Review Article

# Perinatal Outcomes Following Assisted Reproductive Technology

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**Abstract**

As the use of routine assisted reproductive technology (ART) becomes widespread along with the extended applications such as ART with donor gametes, surrogacy, and preimplantation genetic testing (PGT), it becomes more pertinent to evaluate risks associated with them. Perinatal outcomes and long-term safety for the women and children are paramount. In this review, we aimed to detail the perinatal outcomes in relation to the ART procedures routinely applied as the extended applications of ART with a focus on singleton pregnancies. While there seems to be a higher risk of adverse perinatal outcomes with some of the ART procedures, the absolute risk increase is generally low. It is important for clinicians to have this knowledge to better counsel and care for their patients.

**Keywords:** *Assisted reproductive technology, low birth weight, perinatal outcomes, preterm birth*

## Introduction

The aim of assisted reproductive technology (ART) is to maximize success, along with safety both short and long term to the woman and the offspring. With ART being on the uprise, and more children being born as a result, there is more interest in the health outcomes of ART-conceived pregnancies and children. The single most important and yet avoidable adverse outcome following ART have been multiple pregnancies and multiple births resulting from the replacement of more than one embryo into the uterus. Multiple pregnancies are associated with significantly higher risks of adverse perinatal outcomes. Maternal complications include increased risk of pregnancy-induced hypertension, gestational diabetes, peripartum hemorrhage, and cesarean section.[1] Multiple pregnancies are also associated with a six-fold increase in the risk of preterm birth (PTB), which is a leading cause of infant mortality and long-term mental and physical disabilities, including cerebral palsy and chronic lung disease.[2]

There have, therefore, been concerted efforts by professional organizations and public policies to reduce multiple births following ART. Elective single embryo transfer (eSET) has been promoted as a first-line approach to reduce multiple pregnancies and has been on the rise in recent years.[3] This rise in eSET can be attributed to advances in ART technologies, particularly laboratory advances in better embryo selection as well as cryopreservation methods. However, ART singletons also have a higher risk of adverse perinatal outcomes compared to spontaneous conceptions. Singleton pregnancies following *in vitro* fertilization (IVF)/ intracytoplasmic sperm injection (ICSI) are associated with higher incidence of hypertensive disorders of pregnancy, gestational diabetes, PTB, low birth weight (LBW), small for gestational age (SGA), and perinatal mortality.[4] These risks are attributed to the underlying infertility in the women undergoing ART, to the ART procedures and techniques which may cause epigenetic modifications of the oocytes or embryos.[5]

In this review, we will focus on the various ART processes to elucidate the evidence for their contribution to perinatal risks in singleton pregnancies. We will address the routine ART practices such as ovarian stimulation use, IVF versus ICSI, cleavage versus blastocyst stage embryo transfer, fresh versus frozen embryo transfer, as well as expanding ART applications such as embryo biopsy with preimplantation genetic diagnosis (PGT), gamete donation, and surrogacy.

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## Ovarian Stimulation and Perinatal Outcomes

Ovarian stimulation is routinely used in ART to increase the efficacy. A large study comparing clinical outcomes following 6168 unstimulated IVF cycles versus 584,835 stimulated IVF cycles showed that as many as 3.5 IVF unstimulated cycles are needed to achieve the same live birth rate as one stimulated cycle, justifying the routine use of ovarian stimulation.[6] Although ovarian hyperstimulation syndrome (OHSS) is a serious iatrogenic risk following the use of ovarian stimulation, the progresses in controlled ovarian stimulation strategies, such as the use of gonadotropin-releasing hormone (GnRH) antagonist over GnRH agonist for pituitary suppression and the alternative GnRH agonist trigger over human chorionic gonadotropin trigger for final oocyte maturation have mitigated the risk. Moreover, the additional back up of freeze all strategy has further envisioned the concept of an OHSS-free clinic.[7]

