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Neonatal outcomes of Offspring Conceived through In Vitro Fertilization

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Abstract

There has been a dramatic rise in the use of Assisted Reproductive Technologies (ART), including In Vitro Fertilization (IVF) throughout the world over the past three decades. Because they represent >1% of the birth cohorts in many developed countries, much attention is being paid to the health and well-being of ART children. Children born after ART have an increased risk of several adverse perinatal outcomes compared with their naturally conceived peers. Morbidity in this particular group of neonates pertains mostly to multiple gestation and prematurity. Morbidities more specific to ART/IVF have however been noted such as elevated risks of congenital malformations and Imprinting Disorders (IDs). Since many factors can potentially influence the neonatal outcome such as risks associated with the ART procedures themselves, advanced parental age, higher incidence of maternal nulliparity and underlying cause of parental subfertility among others, the exact pathological role played by ARTs in the occurrence of congenital malformations and genetic disorders is still unclear. In this review we aim to discuss the important epidemiological aspects of ART/IVF and the neonatal outcomes of IVF-conceived offspring.

***Key Words*:** China, In Vitro Fertilization, Neonatal, Offspring Conceived.

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Introduction

Assisted reproduction technology (ART) refers to all treatments or procedures that include the in vitro handling of both human oocytes and sperm or of embryos for the purpose of establishing a pregnancy (1). The primary purpose of ART is the treatment of infertility and the conception and safe delivery of healthy children with the potential to become healthy adults (2). The most frequently used ART technique is in vitro fertilization (IVF), a procedure that involves extracorporeal fertilization, sometimes called the "test tube baby procedure"(1, 3). With conventional IVF, eggs and sperm are mixed in a petri dish in the laboratory and allowed to achieve fertilization without assistance (3). Intracytoplasmic Sperm Injection (ICSI) is a treatment variation within IVF in which a single spermatozoon is injected into the oocyte cytoplasm (1). Because each egg is fertilized by injection with a single sperm, the natural selection process that occurs during conception is bypassed with ICSI, which raises particular concerns for potential offspring (3).

Epidemiological facts

Since the birth of the first baby conceived by in vitro fertilization more than 30 years ago (Louise Brown in 1978), the combination of improving success rates and increasing demand for treatment has led to a dramatic rise in the number of infants born utilizing ART. Today, well over 5 million babies worldwide have been born by medical interventions and the number of ART babies is steadily growing with approximately 1% to 4% of the current births in developed countries conceived by IVF (4, 5).

According to the latest International Committee for Monitoring Assisted Reproductive Technologies (ICMART) report for ART conceptions of year 2006 (published in year 2014), a total of >1 050 300 ART cycles initiated in 2352 clinics in 56 countries resulted in an estimated >256 668 babies in the year 2006 (6). The latest data concerning ART conceptions throughout the United States (US) (published in the year 2014) revealed that in the year 2011, a total of 151,923 ART procedures performed in 451 U.S. fertility clinics were reported to Centers for Disease Control and Prevention (CDC). These procedures resulted in 47,818 live-birth deliveries and 61,610 infants (7). These values show an increase compared to the national US data for the year 2010, which stated that a total of 147,260 ART procedures performed in 443 U.S. fertility clinics were reported to CDC in 2010 and these procedures resulted in 47,090 live-birth deliveries and 61,564 infants (8).

In contrast to developed countries, assisted reproductive technology (ART) were not offered in China until the mid-1980s with the first in vitro fertilization (IVF) infant born in Taiwan in 1985, then Hong Kong in 1986, and mainland China in 1988, respectively. Since those inceptions, the practice of ART in China has evoked a variety of social, cultural, political and one-child policy responses that have resulted in restrictions on the number of IVF cycles performed annually (9).

A recent epidemiology study estimated that 10-12% of men (45 million) suffer from male infertility, with a higher incidence of infertility in men residing in rural areas (15%) compared to their urban counterparts (10%).

The study also concluded that 15% to 20% of the women of reproductive age in China suffer from infertility. That percentage translates into 40-50 million women, many of whom are demanding treatment, yet have limited access to ART facilities, especially in western area of China. Exposure to radiation, pesticides and other environmental pollutants as well as work-related stress and unhealthy

lifestyles are believed to contribute to the increasing incidence of infertility in China (9).

Factors affecting neonatal outcomes in IVF-conceived offspring

There are a range of possible factors associated with ART treatment that may contribute to potential adverse outcomes. These factors include the relatively advanced age of infertile couples seeking ART, and the underlying causes of their infertility (10). There is increasing evidence that infertility or subfertility is an independent risk factor for obstetrical complications and adverse perinatal outcomes, even without the addition of assisted human reproduction (11). Human manipulations of the egg and sperm, fertility drugs, and effects of embryo culture and transfer also have the potential to affect the growing fetus (3). Other factors affecting outcome of assisted reproduction include the level of basal follicle-stimulating hormone, the number of embryos or gametes transferred, response to ovarian stimulation, and the quality of gametes and eventually of the embryo (12).

Neonatal Outcomes in IVF-conceived offspring

Numerous studies conducted in China and other countries have explored the type and incidence of ART-related side effects in offspring. Although most studies of ART offspring to date have demonstrated no added risk for developmental problems, potential difficulties for children born after ART include issues such as multiple gestation and prematurity and elevated risks of birth defects and genetic disorders.

