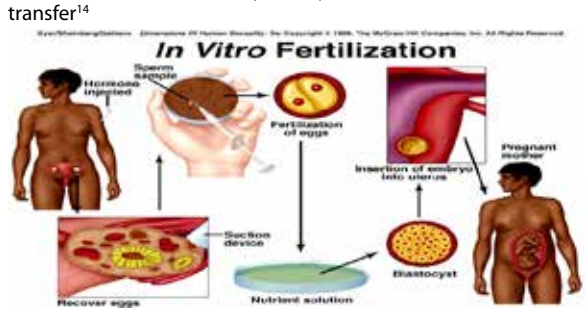
By the third day, a normally developing embryo will contain approximately 6 to 10 cells. By the fifth day, a fluid cavity forms in the embryo, and the placenta and fetal tissues begin to separate. An embryo at this stage is called a blastocyst. Embryos may be transferred to the uterus at any time between one and six days after the egg retrieval. If successful development continues in the uterus, the embryo hatches from the surrounding zona pellucida and implants into the lining of the uterus approximately 6 to 10 days after the egg retrieval[11]

Assisted hatching (AH) is a micromanipulation procedure in which a hole is made in the zona pellucida just prior to embryo transfer to facilitate hatching of the embryo. Although AH has not been demonstrated definitively to improve live birth rates, AH may be used for older women or couples who have had unsuccessful prior IVF attempts. There is no clear benefit of AH to improve pregnancy or live birth rates in other groups of IVF patients. Please refer to the fact sheet on assisted hatching for more details[12]

Preimplantation genetic diagnosis (PGD) is performed at some centers to screen for inherited diseases. In PGD, one or two cells are removed from the developing embryo and tested for a specific genetic disease. Embryos that do not have the gene associated with the disease are selected for transfer to the uterus.These procedures require specialized equipment and experience together with IVF (in a couple who may otherwise not need IVF to conceive). Some couples, especially those who are carriers of genetic diseases, consider embryo screening beneficial in reducing the risk of having an affected child. While PGD can reduce the likelihood of conceiving a pregnancy with an affected child, it cannot eliminate the risk. Confirmation with chorionic villus sampling (CVS), amniocentesis or other testing is still necessary[13]

Embryo Transfer

The next step in the IVF process is the embryo transfer. No anesthesia is necessary, although some women may wish to have a mild sedative. The physician identifies the cervix using a vaginal speculum. One or more embryos suspended in a drop of culture medium are drawn into a transfer catheter, a long, thin sterile tube with a syringe on one end. The physician gently guides the tip of the transfer catheter through the cervix and places 11 the fluid containing the embryos into the uterine cavity (Figure 7). The procedure is usually painless, although some women experience mild cramping. ASRM publishes guidelines regarding determination of how many embryos should be considered for transfer[14]



The maximum number of embryos transferred is based on the patient's age and other individual patient and embryo characteristics. Since each embryo has a fair probability of implantation and development, the number of embryos to be transferred should be determined for each patient, taking into account the odds of achieving a pregnancy based on the number of embryos transferred weighed against the risk of multiple gestation. These guidelines have been effective in helping U.S. ART programs maintain their high success rates while significantly decreasing the number of high-order multiple pregnancies (triplets and higher). The reproductive endocrinologist or embryologist will discuss this with the patient prior to the transfer[14]

CRYOPRESERVATION

Extra embryos remaining after the embryo transfer may be cryopreserved (frozen) for future transfer. Cryopreservation makes future ART cycles simpler, less expensive, and less invasive than the initial IVF cycle, since the woman does not require ovarian stimulation or egg retrieval. Once frozen, embryos may be stored for prolonged periods, and live births have been reported using embryos that have been frozen for almost 20 years. However, not all embryos survive the freezing and thawing process, and the live birth rate is lower with cryopreserved embryo transfer. Couples should decide if they are going to cryopreserve extra embryos before undergoing IVF. There are two methods used to cryopreserve embryos: conventional (slow) freezing and "vitrification" or fast freezing. Your center will determine which method is best to use based on their experience and the developmental stage at which the embryos are frozen. Although some reports claim that vitrification may have higher success rates after thawing/warming, this is not the case at all centers[15]

It should also be noted that more and more ART centers are cryopreserving oocytes (eggs) prior to fertilization. This is done most commonly in young women who are about to undergo treatments or procedures that may affect their future fertility, such as chemotherapy for cancer. However, it is also used for couples who do not wish to freeze embryos because of concerns over their survival during freezing and thawing or the dilemma of what to do with remaining embryos after they have completed their families. Egg freezing is still considered experimental by the Society for Assisted Reproductive Technology (SART), although many clinics offer this procedure. Clinic success rates may vary[16]

Finally, it should be noted that although there are theoretical risks, freezing of sperm, eggs, and embryos is very safe. There have been no documented cases of infectious disease transmission, nor do the risks or birth defects, chromosomal anomalies, or pregnancy complications appear to be increased compared with using fresh sperm, eggs, or embryos[16]

SUCCESS RATE

The success rates of an IVF center depend upon a number of factors, and a comparison of clinic success rates is not meaningful because patient characteristics and treatment approaches vary from clinic to clinic.The success of a program is also established by the patient population enrolled in the program, the indication(s) for the procedure, and the patient's age at the time of ovarian stimulation. Some IVF programs enroll only patients with good prognoses in order to maintain a higher pregnancy rate[17]

