Indian College of Obstetricians & Gynaecologists

ICOG Campus

High-Risk Pregnancy: Beyond Obstetrics

Recent Developments and Current Practice

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Pregnancy Post-assisted Reproductive Technology

Jigyasa Dengra

INTRODUCTION

Assisted reproductive technology (ART) is biggest research in field of medicine of the century. After the birth of the first in vitro fertilization (IVF) baby in 1978, it transformed from research to clinical treatment of infertile couples. Till today, >5 million births worldwide have been devoted to ART.[1]

The various conditions related to the mother and fetus whose incidence increases in ART pregnancies are multiple pregnancies, gestational diabetes mellitus (GDM), gestational hypertension, placenta previa, abruption, prelabor rupture of membrane (PROM), parturition premature imminent (PPI), preterm births, and low birth weight (LBW).

Increased risk of complications of antenatal, perinatal, neonatal period, resulting from high incidence of multiple gestation and manipulation involved in ART processes.[2]

MATERNAL COMPLICATIONS

Hypertensive Complications (Pregnancy-induced Hypertension and Preeclampsia)

These are common antenatal complications of ART pregnancies.[3,4] Risk of hypertensive complications is increased in pregnancy when cryopreserved embryos are transferred[5,6] and donor egg recipient IVF is associated with an increased risk of preeclampsia. The increased risk of preeclampsia in IVF pregnancies may be due to the impact of the IVF protocol on the maternal hormonal environment. The increased preeclampsia risk in IVF-conceived pregnancies may be partly attributable to the degree by which the IVF protocol impacts the maternal hormonal environment in the first trimester when the corpus luteum (CL) is a major source of reproductive hormones. While unassisted (spontaneous) pregnancies usually develop in the presence of one CL, IVF involves two extremes—either formation of supraphysiologic numbers of CL associated with ovarian stimulation in fresh IVF cycles or hypothalamic-pituitary suppression and absence of the CL in artificial, programmed cycles routinely used for donor egg recipients and frozen embryo transfer (FET). Although estradiol and progesterone are

replaced during a programmed FET or donor egg cycle in the first trimester, other vasoactive products of the CL which may be important for maternal cardiovascular adaptation to pregnancy, such as relaxin.

Gestational Diabetes Mellitus

Assisted reproductive technology raises the risk of GDM by 28%.[7] This risk is higher in IVF group than intracytoplasmic sperm injection (ICSI) groups for fresh transfer, than cryopreserved embryo transfer.[8] Meta-analysis of 29 studies by Sha et al. found that ART pregnancies with polycystic ovary syndrome (PCOS) have higher risk of developing GDM.[9] Multicenter studies are required to confirm the relation between IVF and the prevalence of GDM, whether this is attributed to preexisting medical conditions or the IVF technique itself.

Placental Abnormalities

These include placenta previa, abruption, and adherence. Increased incidence is due to ART procedures of intrauterine operation and manipulation of embryos, improper orientation, or implantation of the blastocyst, increased sensitivity of trophectodermal cells to epigenetic disturbances in preimplantation phase than inner cell mass causing abnormal development location and function of placenta, apart from that infertility and its causes (endometriosis, PCOS, etc.) also are the causes for abnormal placentation.[2,3]

The stage of embryo transfer increases risk of placental abnormalities. Blastocyst stage embryo transfer increases risk of placenta previa.[10] Spangmose et al. found a reduced rate of placenta previa rate when frozen embryos were used than fresh embryo transfer. This can be due to reduced endometrial stimulation when cryopreservation is used.[10] There is a rapidly increasing interest in placentation in obstetric adverse outcome, neonatal and adult life health after infertility, and its related therapies.

A recent meta-analysis of 50 cohort studies including 161,370 ART and 2,280,241 spontaneously conceived singleton pregnancies found increased risks for several obstetric complications. Significant worst outcomes regarded pregnancy-induced hypertension, placenta previa, abruption, antepartum hemorrhage, oligohydramnios, cesarean delivery, preterm birth, very low birth weight (VLBW), LBW, and perinatal mortality and morbidity.

