

A tale of Louise Joy Brown : Story goes on

Nusrat Mahmud¹, Fariha Nehreen Mirza²

Abstract:

The 1960s and 1970s witnessed major developments in the field of reproductive medicine that increased the overall outlook and knowledge about reproduction and fertility. In its early days, reproductive medicine could offer limited solutions to the infertile couple. A breakthrough came when Frank Palopoli and his team developed Clomiphene citrate - an ovulation inducing agent - in the late 1950s. This paved the way for further developments in the field of reproductive medicine. The efforts of pioneers Sir Robert G Edwards and Patrick C Steptoe resulted in the birth of the first monograph by chronicles of development of IVF. The first test tube baby, Louise Brown, was born in 25th July 1978 in Oldham General Hospital, UK. They were both awarded the Nobel Prize for Physiology in Medicine in 2010. A breakthrough had been made in the vast subjects of reproductive medicine and clinical embryology. The development of technology opened further doors in this field. For example, the development of ICSI (Intracytoplasmic Sperm Injection) in the 1990s³ by Dr. Palermo and his team opened a new era for the treatment of male infertility. It made concepts which were previously dreamt of achievable. Commendable advancements have happened in the field of Clinical Embryology and ART laboratory. Introduction of Pre Implantation Genetic Diagnosis and Next generation Sequencing has given a new ray in the treatment of recurrent implantation failure and recurrent pregnancy loss. The future of reproductive medicine has been crossed beyond the boundaries. Recent advances in genetics and the stem cells biology will take the management approach of infertility treatment into a new dimension.

The course of human life has been changed since the human first walked on the moon in 1969. Many innovations have been happened. The 1960s and 1970s witnessed major developments in the field of reproductive medicine that increased the overall outlook and knowledge about reproduction and fertility.¹ In its early days, reproductive medicine could offer limited solutions to the infertile couple. A breakthrough came when Frank Palopoli and his team developed Clomiphene citrate - an ovulation inducing agent - in the late 1950s.² This paved the way for further developments in the field of reproductive medicine.

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1. Associate Professor, Centre for Assisted Reproduction, Dept of OBGYN, BIRDEM General Hospital, Dhaka, Bangladesh.

2. Trainee, Dept. of OBGYN, BIRDEM General Hospital, Dhaka, Bangladesh.

Corresponding Author: Dr. Nusrat Mahmud, Associate Professor, Centre for Assisted Reproduction, Dept of OBGYN, BIRDEM General Hospital, Dhaka, Bangladesh. <nusratmahmud18@gmail.com>

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Sir Robert G Edwards, Jean Purdy(Nurse) and Dr.Patrick Stepto with baby Louise Brown

Changes in Clinical Embryology and laboratory:

An obvious metamorphosis has taken place in the embryology laboratory since the dawn of the IVF era. Success rate in ART increased largely because of the continuous upgrading of technologies including improvements in the quality control and embryo culture systems. Surgical sperm retrieval, gamete donations, micro manipulations, cryopreservation have come up with the add-on procedure. Embryo transfer catheter, follicular fluid aspirator, egg collection tubes were the first specific IVF equipments developed in the 1970s. At present a complete makeover has occurred. Identification and observation of embryo through superior microscopy could add up better understanding of the morphology and timing development events and to select right embryos for transfer and cryopreservation.

There have been major changes of culture media and the technique to grow embryos, from simple solutions to complex optimized culture media. Development of new culture system has supported the development of human embryos up to 6 to 7 per day in vitro. Home brew culture media has been replaced by commercially available culture media, strictly maintained by equality control and shelf life has also been prolonged.

The horizons of IVF expanded from zonal dissection to subzonal insertion of sperm to intracytoplasmic injection intracytoplasmic morphologically selected sperm injection, slow freezing to vitrification, morphology to genetics.⁴

In recent years the IVF laboratory has incorporated many new technologies that have helped to refine and perfect the Assisted Reproductive Technologies.

Remarkable advancements have been made in oocyte and embryo cryopreservation,⁵ assisted fertilization for the treatment of male factor infertility. Genetic diagnosis of embryo before transfer and development of new embryo selection methodologies and platforms, including embryo morphokinetics using timelapse microscopy have given the hope for the treatment of Recurrent Implantation failure. Preimplantation genetic testing has opened a new era for the successful genetic diagnosis of single gene defects through blastomere biopsy. PGT has been of tremendous benefit to couples at risk of transmitting genetic disease⁶. Initially in vitro maturation(IVM) was introduced as a method of choice of technique to avoid OHSS in women with PCOS⁷. Recently it has gained popularity for fertility preservation also. Oocyte donations remains an important component of treatment of infertility, even so with much debate⁸. It gives new hope and remains essential treatment for women whose ovarian function is lost due to premature ovarian insufficiency and gonadotrophic treatment for malignancies.

Another new development, uterine transplantation, certainly brings joy to the patients with no uterus or non functioning uterus. Reproductive genetics has gained new dimension side by side with the development of assisted reproductive technologies. Gene editing gives new era to the treatment of germ line genetic disease.