Success rates for fresh cycles were as follows:

- Overall pregnancy rate per initiated cycle - 35.0%
- Live birth rate per initiated cycle - 28.6%
- Live births per oocyte retrieval - 31.9%
- Live births per embryo transfer - 35.7%

The incidence of miscarriage (spontaneous abortion, 15.0%), stillbirths (0.5%), congenital malformation, or chromosome abnormality is similar to that of the general population. Ectopic pregnancy has been reported after IVF due to migration of the embryo through the cornual ostium. Ectopic pregnancy occurs in approximately 0.7% of cases. In some instances, ectopic pregnancy is associated with heterotopic pregnancy[17]

CONCLUSION

Studies indicate that the chance for pregnancy in consecutive IVF cycles remains similar in up to four cycles. However, many other factors should be considered when determining the appropriate endpoint in therapy, including financial and psychological reserves. Members of the IVF team can help couples decide when to stop treatment and discuss other options such as egg and/or sperm donation or adoption, if appropriate. The physician, support groups, and other couples undergoing infertility treatment can provide valuable support and guidance. The decision to seek treatment for infertility is a viable one due to the assisted reproductive technologies available today. With patience, a positive attitude, and the appropriate treatment, most infertile couples will eventually experience the joys of parenthood.

REFERENCES

1. Priya LM. A study of nursing students on ART and the effectiveness of the planned teaching programme. Nightingale Nursing Times 2006 Jul-Oct;2(4-7):65-6.
2. Jejerbhay, Shireen.J. infertility in india-levels, patterns and consequences: priorities for social science research. Journal of family welfare Jan 2002;44(2)15-24
3. Dr.Sudhakar Krishnamurthi. Infections, pregnancies and infertility 2003;47(1)964-968.
4. B T Basavanthappa. Text Book of Midwifery and Reproductive Health Nursing. New Delhi: Jaypee Brothers;2006
5. Jacob .Annamma;A comprehensive text book of midwifery; published by Jaipee brothers; 2007;New Delhi ; page 717-724
6. David M.B. Information on IVF and pregnancy. SR solutions; march 2010.
7. Berg van de-Helder, A., Helmerhorst, F. M., Blankhart, A., Brand, R., Waegemaekers, C. &Naaktgeboren, N. (1990). Comparison of ovarian stimulation regimens for in vitro fertilization(IVF) with and without a gonadotropin-releasing hormone (GnRH) agonist: results of arandomized study. J. In Vitro Fert. Embryo Transfer 7: 358–62.
8. Buvat, J., Marcolin, G., Guittard, C., Louvet, A. L., Couplet, G. & Renouard, O. (1991). Randomizedcomparison of 2 long and short protocols of ovarian stimulation with LHRHagonist for IVF including 342 cycles in 175 women. Hum. Reprod. and Abstract Book, 7thAnnualMeeting of the ESHRE and 7thWorld Congress on IVF and Assisted Reproduction, Paris,pp. 335–6.
9. Dean, N. L., Phillips, S. J., Buckett, W. M. et al. (2000). Impact of reducing the number ofembryos transferred from three to two in women under the age of 35 who produced three ormore high-quality embryos. Fertil. Steril. 74: 820–3.
10. Egbase, P. E., al Sharhan, M., al Othman, S. et al. (1996). Incidence of microbial growth from thetip of the embryo transfer catheter after embryo transfer in relation to clinical pregnancy ratefollowing in-vitro fertilization and embryo transfer. Hum. Reprod. 11: 1687–9.
11. el Hussein, E., Balen, A. H. & Tan, S. L. (1992). A prospective study comparing the outcome ofoocytes retrieved in the aspiratewith those retrieved in the flush during transvaginal ultrasound directed oocyte recovery for in-vitro fertilization. Br. J. Obstet. Gynaecol. 99: 841–4.
12. Wang YA, Healy D, Black D, Sullivan EA. Age specific success rate for women undertaking their first assisted reproduction technology treatment using their own oocytes in Australia, 2002-2005. Hum Reprod. 2008;23(7):1633-8.
13. Stern JE, Cedars MI, Jain T, Klein NA, Beaird CM, Grainger DA, et al. Assisted reproductive technology practice patterns and the impact of embryo transfer guidelines in the United States. Fertil Steril. 2007;88(2):275-82.
14. Human Fertilization Embryology Authority [Internet].London: HFEA; Multiple births and single embryo transfer review; 2009 April 7 [cited 2011 Oct 10]; [about 1 screen]. Available from: http:// www.hfea.gov.uk/530.html
15. D C Dutta. Text Book of Gynaecology including contraception. New Delhi.New central publications;2007.
16. Dyer S.J, Abraham S.N, Hoffman .M, Vander spery Z.M. Women's Reproductive health knowledge and treatment seeking behaviour for infertility 2002 Jun; 17(6) 1657-62.
17. MEAziken,etaOsemwemkha}http://www.ajol.info/index.php/tjog/index Knowledge, perception and attitude of infertile women in Benin City, Nigeria to the causation of infetility and in vitro fertilisation and embryo transfer. Journal Home ,Vol 27, No 2 (2010)