Based on these observations, the main question to address is whether placental alterations (from macroscopic to molecular level) observed in treated infertile patients are the result of ART or if they originate from infertility itself **(Fig. 1)**. A deeper investigation of the underlying molecular basis of reduced placental functions in infertility condition and especially after ART treatment is then needed.

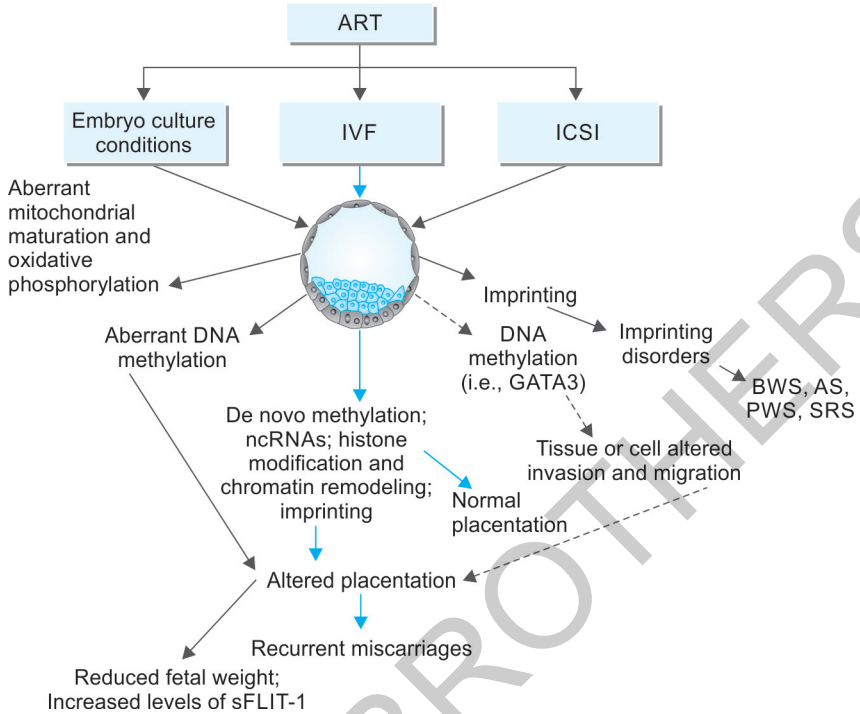

Fig. 1: Cascade of events in ART pregnancies leading to abnormal presentation and sequences. (ART: assisted reproductive technology; DNA: deoxyribonucleic acid; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilization)

Preimplantation genetic testing for aneuploidies (PGT-A) is an ART technique that is increasingly performed. Its aim is to discover if produced embryos are aneuploid and, in this case, they should not be transferred into the uterus, in order to prevent implantation failure and miscarriages. PGT-A preliminarily requires the in vitro development of embryos up to the blastocyst stage, in order to collect 5–10 trophoblast cells. Embryos are then frozen while waiting for the genetic analysis results. Embryos with no or few aneuploidies are thawed and transferred (FET) in the uterine cavity after endometrial hormonal preparation using estrogen and progesterone. In this condition, natural ovulation and formation of the CL are suppressed. Similar to PGT-A, preimplantation genetic test for monogenic diseases (PGT-M) allows to screen for embryos affected by monogenic diseases.

Some authors have expressed concerns on the possibility that trophectoderm biopsy might disturb embryo development, leading to potential adverse consequences on obstetric outcomes. It has been hypothesized that removal of cells from the tissue that will become the placenta does not affect embryo implantation rate but may negatively

influence later phases of placentation. Placenta-derived anomalies, such as placenta previa and accreta, hypertensive disorders of pregnancy (HDP), and fetal growth restriction (FGR) might be consequences of this abnormal placentation.

