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Medically assisted reproductive technologies – A clinical perspective

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The birth of Louise Brown by *in vitro* fertilization and embryo transfer in 1978 marked the beginning of Reproductive Medicine. Since then several new medically assisted reproductive technologies have been introduced. Every aspect of *in vitro* fertilization and embryo transfer has undergone major changes. The probability of achieving parenthood for many barren couples has improved significantly during the last few decades. India is a late entrant to this field but has the potential of being in the forefront of research and development because of the vast opportunities available for such endeavours here.

THE world's first test tube baby, Louise Brown is today a 16-year-old bubbling teenager, just as any other teenager of her age. Her mother, Lesley Brown, was told by her gynaecologist that she had a one in a million chance of ever having a baby, she was not only lucky at the first attempt at *in vitro* fertilization and embryo transfer but also for the second time and have two babies in succession. The credit for this pioneering work goes to Edwards, Steptoe and their colleagues at the Oldham General Hospital, UK. The field of reproductive medicine has come a long way since Louise Brown was born. This article gives a clinical perspective of medically assisted reproductive technologies.

Medically assisted reproductive technologies

Medically assisted reproductive technologies (MARTs) are defined as techniques which assist a couple in achieving parenthood by the manipulation of the oocytes and spermatozoa. The currently available MARTs include: *In vitro* fertilization and embryo transfer (IVF-ET), Gamete intra-fallopian transfer (GIFT), Zygote intrafallopian transfer (ZIFT), Tubal embryo stage transfer (TET), Pronuclear stage tubal transfer (PROST), Transcervical oocyte and sperm transfer (TOAST), Peritoneal oocyte sperm transfer (POST), Direct intra-follicular transfer (DIFT), Subzonal insemination (SUZI), Micro insemination sperm transfer (MIST), Intra-cytoplasmic sperm injection (ICSI), Micro insemination fallopian transfer (MIFT), Zona drilling, Zona cutting, Partial zona dissection (PZD), Micro epididymal sperm aspiration (MESA), Sperm retrieval from the testes (SPERT), Oocyte donation (OD) and Embryo donation (ED).

The availability of such an array of technologies has greatly improved the prospects of barren couples bearing a child and achieving parenthood.

In vitro fertilization and embryo transfer (IVF-ET)

Ovarian stimulation protocols

After initial unsuccessful attempts at menstrual cycles stimulated for folliculogenesis, Edwards and Steptoe achieved their first pregnancy following IVF-ET performed in an unstimulated 'natural' cycle[1]. The clinical practice of IVF-ET underwent a sea change with the successful introduction of clomiphene citrate (CC) and human menopausal gonadotropins (hMG) 'pure' follicle stimulating hormone (pFSH) and human chorionic gonadotropin (hCG) for folliculogenesis[2]. More follicles and hence more oocytes and embryos were obtainable with the introduction of these drugs and consequently multiple-embryo replacements became possible. This resulted in improved pregnancy rates and also in an increase in multiple pregnancy rates. The introduction of controlled ovarian hyperstimulation protocols with CC and hMG, led to a hyper-estrogenic state due to multiple follicular development and consequently led to a greater risk of premature LH surge followed by early rupture of the follicle or premature luteinization leading to cancellation of further treatment. The cycle cancellation could be as high as 20%. The introduction of GnRH analogues to 'down' regulate the pituitary led to the avoidance of premature LH surge and consequently to a decrease in the number of cancelled cycles[3]. The use of GnRH analogues in IVF stimulation protocol has now become very common. Growth hormone was introduced as a co-stimulant in patients who are poor responders[4].

Aspiration or retrieval of the oocyte

In the early days of IVF, oocyte aspiration was timed to the natural LH surge and consequently the procedure had to be attempted at any awkward time. The introduction of ovarian stimulation protocols gave some control over folliculogenesis but still the problem of premature LH surge remained. The introduction of GnRH analogues has not only increased the oocyte yield, but with the avoidance of LH surge, has given greater control over the stimulated cycle. Oocyte aspiration can now be planned to suit the requirements of the patient, doctor and the clinic.

