How safe is your IVF program?

As greater number of people opt for assisted reproductive technology (ART), it has become imperative to look into the safety aspects of *in vitro* fertilization (IVF) programs carefully. It should be appreciated that most women do not suffer any serious complication during IVF procedures; however, the risks of ovarian hyperstimulation syndrome (OHSS), multiple pregnancy, miscarriage, and premature birth are high for a small percentage of patients.

Apart from these medical side effects, there are risks of possible human errors in IVF labs that need to the looked into. The minor complications associated with IVF treatment are usually due to drugs used during ovarian stimulation and for luteal support. These include skin allergy, fever, and local irritation. Besides these, there are anesthetic complications, which are, again, very rare. Pelvic infections and hemorrhage have been reported in a few cases, though the incidence is very sporadic. Pelvic hemorrhage *post* oocyte retrieval may be fatal if not detected well in time. A definitive strategy, therefore, needs to be evolved so as to minimize risks and complications in IVF programs.

Identification of risk areas is the first step in formulating an effective approach to develop a risk-free IVF program. As the IVF sector has grown phenomenally over the recent past, the need for safe ART practice has been felt and extensively discussed; however, no comprehensive policy has emerged till date. Whatever suggestions have been made in the literature are usually event-based and practiced accordingly.

The European Society of Human Reproduction and Embryology (ESHRE) consensus meeting in 2002 suggested four important areas to be focused upon to reduce risks and complications. Multiple pregnancies, the effect of ART on women and offspring, and morbidity and mortality following ART were identified as key problem areas. A lot of emphasis was placed on the reduction of multiple pregnancy rates in this consensus meeting. Elective single embryo transfer (ESET) has been advocated in those patients who have high chances of multiple pregnancy.[1]

It was also proposed to establish a definite policy to practice ESET in the identified group of patients, i.e., those aged <36 years who are well counseled, and on demand to those patients who want to avoid twin gestation at any cost. It was also proposed that strict morphological assessment should be done so as to select the best-quality single embryo to ensure an uncompromised outcome. However, it should also be kept in mind that indiscriminate applications of ESET in patients with poor prognosis may result in significant reduction of cumulative pregnancy rates. Joint Society of Obstetricians and Gynaecologists of Canada-Canadian Fertility and Andrology Society clinical practice guidelines, 2010 analyzed barriers in the implementation of ESET and gave recommendations to practice ESET based on the data available on ESET with the aim of reducing complications associated with multiple gestation, while maintaining an acceptable live birth rate at the same time.[2]

It is recommended that women aged 35 years or less with at least two good-quality embryos at the blastocyst stage and who are well motivated should be offered ESET, provided that an effective cryopreservation program is in place. It is also recommended that when good-quality embryos are available in a donor oocyte program, ESET should be offered.

CONGENITAL MALFORMATIONS *POST* ART

The incidence of congenital malformations might be higher after IVF and intracytoplasmic sperm injection (ICSI). However, this may be due to infertility *per se* rather than the ART techniques. Therefore, more and larger prospective controlled studies are required to address this issue definitively. The ESHRE consensus meeting, 2002 recommended that genetic counseling should be offered as a routine part of treatment and that laboratory testing including chromosomal analysis and microdeletion should be done in nonobstructive azoospermia, severe oligozoospermia and cystic fibrosis transmembrane regulation (CFTR) gene analysis in cases of congenital bilateral absence of the vas deferens (CBAVD).[1]

It is also observed that though ART procedures are offered to large populations across the world, their risks and complications are hardly documented. The ESHERE consensus meeting, 2002 recommended that all registries should include data on maternal and fetal morbidity and mortality, pregnancy complications, congenital malformations, zygosity of twins, multifetal reductions, and new procedures, so as to enable a proper analysis of risk and safety.[1]

OHSS: The chief culprit

OHSS is the iatrogenic condition seen in as many as 30% of all induced cycles, with the severe form reported in 0.5-5% of

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cases. True morbidity and mortality are unknown because most of the cases go unreported. The reported mortality in an article by Brinsden in 1995 was 1:50,000 IVF cycles.[3] According to a recent study from the Netherlends, overall maternal mortality was much higher (42 deaths /100,000 IVF pregnancies) as against the national average of 6 deaths/100,000 pregnancies.[4] In today's modern era of ART, mortality from OHSS is unacceptable. The concept of an OHSS-free clinic was first proposed by Deveroy *et al*. in 2011.[5] Though many interventions have been suggested and practiced to avoid OHSS, any single intervention may not be effective; thus, combining various strategies is a wiser approach for preventing and reducing the severity of OHSS.