In a comparative study, investigating obstetric and neonatal outcome following PGT-A in blastocyst-stage biopsy with FET and cleavage-stage biopsy with fresh embryo transfer, Jing et al. (2016) found that PGT-A-FET was associated with a higher incidence of gestational hypertension (9.0% vs. 2.3%; $p = 0.017$). These data might indicate a higher risk of placental injury as a consequence of PGT-A procedure on the trophectoderm. Similar indications came from the results of a study on 345 singleton and 76 twin deliveries after PGT-M. PGT-M showed an increased risk of obstetric complications, when compared with pregnancies conceived spontaneously or by IVF without PGT.

Prelabor Rupture of Membrane

Shiqiao et al.'s retrospective case control study found that ART-ICSI increases the risk of PROM.[11]

Cesarean Delivery

Pregnancies following ART have a higher risk of adverse maternal and neonatal outcomes, which can explain the higher rate of emergent cesarean sections compared to spontaneous conceptions as IVF patients usually are of elder age, have complications associated with underlying medical conditions (diabetes and high blood pressure) or prior uterine surgeries.

However, provider or patient factors associated with a higher rate of elective caesarean section in ART pregnancies.[12]

Postpartum Hemorrhage

The risk of postpartum hemorrhage (PPH) is highest in ART pregnancies.[2,13]

The various retrospective studies show increased risk of PPH among women conceived through ART procedures was due to ART treatment themselves or maternal factors associated with infertility.[14]

Multiple Pregnancy

Assisted reproductive technology pregnancies are associated with multiple pregnancy and its adverse outcomes.[15] Given the increase in maternal and perinatal morbidity and mortality associated with twins and higher-order multifetal pregnancies, efforts should be made to limit multifetal pregnancies during ART. However, even when a single embryo is transferred, the risk of monozygotic twins is increased.

Venous Thromboembolism

Risk of venous thromboembolism (VTE) in pregnancy is doubled by ART. The risk is greater in the first trimester.[16]

PERINATAL COMPLICATIONS

Prematurity and Low Birth Weight

Preterm birth in ART pregnancy occurs even when male infertility is the sole cause. Preterm birth in female infertility caused the earliest deliveries.[17]

Higher rates were observed in the ART group. This could be due to twin pregnancies as they are one of the important factors in the complications for mother and newborns after ART.[2]

Single embryo transfer is the best approach to ensure a live and healthy child. However, increased risks for preterm birth are also associated with a singleton IVF pregnancy and should be discussed and contrasted with spontaneous conception. Increased preterm birth and other adverse pregnancy outcomes in singleton IVF cycles warrant investigations to elucidate and mitigate. Minimizing embryo manipulation during cell culture is recommended. Increased risk of preterm birth and other pregnancy complications in ART could reflect the underlying reasons for infertility. This information should be discussed and further explored.

Congenital Anomalies

Autologous oocytes, fresh embryos, and no ICSI conceptions had 18% more risk of having a major nonchromosomal congenital anomaly; with ICSI but without male factor, the risk was 30%; with male factor, 42% was the risk.[18]

Intracytoplasmic sperm injection has risks of using sperm with genetic abnormality;[19] sperm with structural abnormalities; risk of mechanical handling; and risks associated with bypassing natural process. Congenital heart defects are increased by threefold in children conceived with ICSI.

Several causes may be related with ART and birth defects. ART causes aneuploid cells to propagate in embryos and oocytes,[19] increased risks of genetic mutation in embryos, epigenetic errors, like DNA methylation and imprinting defects, causing increased risk of birth defects.[20-22]

StillBirth

Pregnancies achieved with IVF have a two- to threefold increased risk of stillbirth even after controlling for maternal age, parity, and multifetal gestations.

Zhu et al. compared maternal and neonatal outcomes in ART pregnancies with similar outcomes following spontaneously conceived births. They concluded that pregnancies conceived by ART were associated with a significantly increased incidence of GDM, gestational hypertension,

preeclampsia, intrahepatic cholestasis of pregnancy, placenta previa, placental abruption, preterm premature rupture of membranes, placental adherence, PPH, polyhydramnios, preterm labor (PTL), LBW, and small-for-date infant compared with spontaneously conceived births. Pregnancies conceived by ICSI showed similar elevated complications, except some of the difference narrowed or disappeared. Singleton pregnancies or nulliparous pregnancies following ART still exhibited increased maternal and neonatal complications.

