J. of Obst. & Gyn. of India Vol. 52, No. 3 : May/June 2002 Pg 28-31

Review Article

Enhancing Success in Assisted Reproductive Technology

Firuza R. Parikh

Reliance Life Sciences Pvt. Ltd., Mumbai., Department of Assisted Reproduction & Genetics, Jaslok Hospital & Research Centre, Mumbai., Yale University School of Medicine, New Haven, U.S.A.

Firuza R. Parikh

Introduction

Assisted Reproductive Technology (ART), as we know it today, has entered the new millennium with many recent advances and holds promises of many rapid developments. Infertility is no longer viewed as insurmountable and has come to be accepted as an extraordinarily common medical problem. A worldwide estimate shows that, 10 to 14% of couples in the reproductive age group (20-40 years) face difficulty in conceiving. However, recent improvement in ART techniques make pregnancy possible in many previously untreatable conditions.

Over the last 23 years, since the birth of Louise May Brown, the first test tube baby in 1978 (Steptoe and Edward, 1978), there have been technological advances, which have contributed to the steady rise in success rates of ART procedures. Newer drugs for ovulation induction, improved embryo culture media and embryo transfer methods have enhanced results, Intracytoplasmic, sperm injection (ICSI) has revolutionized the management of male factor infertility. Laser Assisted Hatching (LAH) has helped to improve the implantation rates and thus, the pregnancy rates. Preimplantation Genetic Diagnosis (PGD) rules out genetically abnormal embryos, thus improving the chances of conception in patients with repeated IVF failures. Cryopreservation technology for semen and embryos and more recently oocyte and ovarian cryopreservation has made prolonged preservation possible. Advancement in Endoscopy techniques have further complemented ART in enhancing pregnancy rates.

Ovulation Induction

Adequate ovarian response is critical to the success of an ART procedure. Cycles are intensively monitored to determine ovarian response, follicular maturation and to reduce the risk of ovarian hyperstimulation. New drugs such as GnRH antagonists hold promise of leading to better ovarian stimulation, egg quality and possibly implantation rates.

For the induction of ovulation the use of GnRH analogues are now widely in practice to synchronize follicular development avoiding a precocious LH surge from leading follicles (MacLachlan et al., 1989). As a possible alternative to the need for induction of superovulation the possibility now exists to recover immature oocytes from unstimulated ovaries. Cha et al. (1991), successfully matured immature oocytes in vitro, fertilized them and then transferred the cleaved embryos leading to a viable pregnancy. Furthermore, treatment option is available to agonadal women, or women suffering from ovarian dysgenesis or premature menopause. Donated oocytes replaced in a sequential hormone replacement cycle in agonadal woman have further increased the scope of the technology for women in the premenopausal and menopausal group

Embryo Culture Technology

The introduction of sequential media has allowed scientists to culture the embryos to the blastocyst stage before implantation. Since it is at the blastocyst stage that a fertilized egg enters the uterus in an unassisted pregnancy, higher implantation, which leads to increased pregnancy rates, can be achieved by carrying out embryo transfers at this stage. IVF embryos are primarily being transferred at the 4 – 8 cell stage on day 2 – 3 post fertilization. The reason for this has been due to limitations of culture media and conditions to sustain normal growth of blastocysts at acceptable rates. More significant results indicate that when good quality blastocysts are transferred, pregnancy rates are above 45%. The blastocyst development rate in sequential media is approximately 45% (Sakkas et al., 2001) thus providing adequate numbers of embryos that make day 5 blastocyst transfers a realistic option. Our experience with blastocyst transfers has shown a significant increase in pregnancy rates while eliminating the need to implant multiple eggs thereby reducing the risk of multiple gestations.