In addition to the immediate ovarian hyperstimulation syndrome (OHSS) risk, there has been speculation regarding the long-term effects with the use of ovarian stimulation, which includes perinatal risks. A recent meta-analysis addressing the perinatal risks with the ovarian stimulation use in ART showed that stimulation use in ART was associated with a higher risk of PTB, <37 weeks gestation (risk ratio [RR]: 1.27, 95% confidence interval [CI]: 1.03–1.58) and LBW <2500 g (RR: 1.95, 95% CI: 1.03–3.67) compared to natural cycle or modified natural cycle IVF.[8] However, given that the absolute increase in the risk of the adverse perinatal outcomes is low, the use of ovarian stimulation in ART could be justified given the efficiency in improving ART success. Furthermore, a large cohort study addressing the association between ovarian response to stimulation quantified as the number of oocytes retrieved, and the risk of PTB or LBW found that the risk increase was noted only with a very high number of oocytes (>20) and not below this.[9] Compared to women who had a normal response defined as 10–15 oocytes retrieved women who had an excessive response with >20 oocytes had a significantly higher risk of PTB (odds ratio [OR]: 1.15, 95% CI: 1.03–1.28) and LBW (OR: 1.18, 95% CI: 1.06–1.31) in a fresh IVF cycle. Furthermore, a recent study demonstrated that supraphysiologic estradiol level in ovarian stimulation cycles affects the birth weight of neonates conceived through subsequent frozen-thawed cycles, a higher estradiol level being associated with an increased risk of LBW.[10] The findings of the study suggest that the supraphysiological estradiol levels have an effect beyond the endometrium. This evidence reiterates the importance of using safe stimulation protocols, avoiding excessive response, and reassures the safety of ovarian stimulation use.

## Perinatal Outcomes Following Intracytoplasmic Sperm Injection

The use of ICSI continues to be on the rise worldwide, and hence, it is of interest, whether ICSI alone poses any perinatal risks.[11-13] A large population-based cohort study from Denmark compared the neonatal outcomes of 446 children born following surgical sperm retrieval procedures such as testicular sperm extraction, testicular sperm aspiration, percutaneous epididymal sperm aspiration, and ICSI with control groups that included children born following ICSI with ejaculated sperm (8967), IVF (17,592), and spontaneous conceptions (63,854) during the same time period 1995–2009.[14] For singleton births, there was no significant difference in the risks of PTB following ICSI with testicular or epididymal sperm versus ICSI with ejaculated sperm (OR: 1.38, 95% CI: 0.66–2.85), ICSI with testicular or epididymal sperm versus conventional IVF (OR: 1.94, 95% CI: 0.70–5.38), and ICSI with testicular or epididymal sperm versus natural conceptions (OR: 1.02, 95% CI 0.60–1.74). There was no significant difference in the risks of LBW following ICSI with testicular or epididymal sperm versus ICSI with ejaculated sperm (OR: 1.00, 95% CI: 0.61–1.65), and ICSI with testicular or epididymal sperm versus conventional IVF (OR 1.28, 95% CI 0.68–2.40). The risk of LBW was higher following ICSI with testicular or epididymal sperm versus natural conceptions (OR: 0.58, 95% CI: 0.44–0.77). A retrospective cohort study comparing perinatal outcomes in singleton births following ICSI found no significant difference in PTB (OR: 1.17, 95% CI: 0.95–1.46) and LBW (OR: 1.14, 95% CI: 0.91–1.44) compared to natural conceptions.[15]

## Perinatal Outcomes Following Blastocyst Stage Transfers

The last decade has seen an exponential rise in blastocyst stage transfers in many countries, in efforts to reduce transfer of multiple embryos by enabling better embryo selection.[16] This change in practice from routine cleavage stage to blastocyst stage transfer has highlighted interest in perinatal and long-term outcomes with blastocyst transfer. A systematic review and meta-analysis showed singleton pregnancies following blastocyst stage transfers to be associated with a higher risk of PTB (adjusted OR (aOR): 1.32, 95% CI: 1.19–1.46).[17] The study also found a higher

risk of congenital anomalies following blastocyst stage transfer versus cleavage stage transfer (aOR: 1.29, 95% CI: 1.03–1.62). Some of the studies included in the systematic review had both fresh and frozen transfers. As it has been reported that frozen embryo transfer may have a protective effect against preterm delivery and these findings would merit validation from further studies as a recent population-based retrospective, Swedish registry-based study involving 4819 singletons after blastocyst transfer, 25,747 after cleavage stage transfer between the period 2002–2013 demonstrated no significant difference in the risk of PTB (aOR: 1.12, 95% CI: 0.99–1.27), a lower risk of LBW (aOR: 0.83, 95% CI: 0.71–0.97), higher perinatal mortality with blastocyst transfer, and no increased risk of birth defects (aOR: 0.94, 95% CI: 0.79–1.13).[18,19] A recent large study has shown a significantly higher rate of monozygotic twinning following blastocyst compared to cleavage-stage transfers.[20]