MANAGEMENT OF ART CONCEIVED PREGNANCY

Assisted reproductive technology conceived pregnancies are managed on same principles as natural pregnancies, with an understanding of risks of such pregnancies and how best to monitor and manage them.[14,23] Such pregnancies need extra care as they need investment of money, time, emotions, and energy.

Women with ART pregnancies report higher levels of fears, such as fear of baby's death during pregnancy or labor or thereafter, diseases, malformations, prematurity, neonatal intensive care unit (NICU) admission, labor, and anxiety regarding their motherhood.[24]

They concentrate on maintaining pregnancy, suggesting that infertility lingers and affects these women's acceptance of motherhood. These feelings are heightened if previous treatments are unsuccessful.

Pharmacological Interventions

Low-dose aspirin, low molecular weight heparin, human chorionic gonadotropin (hCG), progesterone, and steroids may be used.[23]

Pregnancy-induced Hypertension and Preeclampsia

Assisted reproductive technology pregnancies should undergo a thorough assessment. High risk ones are started aspirin (150 mg) from 12 weeks till delivery.[25] Pregnancies in these cases, should undergo close maternal and fetal surveillance; every 3 weeks from 24 to 32 weeks of gestation, thereafter every 2 weeks. Low-dose aspirin in patients with an IVF pregnancy as the sole indication for preeclampsia prophylaxis is not recommended; however, if one or more additional risk factors are present, low-dose aspirin is recommended and if nuchal translucency (NT) scan is suggesting high risk for preeclampsia.

Gestational Diabetes Mellitus

All women, irrespective ART or natural conception, should undergo Diabetes in Pregnancy Study Group of India (DIPSI) test in the first visit and possibly in first trimester.

Venous Thromboembolism

First trimester prophylaxis is advised if there are added three risk factors, from 28 weeks onward, if there are two added risk factors. These include age >35 years, parity >3, body mass index (BMI) >30 kg/m^2, gross varicose veins, smoking, immobility, low risk thrombophilia, and multiple pregnancy. Others such as hyperemesis, long distance travel, systemic infection, and dehydration, surgery also increase the risk of VTE. The risk period is covered with thromboprophylaxis.[26]

Multifetal Gestation

When multifetal pregnancies do occur, counseling should be offered regarding the option of multifetal pregnancy reduction.

Multifetal pregnancy reduction has been shown to significantly reduce the risks of preterm birth, neonatal morbidity, and maternal complications.

Fetal chromosomal and structural abnormalities: ART pregnancies should undergo antenatal screening such as first trimester NT, nasal bone (NB), cell-free DNA (cfDNA) testing, and biochemical testing.

Screening tests need accurate gestational age, so it is important that estimated due date (EDD) is calculated from the date of oocyte pick-up (OPU).

Meta-analyses demonstrate associations between IVF/ICSI and congenital malformations, although it remains unclear if this association is due to infertility, factors associated with the procedure, or both. It is also difficult to distinguish the risk associated with IVF alone versus IVF with ICSI.

Therefore, a detailed obstetrical ultrasound examination should be performed for pregnancies achieved with IVF and ICSI.

Several studies report higher rates of total congenital heart disease (CHD) in the IVF/ICSI population compared with naturally occurring pregnancies, while other studies report that the incidence of CHD in IVF pregnancies without other risk factors is not significantly different from baseline population rates. The cost-effectiveness of routine screening for CHD in pregnancies following IVF has also been questioned. Therefore, fetal echocardiography be offered to patients with pregnancies achieved with IVF and ICSI.

Preterm Births

Assisted reproductive technology is a risk factor for PTL, but no added monitoring or treatment is useful in decreasing incidence of PTL in these pregnancies.[23] Meta-analysis of singleton pregnancies demonstrated that IVF is associated with higher odds of preterm delivery, LBW, and VLBW compared with naturally occurring pregnancies.