The earliest attempt at oocyte retrieval by Edwards was from ovarian tissue resected at laparotomy[5]. Laparoscopy became the preferred mode of oocyte retrieval following the lead given by Steptoe and Edwards[6] in 1970. However, with the introduction of ultrasound, most centres now prefer ultrasound-guided aspiration of the oocyte usually by the transvaginal and sometimes by the transabdominal route[7, 8]. The concept of repeatedly flushing the follicle for oocyte retrieval has been given up and most clinics attempt only a single aspiration from each follicle. Repeated flushings may lead to loss of granulosa cells and consequently to a poor corpus luteum function.

In vitro fertilization

IVF was introduced as a treatment for irreparable tubal disease. It was soon realized that to effect IVF much less number of spermatozoa was required and consequently IVF came to be used for male factor infertility like oligozoospermia and asthenozoospermia[9] and even those with obstructive azoospermia were able to father children by MESA[10], SUZI or ICSI. With successful sperm retrieval from the testes and successful cryopreservation of epididymal spermatozoa[11] virtually all men with spermatozoa have a good chance of achieving fatherhood by a sperm retrieval followed by ICSI[12].

Embryo transfer

Initially as only a single embryo was available single embryo was transferred. However, with the advent of multiple ovulation as many as 3 or 4 embryos could be transferred. Spare embryos, if any, could be frozen for transfer to the same patient in a natural cycle at a later date or were used in an embryo donation programme or for research purpose with the couple's consent.

Embryo freezing

The first successful report of a pregnancy with frozen embryo came from Trounson and his co-workers[13]. Since then cryopreservation of embryos has become a routine practice in most infertility centres. In 1986 Chen reported successful pregnancy with cryopreserved human oocyte[14].

Gamete intra-fallopian transfer

Ricardo Asch and his co-workers reported on the success of GIFT in achieving pregnancy in women with open healthy fallopian tube[15]. Since then GIFT has come to stay as an important mode of treatment of women with patent tubes. GIFT is generally being done either by laparoscopy or by mini laparotomy. With the introduction of fallopian catheterization by Jansen and Anderson in 1987, GIFT by transcervical fallopian catheterization became possible and successful[16]. Pregnancies have been reported by Lucena and others[17].

In GIFT failures it is indeed not possible to ascertain whether the failure was due to non-fertilization or due to lack of implantation.

Zygote intra-fallopian transfer

Paul Devroey and his co-workers reported in 1986 on the successful delivery of a neonate conceived by laparoscopic ZIFT[18]. ZIFT is believed to combine the benefits of both GIFT and IVF. Successful transcervical ZIFT has been reported by Jansen and others[19]. Intrafallopian transfer can also be effected in different stages of embryo development as in TET, PROST.

Micromanipulation

With the advent of micromanipulation in MART the management of hitherto difficult male infertility cases became possible[20]. The techniques of zona drilling, zona cutting, partial zona dissection, MIST, SUZI or ICSI have all raised new hopes for men with gross sperm deficiencies.

The clinical scenario

The introduction of every new technology in MARTs raises further hope for the infertile couple. These new techniques, however, introduce higher degree of complex technology. It is time, that attempts are made to improve the technology and make it patient-friendly, efforts should be made to make it less expensive and simple. The long-term sequelae of MARTs, particularly hyperstimulation, is not clear. In the short-term, occasionally serious morbidity and very rarely mortality could happen due to ovarian hyperstimulation syndrome or operative ovum pick up. These are by and large very rare.

The Indian scene

India is a relatively late entrant to the field of MART. The first IVF baby was born in 1986 due to the pioneering effort of Anand Kumar and Hinduja[21]. Though several hundred babies have been born in India since then, the field is yet to be standardized. There are very few guidelines, if any, to the Indian practitioner of MARTs. Most MART centres do not have qualified scientists to run them. The lack of adequate scientific manpower in reproductive biology, the mushrooming of MART centres in some metropolis, lack of quality control, both external and internal, the fierce but unhealthy competition amongst centres have all led to a muddled picture in the Indian scene. The cost of per MART treatment cycle in India is far above the affordability of the average Indian middle class and thus remains inaccessible to most Indian couples requiring treatment. The unwillingness of Insurance companies and many private companies to reimburse the expenses complicates the issue. The non-availability of good facilities in any Government Hospital is a sad story. It is time that Indian scientists and clinicians got together to evolve new strategies to make MART less expensive and more cost-effective.

