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Review Article

Perinatal Outcomes of Children Born After Assisted Reproduction Technology: A Review

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Abstract

The Assisted Reproduction Technology (ART) as an effective method of infertility treatment is used worldwide. With the increase of offspring from ART, the security of ART gets more attention. Children born after ART are associated with a higher rate of adverse perinatal outcomes, such as preterm birth, low birth weight and small for gestational age. The mechanism is not yet clear; however potential infertility background, ART procedures and ovarian stimulation may be the cause of adverse perinatal outcome. Couples seeing for ART should be counseled about the increased risk of adverse outcomes and the prenatal diagnosis should be improved to prognosis of ART pregnancies. In this review, we will discuss the perinatal outcomes of offspring from ART and its possible explanatory factors, to provide the possible method for the safe of clinical work.

Keywords: Assisted reproduction technology; Perinatal outcomes; Sub fertility; Ovarian stimulation

Introduction

Assisted Reproductive Technology (ART) which is available in the vast majority of countries offers hope to sub fertile couples worldwide. To date, at least 5 million children have been born after ART treatment [1]. With the development of the assisted reproductive technology, there are more and more concern about potential risks to these children.

In recent years, evidence has emerged that ART pregnancies are at an increased risk of adverse outcomes compared with spontaneously conceived children, such as prematurity and low birth weight [2]. As we all know, multiple pregnancies have a higher risk of Preterm Birth (PTB), Low-Birth Weight (LBW), being Small for Gestational Age (SGA). However, studies have suggested that twin pregnancies conceived with the assistance of IVF were at increased risk for gestational diabetes mellitus and SGA [3]. Regarding ART-conceived singleton pregnancies, current evidences suggest that the adverse perinatal risks are still increased [4,5].

The reasons for the adverse outcomes are not known, however, potential infertility background, ART procedures, and ovarian stimulation may be the cause of adverse outcomes of offspring from ART. Further understanding of the outcome of assisted reproduction which distinguishes between outcomes that may be the result of ART and those resulting from underlying infertility is needed.

Perinatal Outcomes

It is well documented that there is a higher proportion of multiple pregnancies in ART pregnancies and multiple gestation is associated with increased risk of adverse perinatal outcomes. Therefore, the strategy of Elective Single Embryo Transfer (eSET) and additional cycles with transfer of frozen/thawed embryos which has to a large extent decrease the incidence of multiple pregnancies is now used in many countries [6]. However, current evidences suggest that risks are increased even in singleton ART pregnancies. For example, data from a meta-analysis by Pandey et al. [7] found that compared with Spontaneous Conceptions (SC), IVF/ICSI singleton pregnancies were associated with significantly higher odds of preterm delivery (Odds Ratio [OR] 1.54, 95% Confidence Interval [CI] 1.47–1.62), Low Birth Weight (LBW; OR 1.65, 95% CI 1.56–1.75), and Small for Gestational Age (SGA; OR 1.39, 95% CI 1.27–1.53). Pinborg et al. [8] had similar findings with a higher preterm delivery rate of IVF/ICSI pregnancies (OR 1.27, 95% CI 1.08–1.49).

The multifactorial reasons for the increase in adverse outcomes with ART are not known. One hypothesis is that underlying infertility-related diagnoses of the women who undergo ART contribute directly to the adverse outcomes. Another possibility is that the ART itself (including embryo culture, embryo cryo-preservation, etc.) could have negative impacts on the ART offspring. Moreover, the influence of ovarian hyper stimulation on the perinatal outcome should not be neglected. Further understanding of the affecting factors and their impaction will not only be beneficial for informative counseling of couples seeking ART treatment, but is also in the interest of children born after assisted reproduction.

Factors Related with Adverse Outcome

Sub fertility

Recently, evidence has emerged that sub fertility itself is one major risk factor for adverse perinatal outcome in ART singletons [9,10]. Several groups have demonstrated that many of the adverse outcomes for ART are also seen in the non-ART offspring, suggesting that underlying infertility can result in adverse perinatal outcomes and that these occur even in the absence of ART treatment. A large longitudinal cohort study compared birth outcomes of women treated with ART, women with indicators of sub fertility but without ART, and fertile women found that the risks for both preterm birth and low birth weight were higher in both the ART and the sub fertile group compared with the fertile group and the risks were higher in ART *vs.* the sub fertile group [11]. Hayashi et al. [12] compared the perinatal

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outcomes of singleton pregnancies conceived after IVF/ICSI, IUI and ovulation stimulation respectively with those of naturally conceived pregnancies, and found that there is an increased risk of adverse perinatal outcomes in the former three groups which is independent of the type of treatment, suggesting that maternal factors associated with infertility may contribute to such adverse outcomes rather than the type of ART procedure used. Moreover, the meta-analysis by Pinborg et al. [8] compared perinatal outcomes of SC in couples with time to pregnancy >1 year versus SC singletons in couples with time to pregnancy ≤ 1 year, found that there is a higher risk for preterm birth sub fertile couples (OR 1.35, 95% CI 1.22–1.50).

IVF procedures

With the rapid development of ART and its derivative technology, more and more people have focused on the safety of the assisted reproduction technology itself, including IVF, Intra-Cytoplasmic Sperm Injection (ICSI), embryo freeze–thawing, *in vitro* embryo culture and so on.

