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REVIEW ARTICLE

IVF - A new exciting horizon

Nikhil Ranjan Rajkhowa

Assistant Professor, Department of Obstetrics and Gynecology, Jorhat Medical College, Jorhat, Assam, India.

Correspondence: Dr Nikhil Ranjan Rajkhowa; Assistant Professor of Obstetrics & Gynecology, Jorhat Medical College, Jorhat, Assam, India. **e-mail: pragybora@gmail.com**

ABSTRACT

IVF is one of the most effective methods of assisted reproductive technology. It may involve eggs, sperm or embryos from a known or anonymous donor. Even, a gestational carrier — a woman who has an embryo implanted in her uterus — might be used. IVF babies are found as normal as any other baby in terms of physical and mental development. Complications of ectopic pregnancy, multiple pregnancy, miscarriage are higher in IVF pregnancies. Although the fertilization and clinical pregnancy rate is higher but the take home baby rate is not more than 27 – 30% in most of the IVF centers.

Key words: Infertility, IVF, newer development in IVF, newer family forms

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The successful birth of first IVF baby, Louis Joy Brown, a 5 pound 12 ounce female baby on 25th July 1978 at 11:47PM at Oldham in England opened up a new exciting horizon in the management of infertility and started bringing rays of hope to millions of childless couples around the globe. Today thousands of IVF clinics are operating around the world to bring smiles to these childless couples. Tremendous development has occurred in the last few decades in all aspects of IVF science, starting from understanding the biology to the development of technology. In this discussion we will try to throw light into these different aspects of IVF science including the historical aspects.

Historical aspect:

Schenk in 1878 has been credited to be the first person who attempted IVF in rabbit and guinea pig oocytes. In 1959 Cheng transferred 4 cell rabbit embryo formed after IVF into the fallopian tubes of recipient rabbits and obtained live offsprings [1].

Scientific development in this field progressed rapidly and on 25th July,1978 history was created in the human race when first IVF baby was born. It was the end result of the untiring effort of a small group headed by Robert G Edwards, Patric Steptoe and Jean Purdey – coming from widely different backgrounds. Edwards who happened to be an animal geneticists working at Edinburgh in 1950s, later turned out as an human IVF scientist. Patric Steptoe who used to play supporting piano for Chaplin movies, had decided to read either music or medicine at Oxford after his Navy service in Second World War. He decided Obstetrics and Gynaecology as his field and later joined at Oldham District General Hospital. While doing routine operations and other works he was disillusioned by difficulties in diagnosing internal disorders, which led him to the development of Laparoscopy. He was also disillusioned by the

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weak methods available to treat infertility and this led to his joining with Edwards in 1966 to work for his dream project of IVF. The third of the trio was Jean Purdy, trained in Cambridge as a nurse and was working as a ward sister in a hospital, later joined Edwards in his physiological laboratory at Cambridge, after hearing about his exciting plans for infertility treatment. This team in their own language combined best of science, medicine, and nursing and worked together for around 12 years to overcome all the hurdles to give birth to the first IVF baby. After the initial failures in the stimulated cycles, it was Lasely and John Brown who was the second couple for natural cycle IVF, happened to be the luckiest couple to give birth to the first IVF baby. Steptoe aspirated the natural cycle single ovum laparoscopically and Edwards did the in-vitro fertilization and transfer work for this first successful IVF baby [2]. After this initial success this team became master not only in achieving pregnancies in stimulated cycles but also in other newer developments of IVF science. Later on they established the Bourn Hall Clinic which holds the credit of giving birth to maximum number of IVF babies in the world by a single clinic.

In India, Indira Hinduja from the Institute of Research in Reproduction at KEM Hospital, Mumbai was successful to give birth to the first IVF baby "Harsha" on 6th August 1986. Today many IVF clinics across the country are operating and giving service to infertile couples from India as well as abroad also.