Intracytoplasmic Sperm Injection (ICSI)

This technique, which has been available only in the past decade, has revolutionized the treatment of male infertility. The procedure, by which a single sperm can be introduced into an egg to bring about fertilization, allows the treatment of the most severe forms of male factor infertility. With ICSI approximately 65% of the injected oocytes show fertilization and the rate of oocyte damage is negligible. ICSI is now a therapeutic option for both obstructive and non-obstructive azoospermia. Techniques like Percutaneous Sperm Aspiration (PESA), Testicular Sperm Extraction (TESA) are simplified methods of sperm isolation in azoospermic men. The first pregnancy in South East Asia was reported by our group in 1994 (Parikh et al., 1994). ICSI addresses severe forms of male infertility such as oligospermia, asthenospermia, teratospermia, globospermia, sperm with complete lack of motility due to absence of dynamic arm and other tubular defects.

Laser Assisted Hatching (LAH)

Disorders in the hatching of the zona pellucida (ZP) accounts for one of the main causes for lack of implantation (De Felici and Siracusa, 1982; Fukuda et al., 1992) and failed conception in an otherwise well managed in vitro fertilization (IVF) cycle, where embryo quality and uterine receptivity have been regularly monitored. Only 10 to 20% of embryos replaced in the uterus after in vitro fertilization complete the initial stages of implantation. One of the important reasons for this is an impediment to hatching of an otherwise healthy blastocyst (Cohen et al., 1990). In the past, the technique of assisted hatching by chemical (Cohen et al., 1992) or mechanical (Depyrene et al, 1988; Parikh et al, 1996) methods has helped the embryos hatch from the ZP and has shown an increase in pregnancy rates. However application of the Acid Tyrode solution requires greater technical expertise and has been reported to be toxic to human oocytes and embryos especially if the zona is thin (Cohen and Feldberg, 1991). Mechanical Assisted Hatching is easier to perform but the slits obtained are variable in size and if too small can interfere with the hatching procedure (Cohen, 1991).

The recent introduction of Laser Assisted Hatching (LAH) has simplified the technique of Assisted Hatching making it precise, safe, simple and reproducible. The safety, technical ease and simplicity of using LAH have been described earlier (Germond et al, 1995).

Embryo transfer

One of the key contributory factors to the successful outcome of an ART cycle is an atraumatic embryo transfer. An ideal catheter has an ease of handling, passes through an undilated cervix, is not toxic, has appropriate markings for depth of insertion and has a catheter tip detectable on USG. It is important that the embryo transfer be performed in as atraumatic manner as possible, as this will affect the outcome. Although many advocate to hold the cervix with an Allis forceps and straighten the uterocervical axis for easier replacement, others feel that uterine and cervical manipulations cause contractions which can make the embryos relocate either to the fallopian tube or to the cervix (Ijland et al., 1998; Lesny et al., 1998; Fanchim et al., 1998).

Preimplantation Genetic Diagnosis (PGD)

Chromosomal abnormalities are one of the major causes for pre and post implantation embryo wastage reflected by decreased implantation and increased miscarriage (Warburton et al., 1986). Efforts to improve the means to diagnose and treat human genetic diseases have a long history in biomedical research and medicine. Presently, most of the genetic testing for such disorders is done at 12 – 18 weeks of pregnancy and the patient has to undergo termination of pregnancy in the event of an abnormality being detected. In contrast preimplantation genetic diagnosis (PGD), a new adjunct to IVF, helps in negative selection of affected embryos prior to implantation, thus avoiding the stress and emotional trauma associated with elective termination of pregnancy (Wells and Sherlock 1998). PGD helps to assess the genetic makeup of the embryos, thus eliminating genetically defective embryos before implantation (Sermon and Liebaers, 1999).

PGD as an emergent technology is particularly useful for couples at risk of transmitting genetic disorders to their offspring, woman with repeated pregnancy losses due to genetic disorders, couples who have had a child with genetic problems and are at a high risk of having another one or couples with a family history of a genetic disorder can avail of PGD in order to enhance the chances of a normal offspring (Parikh et al., 2001).