The segmentation of the IVF program has been suggested by Devroey in 2011. He proposed segmentation of the whole program into three parts, as follows: Segment A-optimization of ovarian stimulations by using gonadotrophin-releasing hormone (GnRH) antagonist protocol, followed by GnRH agonist trigger; segment B- oocyte or embryo cryopreservation in all cases; and segment C- embryos are replaced in an artificial cycle in a receptive endometrium, thereby achieving the complete elimination of OHSS. However, there are many issues and concerns that might restrict the use of this concept in day-to-day practice as it may not be applicable in all settings, has a less flexible approach, increases the cost of the cycle, and requires a robust vitrification program. Moreover, the concept should be evaluated on a wider platform and should be compared with other prevalent approaches.

Another approach that is more flexible and practical was introduced by Papanikolaou *et al*.[6] In this approach, prevention is the chief intervention that should be applied from the follicular phase by identification of high-risk patients on the basis of their age, Anti-Müllerian hormone (AMH) levels, and antral follicle count (AFC). Multiple interventions have been suggested, including choice of protocol, trigger using agonist, supplementing luteal phase with 1500 IU hCG, and the option of freeze-all or day-5 transfer.

Use of the GnRH trigger has been evaluated by many authors and has been recently reviewed by Youssef *et al*.[7] Seventeen randomized control trials (RCTs) with 1847 patients were reviewed in the Cochrane Database of Systematic Reviews and it was concluded that in donor-recipient cycles the incidence of OHSS was less and there was no difference in live birth rate. On the contrary, in fresh autologous cycles, a lower live birth rate, a lower ongoing pregnancy rate, and a high early miscarriage rate were observed. Thus, it was concluded that the GnRH agonist trigger could be beneficial in patients who chose to go for the freeze-all protocol, or in donor cycles.

Another important strategy is the use of GnRH antagonists in the luteal phase on day 5-8 *post* oocyte retrieval, which results in rapid resolution of OHSS and thereby avoids hospitalization.[8] Current recommendations to prevent OHSS are summarized by Corbett and consists of the use of metformin in polycystic ovary syndrome (PCOS); gonadotropin dosing as per age, body mass index (BMI), AFC, and previous response; the use of GnRH antagonist protocol; ESET, the use of cabergoline, and freezing of all embryos.[9]

Risk of viral/infective transmission

The risk of blood-borne viral transmission and infection is real in all patients undergoing IVF/ICSI cycles. As the concept of third-party reproduction is gaining popularity and is being offered to a large number of patients seeking ART services, the risk of transmission of human immunodeficiency virus (HIV), hepatitis, and other viral infections has reached a damaging proportion, especially as the preventive protocols are not in place. It is important to screen all couples, gamete donors and intended surrogate mothers for HIV, hepatitis B, hepatitis C (HCV), and other infections such as syphilis before they are enrolled in the ART program. The status of gametes must be ensured before freezing, and all frozen samples should be quarantined for at least 6 months before being released for clinical use.

The protection of the staff and the prevention of contamination are the main areas of risk management in ART. Universal precautions should be in place at all steps. The American Society for Reproductive Medicine (ASRM) Practice Committee recommends separation in time and space, separation of frozen gametes, embryo storage, special sperm washing, and viral load checking prior to freezing.[10]

The Human Fertilisation and Fertilisation Authority (HFEA) recommends separate tanks for storage and a closed system for embryo storage, which may provide a highly effective seal against the migration of microorganisms into or out of straws. These measures have been proven to be effective in short-term evaluation; however, their long-term safety and efficacy remain to be evaluated. Heat-sealed straws are to be used by IVF centers treating those seropositive for HIV, hepatitis B, and HCV.[11]

Sperm washing is known to reduce the risks of viral transmission; however, it does not ensure complete elimination of the risk. All HIV-positive male partners should be on antiretroviral therapy and should have a good CD4 cell count along with an undetectable viral load.[12]

