

Complications of Assisted Reproductive Technologies

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Abstract

ART methods are boon to infertile couple. Though ART methods are practiced widely in every country today. There is debate regarding their efficacy, cost effectiveness and risk factors. Women who conceive by ART have high risk of maternal and perinatal complications such as ectopic pregnancy, pregnancy induced hypertension, placenta previa, placental abruption, morbidly adherent placenta, preterm birth and low birth weight. Gynaecological complications associated with ART are: OHHS, pelvic infection, psychological and laboratory risks. Couples are encouraged to consider psychological counselling as an additional means of stress management. There is higher incidence of multiple gestation in ART associated pregnancies.

Keywords: Assisted Reproductive Techniques; Multiple Gestation; Counselling; Infertility; Birth Defects.

Introduction

Infertility is a problem that causes intense agony and trauma that cannot be quantified in scientific terms. Infertility has far reaching social implications. Therefore, with rapidly increasing the use of ART in our country, it is essential to ensure safety and help safeguard against misuse. ART is a boon to infertile couple, however it has many complications. So, for optimum outcome of various treatment modalities in ART, it is essential to study prevention and management of complications in ART.

Assisted reproduction is a common practice in reproductive medicine, but still there is debate regarding their effectiveness, risk factors and socioreligious aspects.¹ In recent years, a substantial number of children have been conceived using

assisted reproductive technology (ART) particularly in high-income countries.² However, women who conceive by ART have a higher risk of maternal and perinatal complications, such as pregnancy-induced hypertension (PIH), placenta previa, placental abruption, morbidly adherent placenta (MAP), preterm birth, and low birth weight.³⁻⁷

Risks from pre-existing conditions on maternal health or pregnancy outcome should be addressed before initiating ART, whether or not these conditions are the source of compromised fertility. Ideally these risks should be discussed with the patient before pregnancy, but also can be reviewed during pregnancy and while establishing perinatal care. This article will highlight all that these aspects of complication of ART.⁸

Complications of Art

Gynecological Complications

OHSS

OHSS results due to vasoactive product released from hyper stimulate do varies. There is ovarian enlargement with hyperproduction of hormones resulting in hyper permeability state with fluidshift to extra vascular spaces with haemoconcentration, renal impairment and thrombo-embolic phenomenon. The exact mechanism is not clearly known. It is related to HCG stimulated ovarian over production of vasoactive epithelial growth factor associated with angiotensin II and interleukins. OHSS it is an iatrogenic condition related to natural or exogenous HCG administration.

Women at high risk include

- Young thin PCOS with typical Necklace sign.
- Very high levels of E2 > 4000 pg/ml.
- Luteal support with HCG.
- Long GnRH agonist protocol.
- Young age less than 35 years.
- Lean habitus.
- PCOS.
- High E2 response.
- Multiple small and intermediate size follicles.^{9,10}

Presentation of OHSS

- Abdominal pain caused by enlarged ovaries and acute ascites.
- Abdominal distention secondary to enlarged ovaries and ascites.
- Bowel disturbance such as constipation or diarrhoea.
- Nausea and vomiting.
- Dark concentrated urine because of reduced renal perfusion and low urine output.
- Shortness of breath caused by splinting of diaphragm.
- Leg and vulval oedema.¹¹

Pelvic infection

Removal of Eggs involves passing a needle through vaginal wall into the ovary and it is possible to introduce infection into the ovary. This is increased if there is an endometriotic cyst in ovary at the time of treatment. If pelvic pain and other signs of

infection develop in the weeks after the procedure it is treated with antibiotics and require abdominal surgery to drain abscess.

Operative Complications

These are risks related to the egg retrieval procedure. Removing egg through an aspirated needle entails a slight risk of bleeding, infection and damage to the bowel, bladder or a blood vessel. Less than one patient in 1000 will require major surgery to repair uterus maybe punctured during embryo transfer.

Psychological

ART involve significant physical, financial and emotional commitment on the part of couple. Couple may feel frustrated and angry. Isolated feeling of frustration leads to depression, low self-esteem especially following failed ART attempt.

Laboratory risk

The processing of sperm and eggs in the laboratory is a complex and skilled process carried out by qualified laboratory personnel. It involves a number of stages including gamete preparation, fertilisation, embryo assessment and culture and replacement. Additionally, there may be a requirement to freeze spare embryos and prepare them for storage.