Historic development of ovarian reserve markers-the need

Ovarian reserve tests are important for counseling infertile patients, based on ovarian response prediction and probability of live birth. Ovarian responses are being predicted to optimize the stimulation protocols. Safety risks have been improved by using the reserve test markers.^{9,10} Besides, family planning, fertility treatment and fertility preservation can also be predicted. Antral follicle count (AFC) and the anti mullerian hormone (AMH) have an added value together with female age. AMH is the best biomarker of ovarian reserve as it is cycle independent.¹¹

Evidence has been supported that oocyte quality but not quantity can accurately predict the probability of pregnancy. It has been seen that the young women

with decreased ovarian response have a small number of high quality oocytes but reasonable pregnancy rates. It is also important to note that decreased ovarian response in all age groups does not necessarily correlate with an inability to conceive.

Endometrial factors:

“The womb may be more important than home”- Barker presented his theory to emphasize the concept of maternal endometrium may have a profound effect on adult physiology. It has been proven that the maternal endometrium can predispose to an increased risk for disease in adulthood, like type II diabetes, hypertension, stroke and atherosclerosis¹². The concept of epigenetic changes, contributes to the pathogenesis of several complex diseases has also been established since then.

Identification of window of implantation (WOI) has opened a new avenue in the field of Reproductive Medicine by initiating the individual targeted treatment.

The recent advancements of Next generation sequencing with the knowledge of bacterial genomes have an impact on reproductive success. The presence of dysbiotic or pathogenic bacterial populations into the uterus has been responsible for repeated implantation failure or recurrent miscarriage.

Gonadotropins in the treatment of infertility:

The first baby Lousie Brown was born in 1978 by natural cycle IVF. Since then a lot of work has been done to optimize the stimulation protocols. The development of gonadotropins and their use in ovulation induction and ART has given the birth of more than 15 million children till now. Recent advancements in this field have given maximum safety and efficacy by using personalized treatment options. Lots of work has been ongoing for the development of orally active FSH agonists and antagonists. As FSH cannot be totally absorbed orally till date no successful outcome has

been reported.¹³

It has been evident that chance of pregnancy will be higher in gonadotropin stimulated cycle rather than natural cycle. Although it has multiple potential drawbacks like complexities of the region, high cost of drugs, risk of development of OHSS, yet ovarian stimulation by gonadotropins upheld the superior position in inducing ovaries.

However, individual ovarian response to stimulation varies significantly. In case of cancer patients needed infertility treatment, adequate stimulation regimens are must as there is no chance of delay and or no time to postpone chemotherapy.¹⁴ Safe and effective ovarian stimulation protocols need to be developed in special conditions like steroid dependant cancer (in cases of breast cancer), oocyte freezing and oocyte donation. There are lots of debates going on even after four decades of first IVF baby. Is there any possibilities to mild stimulation or natural cycle IVF if so in which patients?

Development of GnRh agonists trigger has given the hope in women who developed hyper response to gonadotropins stimulation and prevents the development of OHSS.¹⁵

The most common strategy developed in recent years is to freeze all embryos for transfer in subsequent cycle.

Luteal Phase Support:

Luteal phase defect in ovarian stimulation is related to supraphysiological levels of steroids. Luteal phase support with HCG as progesterone especially after assisted reproductive technique results on higher pregnancy rates¹⁶. However; it is associated with a greater risk of OHSS. Comparable outcomes have been seen by using vaginal progesterone in different routes.

The new concepts of personalized medicine has been given the opportunity on; luteal phase after final maturation with GnRH agonists in a GnRh

antagonist protocol. The HCG dose and timing can be individualized based on individual luteolysis pattern. Luteal coasting in higher responding patients can give a higher chance of pregnancy in fresh embryo transfer without adversity.

Ovarian Hyper Stimulation Syndrome OHSS:

The first IVF managed with natural cycles. Since then work has been done to improve the chances of pregnancy by improving the stimulation protocols to have greater number of oocytes Ovarian hyperstimulation syndrome (OHSS) is the most serious complication resulting to that.¹⁷

Intravenous administration of Dopamine has been tried to reserve renal function in case of OHSS, not yet stable.¹⁸ Letrozole has been tried to reduce the development of ascites in OHSS, still in trial. Cabergolin, Quinagolide both has shown to have effect in reducing OHSS development in non pregnant women.¹⁹ Kisspeptin-a group of hypothalamus peptides (specially Kq 59 has got positive effect in egg maturation in ART cycle with reducing the chance of OHSS.²⁰ GnRh anatagonists with use of pregosetrones (medroxy peregesterones) 4 to 10 mg/day has shown effect in reducing development OHSS. GnRH agonists use give lower incidence of development of OHSS.²¹

Transvaginal sonography (TVS):

Development of TVS has given a new way in the treatment of infertility and ART starting form better monitoring in oocyte maturation, oocyte retrieval and embryo transfer. Ultrasonogram has become the key instrument in clinical management of infertility and ART.

Conclusion:

The future of reproductive medicine has been crossed beyond the boundaries. Recent advances in genetics and the stem cells biology will take the management

approach of infertility treatment into a new dimension.

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