Basic steps of IVF: [3]

1. Controlled ovarian hyper stimulation: Here the idea is to stimulate the maturation of a good cohort of follicle so that maximum number of oocytes (at last 6 to 10) can be retrieved for the IVF programme.
2. Monitoring of the stimulated cycle: TVS monitoring of the follicles is generally started from Day 9 of stimulated cycle. Endometrial growth is also monitored.
3. Collection of pre-ovulatory oocyte: This is done by aspirating the follicular fluid with ovum pick-up needle as TVS guided procedure and done under short GA.
4. Oocyte culture: From the follicular fluid the oocyte cumulous cell (OCC) complexes are identified & transferred to the culture media & incubated at 37 ^{o}C till next procedure.
5. Preparation of sperm: In the mean time, semen is collected from the husband/donor and prepared by one of the suitable semen preparation methods, so that most normal and motile sperms are recovered from the semen sample.
6. Insemination: Done 4 to 6 hours of oocyte collection.
7. Culture of the fertilized ovum: After overnight incubation of the inseminated oocyte, fertilization is checked next day. Fertilized ovum is incubated in fresh media until transfer is done on Day 2 (oocyte collection day is day 0).
8. Luteal phase support: Started from next day of ovum pick up with 600 mg of natural micronized progesterone per day.
9. Embryo transfer (ET): Done on day 2 and sometimes on day 3 with the help of transfer catheter into the endometrial cavity under transabdominal USG guidance. Maximum 3 embryos are transferred.
10. Serum β HCG assay: Done of 15 days after ET.

Patient selection: [4]

Idiopathic tubal blockage was the primary indication for the initial patients treated with IVF. Later on this spectrum widened and some indications are –

1. Tubal disease
2. Unexplained infertility
3. Endometriosis
4. Male sub-fertility
5. Immunological infertility
6. Failed donor insemination
7. Cervical hostility
8. Failure of ovulation induction
9. Absent or inappropriate oocyte
10. Therapy for cancer
11. Absent uterus

Preparation of couple for IVF:

1. Counselling and consent**:** Once the need for IVF is identified, the couple should be counselled about the different aspects of IVF including different procedures, success rate, cost involved etc. IVF involves tremendous amount of mental, physical, social and financial strain. So, these aspects should be looked into properly. A realistic expectation regarding the result should be given. Consent should be taken in the proper format for the particular procedure.
2. Investigations**:** IVF patients have often completed the majority of the investigations. Apart from thorough medical examination all the following investigations are done – screening for HIV, hepatitis B & C, syphillis screening, semen analysis, hormonal assessment, TVS to rule out pelvic pathology, etc.
3. Laparo-hysteroscopy**:** A pre IVF laparo-hysteroscopy has almost become a routine to assess the tubo-peritoneal factors and the endometrial cavity. If indicated some fertility enhancing surgeries are also performed in the same sitting like fulgeration of endometriotic spots, endometrial cyst aspiration, adhesiolysis, removal of hydrosalpinx, uterine septa resection, etc.
4. Pre IVF Medication**:** Folic acid supple-mentation is started from 1 month prior to IVF. Diabetes and any chronic disease if present is controlled properly. Pre-conceptional low dose aspirin, estrogen, etc. also used to improve the endometrial receptivity in indicated cases. Any vaginal, cervical or pelvic infection is treated properly.

Prognosis of IVF: [5] Mainly depends on –

1. Woman's age
2. Duration of infertility
3. History of pelvic surgery or PID
4. Semen quality

Although the fertilization and clinical pregnancy rate is higher the take home baby rate is not more than 27 – 30% in most of the IVF centers.

Complications of IVF: [6]

- IVF babies are found as normal as any other baby in terms of physical and mental development. Congenital anomaly rate is not higher but ICSI done for some genetic factor male infertility is liable to transmit the same genetic problem to the offspring [7]. In properly screened cases infection transmission rate for HIV, hepatitis B & C, etc are nil.
- Complications of ectopic pregnancy, multiple pregnancy (more than 50% of IVF pregnancy), miscarriage are higher in IVF pregnancies. Other pregnancy related complications are not significantly higher than the normally conceived pregnancies.

Newer developments:

Relentless efforts are going on around the world to improve the IVF results. Some of them are:

1) Intracytoplasmic sperm injection (ICSI)**:** A group from Brussels, Palemo et al in 1992 reported first pregnancy by ICSI procedure. In this procedure a single sperm is directly injected into the cytoplasm of the denuded oocyte with the help of micromanipulator[8]. The rest of the procedure is same as IVF. Sever OAT syndrome, immotile sperm, azoospermia, epididymal or testicular sperm, failed IVF are some of the indication for ICSI [9]. Pregnancy rate per treatment cycle is approximately 40%. ICSI revolutionized the male factor infertility treatment.