Future directions

Many forms of infertility untreatable a decade ago are treatable now due to advances in MART. Most women have a realistic chance of achieving motherhood either by egg donations, embryo donation or by surrogacy. However, the same cannot be said about men. The prognosis for men with borderline azoospermia as described by Pandiyan[22] or seminiferous tubular failure or maturation arrest continues to be poor. The advent of ICSI raises hope for some men with borderline azoospermia. Those men who have hypospermatogenesis may benefit from sperm retrieval from the testis and ICSI. In men with borderline azoospermia, where the maturation arrest has been in the post meiotic phase one could consider ICSI with sperm precursors recovered from the testis and if it is successful this would relieve the infertility of many couples. The advances in knowledge of foetal organ transplant, and the awareness that foetal gonads contain many transplantable or donatable gametes improves the probability of parenthood for many couples with gonadal failure.

Conclusions

The birth of Louise Brown in 1978, raised the hope of millions of couples the world over. The eighties saw the growth and establishment of Reproductive Medicine as a speciality. In the nineties further strides are being made with the establishment of micromanipulative techniques. India, though a late entrant into reproductive medicine is fast catching up with the more advanced countries, and it is likely it would soon be on par with the advanced countries. The lack of restrictive laws in reproductive medicine in India should serve as an impetus to the Indian scientist and the clinician to research further into new methodologies for the treatment of the infertile couple. Hopefully by the year 2000 India would be a forerunner in the field of reproductive medicine.

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Social and ethical issues in medically assisted reproductive technologies

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Medically assisted reproductive technologies (MARTs) have proven to be a boon for the barren couple and have opened out new opportunities to study early human development extracorporeally. However, these new reproductive technologies have raised a number of novel situations never experienced by mankind before. There is a need for societal readjustments to the new norms of parenthood introduced by MARTs. There are also several delicate ethical issues associated with MARTs particularly when one can visualize the temptation to carry out experiments to understand the processes of early embryonic development in humans. These must be resolved mutually by consensus amongst scientists and practitioners of MARTs as well as the beneficiaries of such research, namely, the infertile couple.

THE concept of human beings reproducing through extracorporeal conception and the creation of 'test tube' babies lay in the realms of science fiction when Aldous Huxley wrote his famous novel *Brave New World* in the 1930s. The actual birth of the world's first test-tube baby took place some four decades later although not quite like the method described by Huxley but by fertilizing human eggs outside the body and replacing the embryo back into the mother's womb – a technique now more popularly known as *in vitro* fertilization and embryo transfer (IVF-ET). Other medically assisted reproductive technologies (MARTs) were soon to follow IVF-ET and given various acronyms (see the article by Pandiyan in this issue).

The new developments in MARTs raised hopes in the minds of several infertile couples whose barrenness could so far not be treated. Consequently, there has been great public concern and debates on the social and ethical issues concerning the new reproductive technologies, especially when a third party is also involved in the procreative act. Public debates have mostly occurred in the Western world where, as a consequence of such public concern, Governments have instituted legislative mechanisms to safeguard the interests of the infertile couple. Unfortunately in India there has been much public interest only in the lay press about the introduction of MARTs in various parts of the country. Some of the press reports are technically erroneous, factually incorrect and some have even raised great hopes in the minds of infertile couple.

All these issues need to be debated widely in our country. To initiate such a debate is beyond the scope of this article, whose aims are to highlight some of the issues as visualized by the authors who have not only been responsible for successfully introducing MARTs in the country for the first time but have been practising MARTs in the private sector for the past few years.

Social issues

Sperm and ovum donation

Therapeutic donor insemination (TDI) has been practised for over a century and a 'strange' male is the biological father of the child born out of this procedure. It has been the normal practice not to reveal the identity of the semen donor to the recipient couple so that the donor is devolved of any moral responsibility for the offspring. Furthermore, the infertile couple would not like to draw attention to the male partner's infertility and the child may need protection from the psychological confusion of multiple parentage.