For PGD, isolation of genetic material is done from the oocyte (polar body biopsy) or the embryo (blastomere biopsy from cleavage stage embryo or trophectoderm biopsy from blastocyst), followed by genetic analysis of the blastomere for establishing the diagnosis by Fluorescent in situ Hybridization (FISH) or Polymerase Chain Reaction (PCR). FISH is used to detect chromosomal anomalies (Munne, 2000) while PCR is used to detect single gene disorders (Wells and Sherlock 1998). At our centre we offer PGD for numerical disorders as well as for thalassemia and cystic fibrosis.

Egg Donation

Oocyte donation is a viable option in women with impending or established ovarian failure either prematurely or at the correct time. More recently the indications have extended to include women with an inherent risk of passing on a serious genetic defect to their offspring. The donor oocyte program is also offered to women with difficulty in egg production or whose eggs carry a genetic defect. It also provides an opportunity for fertile women to become egg donors, helping a childless couple build a family. Donors undergo ovarian stimulation and egg retrieval, while recipients undergo fertilization and transfer. Donors are carefully screened and matched with prospective recipients (Noyes et al., 2001).

Cryopreservation

Sperm cryopreservation allows males undergoing chemotherapy and / radiotherapy, possible to have children in later years. This technology can also be made available for couples who are separated due to work related issues for long periods of duration. Embryo cryopreservation obviates the need to resort to ovulation induction and oocyte retrieval in subsequent cycles (Van den Abbeel et al., 2000). Oocyte cryopreservation is potentially an alternative solution to preserve the reproductive capacity for women at risk of losing it because of premature ovarian failure, pelvic diseases, surgery, or antineoplastic treatments (Porcu 2001).

Endoscopic Surgery

Correct diagnosis is a crucial step in determining appropriate therapy. Once the diagnosis has been established, treatment can be tailored specifically to the individual needs of the couple. The goal of endoscopic surgery in infertility practice is to restore the normal tubo-ovarian anatomy of the pelvis to whatever extent is possible. Hysteroscopic resection of septum, excision of polyps and myomas, lateral metroplasty all contribute to restoring the normal cavity, increasing the area of the uterine cavity for implantation. Laparoscopic adhesiolysis, myomectomy, excision and cauterization of endometriotic areas have shown to enhance oocyte quality and safer oocyte retrieval.

Current thinking indicates that the presence of hydrosalpinx brings down the implantation rates following IVF. A meta-analysis of 15 published studies showed negative consequence on pregnancy rate, implantation rate and live born rate in women with tubal infertility with hydrosalpinx undergoing IVF than in women with hydrosalpinx (Camus 1999). Recent data suggests that hydrosalpinx that is visible on transvaginal sonography requires removal (De Wit et al., 1998). Indiscriminate salpingectomies in all hydrosalpinges is clearly not the consensus.

Psychiatric Stress

Patients undergoing in vitro fertilization IVF experience high levels of stress, depression and anxiety (Sonawalla et al., 1999). Contributing factors include treatment related stress, cultural factors such as increased social and family pressures, a vulnerability to stress, poor coping skills and pre-existing depressive or anxiety disorders (Beutel et al, 1999; Sonawalla et al., 1999). Increased vulnerability to stress is associated with a poor outcome of IVF – embryo transfer treatment (Facchinetti et al., 1997). Counseling and cognitive behavior therapy are reported to be beneficial to some patients.

Conclusion

Newer technologies have allowed IVF centres world over to fulfill the infertile couple's wish to beget children. Although there have been great studies in the field of reproductive technology in the last few decades, more research and randomized control trials need to be done to offer new hopes and vistas.