2) Assisted hatching: To improve the implantation rate partial zona dissection (PZD), zona puncture and zona drilling are done with micro manipulator needle, laser or with acid tyrode [10]. Assisted hatching with laser is showing improved pregnancy rate.

3) Blastocyst stage transfer: In order to improve the implantation rate and also to avoid multiple pregnancy and hence to avoid increased miscarriages, single embryo in the blastocyst stage on day 5 is transferred. Improve pregnancy rate per transfer is achieved.[11]

4) Embryo cryo-preservation**:** Excess of fertilized ovum are cryo-preserved in liquid nitrogen at –196 ^{0}C. After thawing they can either

be used in subsequent unstimulated cycles if previous cycle fails or can be used for subsequent pregnancy. This reduces the cost and stress of the patient for subsequent cycles [12]. With due permission from the host, they can be used for donor programmes also. (An interesting case – A 36 yrs old Gujrati lady with a 5 year old boy attending an IVF clinic at Ahmedabed told the doctor that this is her first IVF baby delivered in 2005 and she had 8 more embryos in the cryo. Now she wishes to have her second child. As she has settled in New York city and its difficult for her to come to India again, so she wants to take her eggs to NY City and get her embryo transfer done there – yes this has become possible with the recent development of technology).

5) Oocyte cryo-preservation**:** Mature metaphase II Oocyte as well as oocyte of Germinal vesicle or primordial follicle stage and ovarian tissue are also cryopreserved for future use. This is specially helpful for patients surviving after cancer treatment by chemo or radiotherapy [13].

6) In-Vitro maturation (IVM) of oocytes**:** Immature Oocytes are collected, matured in vitro and subsequently fertilized and transferred – improves the results in cases of PCOD and in patients who repeatedly produce poor quality embryos [14]. From cryo-preserved immature oocytes and ovarian tissue mature oocyte can be produced through IVM programme at a later date and can be used for cancer survivors [15]. For donor programme, immature oocyte or ovarian tissue can be collected at caesarean or any other laparotomy/laparoscoy operation. This raises the probability of a future 'Oocyte Banking' system. Since oocytes of young age are more fertile than the oocytes of say 35+ age, so oocytes collected and cryo-preserved at a young age can subsequently be used by the same women who would like to become pregnant at her 35+ age due to her involvement in career aspect. Cryo-preservation and IVM will be able to fulfil such expectations also.

7) Sperm cryo-Preservation**:** This allows males undergoing chemo or radiotherapy or any surgical treatment leading to testicular failure or ejaculatory dysfunction, possible to have children in later years.[16]

8) Ooplasmic transfer: Cytoplasmic DNA which plays crucial role in the early embryogenesis is more efficient in oocytes of younger women than oocytes of older women [17]. So cytoplasm of an oocyte of older woman is replaced by micromanipulative technique with the cytoplasm of a younger woman's oocyte to improve the success rate of IVF. The older woman will have her own genetic offspring as the nuclear genomic material is not altered.

9) Nuclear transfer: Here the oocyte nucleus at the germinal vesicle stage of a theoretically compromised patient's egg is transferred to an enucleated healthy donor oocyte [18]. The healthy cytoplasm of the donor oocyte is supposed to help the embryogenesis process.

10) Donor programmes:

(a) Donor oocytes: Donor ooctye is used when the women cannot produce ovum (premature ovarian failure, menopause, ovarian removal by operation) or when there is high chance of transferring genetic diseases [19]. Excess oocytes from other women on IVF Programme are used mostly on cost sharing basis. Other donors can be either family member or volunteer or paid donor. This raises the future possibility of selling oocytes by celebrities at million dollars!!

(b) Donor embryo**:** In case of severe male and female factor infertility, donor embryos can be used for transfer. As the couple is genetically not related to the would be child, so this is in other words homologous to 'pre-natal adoption'.