In a recent study, >4500 inseminations of serodiscordant couples with male partner being retrovirus-positive were analyzed. None of the female or children born were found to be infected.[13] Newer techniques to reduce horizontal transmission have been suggested, such as treatment of sperm with trypsin before washing to reduce the infectivity of HIV RNA.[14] or the addition of the microbicide poly-acidic oligomer, code-named PPCM (formerly known as Sulfuric Acid-Modified Mandelic Acid, or SAMMA), to washed sperm to reduce HIV infectivity.[15] These have been found to be quite promising. The use of polymerase chain reaction (PCR) for the screening of prepared semen has been advocated to further reduce the risk of transmission. It has been estimated that 3-8% of washed specimens contain detectable HIV virus after washing and cannot be used.

Cryopreservation of washed sperm before insemination can be done so as reduce the loss of sperm while the results of the PCR report are awaited.[16] IVF lab handling in general and during the ART cycle of serodiscordant couples in particular requires following of universal precautions, such as the use of scrubs, hat, shoe covers, gloves, mask, face shield, and eye shield. All sharps

should be avoided. Routine handwashing and decontamination is recommended. Attention should be paid to proper sanitation and sterilization of the lab. The use of viricidal wipes and ethanol for the cleaning and covering of tubes must be practiced to take care of airborne viruses. No mouth pipetting should be practiced, and air exchange should be done every 10 min to reduce contamination.

All ART procedures involving gametes of seropositive patients should be separated in "space or time" so as to minimize cross-contamination. A physically separate area with an exclusive set of equipment and instruments and the use of disposable contact material is ideal. Scheduling seropositive patients at a different time allows undivided attention and adequate time to sanitize the area. The Practice Committee of ASRM, Fertility and Sterility, 2013 suggested the following recommendations to reduce the risk of transmission during fertility treatment.[10]

1. All infertile couples should be counseled about the possible risk of viral transmission and that, though the risk is low, the magnitude is unknown.
2. Good clinical practice dictates that services should be provided to serodiscordant couples seeking fertility treatment if the ART center is well equipped to handle such cases and provide adequate care. A referral is also appropriate.
3. It is recommended to administer antiretroviral therapy to reduce viremia.
4. It makes sense to store gametes in separate tanks to reduce theoretical risks of transmission.
5. Sperm washing should be practiced to minimize viral transmission if the male partner is infected.
6. The seronegative partner should be vaccinated in couples discordant for hepatitis B surface antigen (HbSAg).
7. HCV-infected women should be counseled about the possible risk of vertical transmission; however, it should also be explained to her that breastfeeding is not contraindicated.
8. Herpes simplex virus (HSV)-infected women should be administered acyclovir to decrease the risk of vertical transmission.

Is ICSI risk-free?

A lot of concern has been expressed regarding the effects of various ART procedures on the health of children born after ART.

Though there is a theoretical risk of passing genetic abnormalities to offspring during ICSI, especially in cases of male infertility as they are associated with Y chromosome microdeletion, X-chromosomal and autosomal aberrations, Kallman syndrome, and ultrastructural sperm defects, it is still too early to draw any definitive conclusion.

Erricson and Kallen (2001) reported an increased risk of congenital malformation following ICSI when compared to natural conception, at 5.4 % versus 3.8%. Most of these were, however, attributed to parental characteristics such as age and parity rather than to the procedure itself, and a clear-cut association remains to be proven. Therefore, more and larger prospective studies are required to address this issue.[17]

Hence, it is recommended to offer genetic counseling to all patients undergoing treatment for infertility. It is also recommended to offer early screening by nuchal translucency scanning, double, triple, and quadruple tests, and detailed level II scan to rule out congenital malformations at the appropriate gestational age.

It is also important to initiate a worldwide registry of congenital malformations in all children born of ART procedures across the globe so as to assess the exact impact of ART procedures.

Kuldeep Jain
Editor in Chief

Address for correspondence: Dr. Kuldeep Jain,
KJIVF and Laparoscopy Centre, 23-24,
Gagan Vihar, Delhi - 110 051, India.
E-mail: drjain@kjivf.com

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