References

1. Beutel M, Kupfer J, Kirchmeyer P, Kehde S, Kohn FM, Schroeder-Printzen I, Gips H, Herrero HJ, Weidner W. Andrologia 1999 Jan; 31(1): 27, 1999.
2. Camus F. Hum. Reprod. 14: 1243, 1999.
3. Cha KY, Koo JJ, Ko JJ, Choi DH, Han SY, Yoon TK. Fertil Steril Jan; 55 (1) : 109 – 1991.
4. Cohen J, Alikani M, Trowbridge J, Rosenwaks Z: Hum Reprod. 7: 685, 1992
5. Cohen J, Elsner C, Kort H, Malter H, Massey J, Mayer MP, et al. Hum Reprod 5:7, 1990
6. Cohen J, Feldberg D. Mol. Reprod. Dev. 30:70, 1991.
7. Cohen J. J In Vitro Fert embryo transfer 8:178, 1991.
8. De Felici M, Siracusa G. Gam. Res. 1982; 6:107, 1982.
9. De Wit W, Gowrising CJ, Kuik DJ, Lens JW, Schats R. Hum Reprod 1998 Jun; 13(6) : 1696, 1998.
10. Depypere HT, McLaughlin KJ, Seamark RF, Warnes GM, Matthews CD. J Reprod Fertil 84:205, 1988.
11. Facchinetti F, Matteo ML, Artini GP, Volpe A, Genazzani AR. Fertil Steril Feb; 67 (2): 309, 1997.
12. Fanchin R, Righini C, Olivennes F, Taylor S, de Ziegler D, Frydman R. Hum Reprod. 13: 1968, 1998.
13. Fukuda A, Roudebusch W. Thatcher S. J Assist Reprod. Genet 9:378, 1992.
14. Germond M, Nocera D, Senn A, Rink K, Delacretaz G, Fakan S. Fertil. Steril. 1995; 64:604, 1995.
15. Ijland MM, Hooglannd HJ, Gerard AJ. Fertil. Steril. 71: 476, 1998
16. Lesny P, Killick SR, Tetlow RL. Embryo transfer – Hum Reprod. 1998; 13: 1540, 1998.
17. MacLachlan V, Besanko M, O'Shea F, Wade H, Wood C, Trounson A, Healy DL, A. N Engl J Med 11:320(19):1233, 1989.
18. Munne S Preimplantation genetic diagnosis of numerical abnormalities using FISH. In : Trounson AO, Gardner DK, editors. Handbook of in vitro Fertilization. London: CRC Press, 2000 : 30[illegible]
19. Noyes N, Hampton BS, Berkeley A, Licciardi F, Grifo J, Krey L. Fertil Steril 2001 Jul, 76(1) : 92, 2001
20. Parikh F. R., Kodwaney G., Kamat S., Parikh R. M. J Obstet and Gynae India. 44(3) : 458, 1994.
21. Parikh F.R., Naik N.J., Manjrekar S.K., Nadkarni S.G., Uttamchandani S.A., Parikh R.M : J Obstet and Gynae India; 50 (6), 2000.
22. Parikh F.R., Naik N., Gada S., Bhartiya D, Athalye A. S., and Madon P. F.; J of Human Genetics. Vol 1 (2). 117, 2001.
23. Parikh FR, Kamat SA, Nadkarni S, Arawandekar P, Parikh RM. J Reprod Fertil Suppl 50: 121, 1996
24. Porcu E. Semin Reprod Med 2001; 19(3): 221, 2001
25. Sakkas D, Percival G, D'Arcy Y, Lenton W, Sharif K, Afnan M. Hum Fertil (Camb); 4(2): 104, 2001.
26. Sermon K, Liebaers I – Preimplantation Genetic Diagnosis. In : Fauser BCJM, editor. Molecular Biology and Reproductive Medicine. New York. The Parthenon Publishing Group, 1999 : 409-32
27. Sonawalla S, Parikh R, Parikh F. Int J Psychiatry Med 1999; 29(2) 251, 1999.
28. Steptoe PC, Edwards RG. Birth after the reimplantation of a human embryo. Lancet Aug 12 2 (8085) : 366, 1978
29. Van den Abbeel E, Camus M, Joris H, Van Steirteghem A. Mol Cell Endocrino Nov 27; 169(1-2) :49, 2002
30. Warburton D, Kline J, Stein Z, Strobino B. In : Porter I, Willey A, editors, Perinatal Genetics: Diagnosis and Treatment. New York : Academic Press, 1986. 133-48.
31. Wells D, Sherlock JK. Prenat Diagn Dec; 18(3) 1389 1998.