11) Pre-implantation genetic diagnosis (PGD): In PGD one polar body or blastocyst is biopsied with the help of micromanipulator and this cell is subsequently studied for chromosomal analysis by FISH technique and for single gene anomaly (fanconi's anemia, cystic fibrosis, thalassemia, hemophillia etc.) by PCR technique [20]. Thus the normal embryos are selected out for transfer and abnormal ones are discarded. The birth of Adam Nash following PGD on 15 embryos to find one which would be potential bone marrow match for his older sibling, suffering from fanconi's anemia,

is the first case of genetic selection of any embryo to save the life of an existing person. The concept of 'Designer Babies' might become a reality in future where selection of non-disease related characteristics like skin and hair colour, eye colour, height, facial look etc. would be possible.

12) Cloning: In this technique an embryo is created through nuclear transfer from a patient derived somatic cell (somatic cell nuclear transfer, SCNT) and in this way the patient can have baby of her own genetic material. This technique can also be used in achieving creation of patient specific embryonic stem cell lines for use in HLA-compatible cellular replacement therapies. Somatic cell cloning by which theoretically an adult would be able to reproduce his replicas is strictly banned for human being. The birth of the cloned animal, Dolly, a sheep that's why led to lot of hot debates [21].

13) Surrrogacy**:** Here a second (Host) women's womb is hired (Volunteer/Paid) to nurture the fertilized embryo of the couple. For the paid surrogate mother adequate compensation is given through prior legal agreements. This has become quite popular in Gujrat and Bombay. The charge of the host varies from 1 lac to 5 lacs and so on. Indications are – patient who can produce eggs but does not have uterus, who cannot take the burden of pregnancy for some disease conditions, repeated IVF failures, recurrent abortion etc [22].

New family forms: [23]

Today 1-2 % of all the births in some of the countries are IVF babies. Amongst these "high tech" IVF generations, some new non-conventional family forms are also coming up.

1) Gamate donation families**:** Here one of the parental (paternal or maternal) genetic sources is an unknown one, taken through gamete donation programme.

2) Embryo donation families**:** Here both (paternal and maternal) genetic source is unknown for the child, i.e. the acting parents are not genetically related to the child.

3) Surrogate mother**:** Here host mother gives the birth of the baby and the genetic parents subsequently upbrings the baby.

4) Lesbian families: Egg from one lesbian partner is fertilized with donor sperm and transfer is done on the other lesbian partner. The baby is brought up by the lesbian couple.

5) Solo mother family: Solo mother's egg is fertilized with unknown donor sperm and the child is brought up by the single mother.

6) Solo father family: Donor egg (generally from a well wishers or volunteer) is fertilized by the person's sperm and transfer is done to a surrogate mother and subsequently the child is brought up by the solo father.

Legal and ethical issues:

Because of all the above mentioned developments, lot of legal and ethical issues are also coming up around the world. But as the social values change with time, these issues also change. They also vary in different countries. So, if a person or couple wishes, then they can definitely find out some suitable place in the big enough world to fulfil their dream to have their own child. So long the welfare and future of the would be child and as a whole of the human race is safe, scientific developments in this IVF field should go ahead with its own pace.

Conclusion:

IVF and related science is developing very fast to bring hope to millions of childless couple around the globe. Not only this, PGD is helping elimination of genetic and chromosomal diseases. However, the take home baby rate is not more than 27 to 30% in most of the IVF centres. So, more research is needed for improvement of the results. At present proper super-ovulation regimen, quality control in the IVF lab and atraumatic embryo transfer are three most important factors contributing to success rate. Higher order pregnancy rate can be controlled with transfer of not more than 3 eggs per cycle and in some cases by doing selective fetal reduction. Cost is the biggest prohibitory factor for IVF. In near future, if low cost media and drugs become available this will solve the problem in part. Govt. can also think of setting up IVF centres in Medical Colleges, at least on PPP (Public Private Partnership) mode, as

there is no dearth of trained manpower in medical colleges. What is required is proper leadership, management strategies and Govt's sincere approach. If these clinics are run at 'No loss-less profit' basis – this will not only keep the IVF centres long viable but also will definitely make low cost IVF possible for the financially weaker section of the society as well.

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