Complications of transabdominal and transvaginal procedures in IVF-ET and GIFT-ZIFT

Sonographic-guided retrieval is associated with pelvic or abdominal visceral and vascular injuries caused by the aspiration needle.

Complications of Sonographic-Guided Oocyte Retrieval

The aspiration needle used in the transvaginal technique may injure the adjacent intestinal, uterine and tubal organ and the vascular wall. Previous history of pelvic inflammatory disease may imply a higher risk of pelvic reinfection. As a mechanical factor is the cause of infertility in most IVF patients, their risk of reinfection during transvaginal procedures is increased. Thus, the use of meticulous vaginal preparation with povidone-iodine and a minimal number of penetrations during the procedures are recommended highly. Avoidance of the vaginal route for oocyte retrieval may be preferred in selective cases.¹

Infectious complications associated with culture medium contamination

Most culture mediums for human IVF use protein as high-molecular-weight serum macromolecules for the enhancement of fertilization and cleavage. The source for protein is homologous maternal serum, foetal cord serum, human serum albumin, bovine serum albumin, or human amniotic fluid, which may expose the culture to the risk of contamination even though it is usually heat inactivated and filtered. Viruses that cause hepatitis and/or human immunodeficiency (HIV) may infect the pre-embryo or the foetus, as well as the laboratory and clinical staff.¹

Obstetric Complications

Miscarriage

First trimester bleeding may signal a possible miscarriage. Foetal loss after 24 weeks gestation which was seen twice as often among women who had ovulation induction as among women who conceived naturally. Early bleeding is more common in women who undergo IVF. Spontaneous abortion rate ranges from 20 to 35%. Abortion rates rise with the increasing age of the mother and multiple pregnancies especially with three or more foetuses. In cases where more than 2 foetuses are present selective embryo reduction should be advised.

Advantages of embryo reduction are:

- Better chances of survival of other foetuses.
- They are likely to be born near term.
- Better birth weight of surviving foetuses.⁹

Ectopic Pregnancy

First trimester bleeding may signal a possible ectopic pregnancy. IVF and related treatments increase the likelihood of an ectopic pregnancy. The incidence of ectopic pregnancy is 1-3 %. Of all pregnancies resulting from embryo transfer, ectopic pregnancy is about twice normal rate. Patients who become pregnant following this treatment should have a scan to ensure the pregnancy is correctly positioned.

Heterotrophic Pregnancy

After IVF, there is an increase in heterotrophic pregnancy with one in the fallopian tube or other abnormal place and one correctly situated in the uterine cavity.

High Order Multiple Pregnancy

Multiple pregnancy can result from any treatment involving use of drug to stimulate egg production or more than one embryo is replaced during IVF or ICSI or egg donation treatment. Twin pregnancy resulting from clomiphene treatment is approximately 10%. Following IVF when two embryos are replaced it is 20 to 30%. Higher order multiple gestation occurs if more embryos are transferred. The risk of triplets following IVF and related treatment is very low if one or two embryos are replaced.

The complications of multiple pregnancy are:

- Increased risk of miscarriage.
- Increased risk of premature labour.
- Increased risk of pregnancy associated problems such as haemorrhage and high blood pressure.
- Increased requirement for caesarean section and its complications.
- Increased loss of baby (stillbirth).
- Increased risk of baby with physical or learning disability (as a result of premature birth).
- Increased risk of abnormal baby.¹²

The complications of aged pregnancy are:

- Increased anomaly risk.
- Low birth weight or pre-maturity.
- Operative delivery.
- IVF patients were 2 to 3 times more likely to require caesarean deliveries.

Twins and higher order multiple gestation:

Multiple gestation especially higher order multiple is a serious complication of infertility treatment and has a medical, psychological, social and financial implications. Amongst reproductive interventions, half of multiple gestation are attributed to ART.

Placenta Previa

Amongst women who underwent IVF, in few pregnancies the placenta is implanted either too near to the cervix or may partially or completely cover it. Heavy cervical bleeding is a common complication and surgical delivery is required.¹²

Preeclampsia

IVF patient by 2.7 times more likely to develop preeclampsia.

Placental Abruption

Woman who had IVF are 2.4 times more likely to experience premature separation of placenta from the uterine wall a condition known as placental abruption.