Preterm birth has been recognized for several decades as the primary independent cause of increased rates of several adverse neonatal outcomes, including neonatal encephalopathy and perinatal mortality, in IVF pregnancies.

Such risks are more than doubled in the presence of IVF twin gestations. Subfertility is also a major risk factor for prematurity. Although there may be an increased risk for spontaneous preterm birth with IVF pregnancies, the utility of serial cervical length measurement to screen for preterm birth risk is unknown when the sole indication is IVF. Visualization of the cervix at routine NT scan and 18 weeks of gestation anatomy assessment with either a transabdominal or endovaginal approach is recommended.

In addition, progesterone supplementation initiated for IVF cycles is not indicated after 12 weeks of gestation if it was solely initiated for IVF purposes without any other indication. Discontinuation of progesterone supplementation initiated for the sole purpose of IVF is recommended by 12 weeks.

Fetal Growth Restriction

An increased risk of small for gestational age (SGA) infants is documented for singleton IVF pregnancies. Meta-analyses have described a higher risk of SGA babies in IVF/ICSI pregnancies from fresh cycles compared with frozen cycles.

The optimal gestational ages for fetal growth scans and their frequency in the presence of additional risk factors (e.g., placental implantation anomalies or maternal age >40 years) are presently unknown.

An assessment of fetal growth in the third trimester for IVF pregnancies is suggested; however, serial growth ultrasounds are not recommended for the sole indication of IVF.

Stillbirth

Given the increased risk of stillbirth, weekly antenatal fetal surveillance beginning by 36 weeks of gestation for pregnancies achieved with IVF is suggested.

Placental complications: Management is essentially the same as a natural pregnancy.

Delivery and Labor

It is currently unknown whether elective delivery at 39 weeks reduces the risks of maternal morbidity and improves perinatal outcomes in IVF pregnancies compared with expectant management.

A systematic review revealed that in asymptomatic uncomplicated singleton gestations, induction of labor between 39 and 40 weeks does

not increase the risk of cesarean delivery compared with expectant management but does not reduce the rates of adverse perinatal outcomes, including perinatal death, low Apgar score at 5 minutes, or need for NICU admission.

In the absence of studies focused specifically on timing of delivery in IVF pregnancies, shared decision-making between patients and healthcare providers is recommended, when considering induction of labor at 39 weeks of gestation.

Elective cesarean section is not indicated for IVF per say but anxiety of having precious baby make patient and relative demand for the same.

In vitro fertilization is associated with an increased risk of adverse maternal and perinatal outcomes. However, evidence is limited regarding whether specific screening, diagnostic, or preventative interventions during pregnancy obviate or reduce such risks. Specific technical characteristics of IVF and the presence of underlying infertility affect the risks of adverse clinical outcomes. Therefore, individualization of care may be ideal for optimizing outcomes.

CONCLUSION

Assisted reproductive technology conceived pregnancy has a huge impact on the couple as well as the family in terms of emotions, financial burden, anxiety, and frequent visits. This makes it necessary for all clinicians to be well aware and educated about taking care of these pregnancies. ART is a long journey that does not end with successful pregnancy only, but with a healthy baby in hands of healthy mother.

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ICOG Campus

High-Risk Pregnancy: Beyond Obstetrics

Recent Developments and Current Practice

The book titled *ICOG Campus—High-Risk Pregnancy: Beyond Obstetrics* is aimed to provide a quick and practical approach to patients with various medical and surgical disorders which were not actually covered in all-time obstetrics books. The content is concise and evidence-based, covering the management and understanding of the complexities of the respective topics. As is said by Peter Decker "Learning is life long process", pregnancies are now possible after the treatment of complex situations which were previously life-threatening, so obstetricians have to manage these patients, keeping those conditions in mind. This book will surely serve as a guide for the management of such pregnancies and help practicing obstetricians in their clinical practice.

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