## Perinatal Outcomes Following Fresh Versus Frozen Transfers

The debate on fresh versus frozen embryo transfer as the first line has been a topic of much debate recently. Alongside clinical outcomes such as live birth and ovarian hyperstimulation (OHSS rates), there has been an interest in the perinatal outcomes. Evidence from a systematic review suggests that transfers of frozen embryos are associated with a lower risk of PTB (RR: 0.84, 95% CI: 0.78–0.90), SGA (RR: 0.45, 95% CI: 0.30–0.66), and LBW (RR: 0.69, 95% CI: 0.62–0.76), while another cohort study reported a higher risk of high birth weight (HBW) (adjusted RR: 1.64, 99.5% CI: 1.53–1.76) following frozen transfers compared to fresh transfers.[18,21] The systematic review included mainly observational studies. There is also evidence emerging from randomized controlled trials of frozen transfers resulting in HBW singletons.[22]

## Perinatal Outcomes Following Oocyte Donation Assisted Reproductive Technology

Oocyte donation (OD) is an alternative treatment option instead of autologous IVF in women of advanced age and is associated with a higher success rate.[23] Over the years, there has been an increase in a number of OD cycles performed across the world.[12,24] Pregnancies following OD have been associated with a higher risk of adverse obstetric and perinatal outcomes compared to pregnancies following spontaneous conceptions, and these poor outcomes have been attributed to a higher prevalence of hypertensive disorders during OD pregnancies.[25,26] The reason for the higher risk of hypertensive disorders in OD pregnancies could be linked to an immunological maladaptation to foreign antigens arising from the fetus.[27]

A large cohort study from the UK evaluated the perinatal outcomes following OD and autologous IVF and included 4248 OD and 95,844 autologous singleton births.[28] The risk of PTB (aOR: 1.56, 99.5% CI: 1.34–1.80) and LBW (aOR: 1.43, 99.5% CI: 1.24–1.66) were significantly higher following OD compared to autologous IVF singleton after adjusting for potential confounders such as age and parity. An earlier systematic review compared perinatal outcomes in singletons after OD compared to autologous IVF and included 35 studies. The authors found a higher risk of PTB (aOR: 1.75, 95% CI: 1.39–2.20) and LBW (aOR: 1.53, 95% CI: 1.16–2.01) following OD compared to autologous IVF.[29]

## Perinatal Outcomes Following Surrogacy

There has been an increase in a number of surrogacy cycles in certain regions across the world due to rise in surrogacy tourism and legalizing of the surrogacy in certain countries. While the pregnancies following OD have been associated with adverse perinatal outcomes, there is a paucity of data regarding perinatal outcomes following surrogacy. An earlier study involving the SART database found no significant increase in the risk of PTB (aOR: 1.01, 95% CI: 0.87–1.18) and a lower risk of LBW (aOR: 0.71, 95% CI: 0.57–0.88) with singleton pregnancies following surrogacy.[30] Another cohort study, which analyzed the HFEA database did not find any significant difference in the risk of PTB (aOR: 0.90, 95% CI: 0.56–1.42) and LBW (aOR: 0.90, 95% CI: 0.57–1.43) between pregnancies following surrogacy compared to autologous fresh IVF cycle.[31]

## Perinatal Outcomes Following Embryo Biopsy for Preimplantation Genetic Testing

Preimplantation genetic testing involves a biopsy of the embryos either at the cleavage or blastocyst stage, and whether such manipulation affects perinatal outcomes has been addressed by studies. A cohort study from HFEA database did not find any increased risk of PTB (aOR: 0.66, 95% CI: 0.45–0.98) or LBW (aOR: 0.58, 95% CI: 0.38–0.88) following PGT compared to autologous IVF.[32] Another study, which followed up 995 children born following PGT, also did not find any increased risk of adverse perinatal and neonatal outcomes.[33]

## Conclusion

Overall, ART appears safe in terms of perinatal outcomes. Although some procedures are associated with perinatal risks, the absolute risk increase should be considered, and patients counseled accordingly, to allay overriding concerns. It is currently uncertain whether the perinatal outcomes bear long-term consequences. As the long-term outcomes of ART are still unraveling, such consequences need to be studied further.

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### Conflicts of interest

There are no conflicts of interest.

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