Discussion

Though ART methods are practiced widely in every country today, there is a debate regarding their efficacy, cost effectiveness, risk factors and socio religious aspects.

Higher incidence of abortion in ART is due to several factors:

- Increased age.
- Increased prevalence of chromosomal abnormalities such as Trisomy.
- Higher rate of multiple pregnancies.
- Early recognition of these pregnancies and abortions because of close follow up.

Majority of infertile women and most of the IVF patients have the potential to experience ectopic pregnancy during treatment attempts because of pelvic adhesions and previous tubal damage or surgery. Tubal disease may affect the luminal surface and result in narrowing and damage to the cilia. These consequences may cause a delayed or even a blocked passage of the developing embryo into the uterine cavity, and tubal implantation of the embryo may ensue.

Another causative factor is the transfer of embryos into the uterus with a large volume of transfer medium and fundal placement of the embryos without appropriate sonography guidance. Heterotopic pregnancy is a combination of intrauterine and ectopic implantation of different embryos spontaneously and is more common in patients treated by induction of ovulation.

The ectopic sites reported are the abdominal cavity, the fallopian tubes and the cervix. In the IVF-ET, ET usually formed by placing all the embryos (upto five) with a variable amount of transfer medium near the uterine fundus. Some of the embryos may reach the tubes and implantation may occur simultaneously the uterine cavity as well as in the tubes. Fewer embryos transferred and decreased transfer medium volume may lower the tubal, as well as the heterotopic, pregnancy rate.¹

Although the perinatal risks that may be associated with ART and ovulation induction are much higher in multifetal gestations, even singletons achieved with ART and ovulation

induction may be at higher risk than singletons from naturally occurring pregnancies. Couples at risk of passing genetic conditions on to their offspring, including those due to infertility-associated conditions, should be counselled appropriately. When a higher-order (triplet or more) multifetal pregnancy is encountered, the option of multifetal reduction should be discussed. In the case of a continuing higher-order multifetal pregnancy, ongoing obstetric care should be with an obstetrician gynecologist or other obstetric care provider and at a facility capable of managing anticipated risks and outcomes.

Patients should be counselled about following information:

- With ART and ovulation induction, higher-order multifetal pregnancy may occur. Multifetal pregnancy and its associated outcomes are the greatest risk of ART and ovulation induction and, consequently, every effort should be made to achieve a single ton gestation. Expanding use of single-embryo transfer is advocated. Patients and couples should be counselled about the risks of multifetal gestation with these techniques.
- Any maternal health problems or inherited conditions should be addressed.
- Couples at risk of passing genetic conditions on to their offspring, including those due to infertility associated conditions, should be counselled appropriately.
- When a higher-order (triplet or more) multifetal pregnancy is encountered, the option of multifetal reduction should be discussed. In case of a continuing higher-order multifetal pregnancy, ongoing obstetric care should be with an obstetrician and gynecologist or other obstetric care provider and at a facility capable of managing anticipated risks and outcomes. Health status of the patient should be optimized. Some maternal conditions may limit the physiologic support a woman can provide to a pregnancy and as a result, a pregnancy may represent a significant risk to the woman's life and health. The presence of pre-existing medical conditions requires careful assessment of the patient's condition and function before initiating ART plans. Even for more common medical disorders (such as diabetes, hypertension, epilepsy, or obesity), optimization of weight, maternal medical status, treatment regimen and other aspects of care may have salutary effects on

becoming pregnant and pregnancy outcomes. Therefore, pre-pregnancy assessment of pregnancy-related risks and counselling regarding risk reduction strategies should be a key element of care before the initiation of ART or any infertility treatment.

Risks regardless of foetal number

Studies that compare obstetric outcome of singleton ART and naturally occurring pregnancies suggest that the former are at increased risk of preterm birth, low birth weight, and perinatal mortality rate, even after adjusting for age, parity and multifetal gestation.

Birth defects:

Any elevated risk of birth defects associated with could be due to manipulation of the oocyte and embryo that are necessary with ART procedures or to factors related to the stimulation. However, risks also may be related to the underlying cause of infertility or other specific health risks and behaviours in those under going ART. Some professional organizations recommend foetal echo cardiography in all ART pregnancies, but the incremental yield of such studies after a targeted ultrasonography that is reassuring is unclear and needs to be balanced against available resources.^{13,14} Of course, patient-specific risks identified during evaluation of a patient's medical history may indicate need for specific studies or other foetal evaluation during pregnancy.