Regarding concerns about ICSI, which including ICSI with ejaculated sperm, PESA (Percutaneous Epididymal Sperm Aspiration) and TESA (Testicular Sperm Aspiration), Morken NH et al. [13] found that IVF pregnancies were at increased risk of preterm delivery when compared to ICSI pregnancies, and this concern was supported by the meta-analysis by Pinborg et al. [8]. In a population-based cohort study in Denmark from 1995 to 2009, neonatal outcomes were compared between children conceived by ICSI with epididymal sperm and ICSI with ejaculated sperm, IVF and NC, and the neonatal outcome for children conceived by ICSI with epididymal sperm was found to be similar to that of children conceived by ICSI with ejaculated sperm [14].

Several meta-analyses have concluded that pregnancies arising from the transfer of frozen thawed IVF embryos seem to have better perinatal outcomes. A meta-analysis by Maheshwari A et al. [15] suggested that singleton pregnancies after the transfer of frozen thawed embryos were associated with better perinatal outcomes compared with those after fresh IVF embryos, the Relative Risks (RR) and 95% Confidence Intervals (CI) of preterm birth (RR = 0.84, 95% CI 0.78-0.90), small for gestational age (RR = 0.45, 95% CI 0.30-0.66), low birth weight (RR = 0.69, 95% CI 0.62-0.76), and perinatal mortality (RR = 0.68, 95% CI 0.48-0.96) were lower in women who received frozen embryos. Ishihara O et al. [16] more recently, had similar findings that Frozen-Thawed Embryo Transfer (FET) was associated with a significantly reduced occurrence of PTB, LBW, and SGA. The reasons for better outcomes for frozen ET cycles compared with fresh ET are not known. It has been suggested that a more natural uterine environment that occurs in a frozen replacement cycle is favorable for early placentation and embryogenesis, whereas ovarian stimulation in fresh cycles alter endometrial angiogenesis and implantation. Another explanation is that the procedure of embryo freezing and thawing may filter out weaker embryos.

As far as *in vitro* embryo culture is concerned, both the type of culture medium used as well as the duration of culture is reported to be implicated. So far, the answer on whether different types of culture medium and the duration of culture are affecting singleton birth weight differentially is still controversial. According to Eskildet al. [17], a significantly lower birth weight was obtained using Medicult ISM1 when compared with Medicult Universal or Vitrolife G-1 PLUS, even after a limited culture period of 1 or 2 days. However, a prospective study and a retrospective study did not confirm any relationship between the medium used for *in vitro* culture and the birth weight of singletons born after IVF/ICSI [18,19]. Moreover, a large retrospective analysis performed by De Vos A [20] found that in a comparison of two culture media, neither the medium nor the duration of culture (Day 3 *vs.* Day 5 blastocyst transfer) had any effect on mean singleton birth weight. It's important to know, however, that a meta-analysis by Maheshwari [15] showed that ET at the blastocyst stage was associated with a higher risk of very preterm delivery (RR 1.27; 95% CI 1.22-1.31) in comparison with those resulting from the transfer of cleavage-stage embryos.

Ovarian stimulation

As a result of ovarian stimulation, there is a much higher level of estrogen and progesterone which can affect embryo implantation. Whether perinatal outcomes of ART children are influenced by the high concentration of estrogen and progesterone is a question to be answered.

A study focused on the relationship between elevated peak serum estradiol levels during controlled ovarian hyperstimulation with perinatal outcomes of Singleton live-birth pregnancies conceived after fresh IVF-ET found that peak serum estradiol level during controlled ovarian hyperstimulation is associated with increased risk of small for gestational age and preeclampsia in singleton pregnancies after *in vitro* fertilization [21]. In a National cohort Danish study including 6,338 singletons born after intrauterine insemination, perinatal outcomes of children born after IUI were compared with children born after IVF/ICSI, trying to assess the effect of parental factors and ovarian stimulation. The study found that singletons born after IUI had higher risk of adverse perinatal outcomes compared with SC children, similar to ICSI, but favorable outcomes compared with IVF. This difference may be related to the fact that the IUI group overall is less sub fertile than the IVF group and the ovarian stimulation is milder. As the study could not identify the potential influence of sub fertile background, we could not conclude that the increased risks of IUI children were related to ovarian stimulation [22]. Another finding in this study is that stimulation with clomiphene citrate was associated with higher risk of SGA compare d with natural-cycle IUI, but follicle-stimulating hormone treatment did not seem to be associated with adverse outcomes. In another study by Luke B, the perinatal outcomes were compared between women with or with no OHSS, and found that women with OHSS were associated with increased risk of LBW.

Conclusion

In summary, children born from ART are associated with an increase risk of PTB, LBW, and SGA. The mechanism is not clear yet, but potential sub fertility background of sub fertile couples plays an important role. Couples considering fertility treatment should be counseled about the increased risk of adverse outcomes, and examined carefully to find the potential sub fertile factors. Current evidence supports that multiple gestation is associated with increased risk of adverse perinatal outcomes, thus, eSET is suggested to decrease the incidence of multiple pregnancy. Considering the potential influence of ovarian stimulation, we suggest mild stimulation. There

is moderate quality of evidence that pregnancies arising from the transfer of frozen thawed IVF embryos seem to have better perinatal outcomes. Additionally embryo culture may also exert an influence on outcome. However, distinguishing the influence of each of these parameters is still a difficult task.

Thus, further research and long-term follow-up is crucial in fully understanding the outcome of assisted reproduction, which will not only be beneficial for informative counseling of couples seeking ART treatment, but is also in the interest of current and future children born after assisted reproduction.

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