Long term paediatric outcomes

- Outcomes related to multifetal gestation.
- Associated prematurity.
- Those related to the ART.
- Adverse neurodevelopmental outcomes.

Prenatal diagnosis is crucial for appropriate management, and ultrasound examination and magnetic resonance imaging are used especially for women with risk factors.^{15,16}

Long-term effects of ART on women

Hormonal and reproductive factors are involved in the aetiology of breast cancer and cancers of the female genital tract. Therefore, the effect of fertility drugs on the risk of these cancers has been investigated. In a large-scale cohort study in The Netherlands, after a follow-up of 5±8 years, no increased risk of breast and ovarian cancer was found in women who had undergone IVF,

as compared with subfebrile women who had received no IVF (Klip et al., 2000). For endometrial cancer an increased risk was observed in those exposed to IVF as well as in the unexposed group, suggesting a subfertility-related effect which needs further evaluation (Klip et al., 2000).¹⁷

Effects of ART on offspring

Much concern has been expressed about the health of children born after ART. In particular, the risk of boys born to couples with male factor subfertility has drawn attention, since in a substantial number of male factor subfertility cases, a genetic cause can be suspected. These include Y-chromosomal microdeletions, X-chromosomal and autosomal aberrations (i.e. Robertsonian translocations), syndromic disorders featuring infertility (i.e. Kallmann's syndrome) and ultrastructural sperm defects with a genetic basis (Meschede et al., 2000).

Theoretically, with ICSI these defects may be transmitted to the following male generation, but it is still too early to draw negative conclusions. A significant increase (0.83%) in sex chromosomal aberrations has been reported in pregnancies after ICSI (Bonduelle et al., 1998). The results of controlled studies indicate that the risk of congenital malformations after ART is increased as compared with natural conception (5.4 versus 3.8%) (Ericson and Kaellen, 2001).

The increased risk of congenital malformations seems to be related to parental characteristics (such as age and parity), and preterm and multiple births. The individual impact of subfertility and of its treatment on the risk of ART children still remain to be elucidated. So far, the absolute risk of major congenital anomalies is small, and is not different after IVF and ICSI (3.8 versus 3.4%) (Bonduelle et al., 2002).¹¹

Patient selection and counselling for ICSI

It was agreed that the essential aim of IVF/ICSI is the birth of one single healthy child, with a twin pregnancy being regarded as a complication. The chances of having a single healthy child after ICSI have increased, and equal the spontaneous pregnancy rate in a normally fertile couple.

Morbidity/Mortality registry:

Although ART is applied a large scale there is poor documentation of risk and complications so maintenance of morbidity / mortality registry for ART recommended.

Registries should include data on:

- Maternal and foetal morbidity and mortality.
- Pregnancy complications.
- Zygosity in twin pregnancy.
- Congenital malformation.
- Multifetal reduction.
- New procedure.

Future Prospects

Technological innovations being developed and perfected currently hold the potential to change the field of ART in still more dramatic and exiting way well into the future. As this relevant application of ART become increasingly utilised, it is an incumbent upon society to ensure that resources are made available in morally responsible and equitable manner.

Lab innovations

Probably the single most significant factor in the dramatic improvement in IVF pregnancy rate over the past 10-15 year has been the technological modifications and innovations in the embryology laboratories, culture media, optimised environment gases PH and other technique like assisted hatching.

Innovations in technologies evaluating embryos

Traditionally embryo morphology has been the most utilised method of determining embryo quality. There are numerous grading systems to grade embryo morphology. However, embryo morphology alone has been shown to be a suboptimal indicator of determining which embryo have normal chromosomal status or optimal implantation potential. For this reason, a variety of different modalities have been developed to evaluate embryo quality both directly and indirectly.

Conclusion

The use of ART has increased world wide and has made pregnancy possible for many infertile couples. However, women who conceived by ART are at higher risk of maternal and perinatal complications. Careful counselling of the couple who wish to conceive by ART is essential. All the complications should be explained to the couple. So, couple should be investigated thoroughly for the cause of infertility. Advanced and emergency obstetrics care should be available to women who conceived by ART.

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