I. Multiple gestation and prematurity

Women who undergo ART procedures are more likely to deliver multiple-birth infants than those who conceive naturally because more than one embryo might be transferred during a procedure (7). Multiple pregnancy is the most powerful predictive factor for adverse maternal, obstetrical, and perinatal outcomes (11).
Low birth weight and pre-term delivery are the most important factors accounting for the excess in perinatal mortality and morbidity in multiple pregnancies compared to singletons (13). According to the latest national U.S. report, ART contributed to 1.5% of U.S. births in the year 2011. ART conceptions are associated with higher rates of multiple pregnancy compared to the natural conceptions. Among infants conceived with ART in the U.S. in 2011, 45.6% were born in multiple-birth deliveries compared with only 3.4% of infants among all births in the general population. Approximately 43% of ART-conceived infants were twins, and 3% were triplets and higher order infants (7). The rates of low birthweight and preterm infants were disproportionately higher among ART infants than in the birth population overall. Overall, among ART-conceived infants, 31% were low birthweight compared with 8.1% among all infants; 5.7% of ART infants were very low birthweight compared with 1.4% among all infants. Overall, among infants conceived with ART, 36.2% were born preterm, compared with 11.8% among all infants born in the general population; 6.7% of ART infants were born very preterm, compared with 1.9% among all infants born in the general population (7).

In a series of 26 656 ART deliveries, it was found that as the number of fetuses increases, the duration of gestation decreases with a mean of 3 weeks per additional fetus. Preterm delivery occurred in 95.9% of triplet pregnancies (mean gestational age 32.7 weeks) and 53.8% of twin deliveries (mean gestational age 35.6 weeks). Very Low Birth Weight (VLBW)

(<1500 g) occur respectively 5 and 17-fold more often in twin and triplet pregnancies (13).
Preterm delivery puts the babies at risk of all the conditions associated with prematurity including intraventricular hemorrhage, Periventricular Leukomalacia (PVL), necrotizing enterocolitis, retinopathy of prematurity, and respiratory distress syndrome, all of which may result in long-term morbidity, for example cerebral palsy associated with PVL and mortality (14).

The neonatal mortality rate of twins is six to seven times that of singleton pregnancies, at 18 per 1000 live births, whereas the neonatal mortality of triplets and higher order multiples reaches 39.6 per 100 live births. The main reason for the elevated perinatal mortality rate seen in multiple pregnancies is the effects of preterm birth (15).

The risk of congenital anomalies is higher in multiple pregnancy and includes an increased risk of fetal trisomies, neural tube defects and structural malformations of the gastrointestinal tract (16). A recent European multicenter epidemiological study of 5.3 million births from 1984 to 2007 found the risk of congenital anomalies to be 27% higher in multiple than in singleton births [RR: l.27; 95% confidence interval (CI): 1.24-1.3] (17).

The excess risk of cerebral palsy in multiples compared to singletons is now well established. Twin babies have been reported to be four times more likely and triplets 18 times more likely to have cerebral palsy compared with singleton babies (15). The overall stillbirth rate is increased with multiple pregnancies at 12.3 per 1000 twin births and 31.1 per 1000 triplet births compared with 5 per 1000 in singleton births (18).

Conception by ART might pose an additional level of risk in the already vulnerable population of twin and triplet pregnancies. Apart from the overall complications of a twin pregnancy per se, ART twin pregnancies usually have additional obstetric risk factors including advanced maternal age, nulliparity, differing etiologies of infertility, fertility medications and interventions associated with infertility investigation/ treatment which may represent potential risk factors for increased perinatal morbidity (15).

Evidence on pregnancy outcomes of twins conceived by ART compared with naturally conceived twins is however conflicting. Most reports suggest that the maternal and neonatal outcomes of ART twins are comparable to that of naturally conceived twins (19-21). Helmerhorst et al. (21) produced a systematic review of 25 studies (17 matched and eight non-matched controls, 3437 assisted and 3429 naturally conceived twins) published from 1985 to 2002 which showed that compared with singleton pregnancies from assisted reproduction (who had significantly worse perinatal outcome than spontaneously conceived singleton pregnancies), ART twins had similar outcomes to those naturally conceived. The review indicated that ART twins had a 40% reduction in the perinatal mortality rate compared with naturally conceived twins (RR: 0.58; 95% CI: 0.44-0.77).

Other more recent studies have on the other hand shown higher rates of morbidity in ART twins compared to non-ART twins. Mothers bearing ART conceived twins had higher rates of Cesarean section (22-24). A meta-analysis showed that compared with spontaneously conceived twins who were matched for maternal age, in vitro fertilization twins have an increased risk of preterm birth between 32 and 36 weeks of gestation (odds ratio, 1.48; 95% CI, 1.05-2.10), and an elevated risk of preterm birth at <37 weeks of gestation when parity is also matched for an odds ratio of 1.57 (95% CI, 1.01-2.44) (23).

Another recent study demonstrated that ART conceived twins were more likely to have Respiratory Distress Syndrome (RDS), secondary to an increase in moderate prematurity in the ART conceived twins compared to spontaneously conceived twins (22). Another study also demonstrated higher rates of prematurity and longer hospital stay in ART twins compared to non-ART twins (24).

To avoid such drawbacks, a policy of elective Single Embryo Transfer (eSET) has been developed by many countries (25). As per the recommendations of the Society of Obstetricians and Gynecologists of Canada, the benefits and cumulative pregnancy rates of elective single embryo transfer support a policy of using this protocol in couples with good prognosis for success, and elective single embryo transfer should be strongly encouraged in this population (11).

I. Low birth weight and Intra-uterine growth restriction(IUGR) in IVF-conceived singletons

Evidence clearly shows that in singleton pregnancies conceived by IVF/ICSI there are increased obstetric and perinatal complications compared with naturally conceived singletons. A recent meta-analysis comparing the perinatal outcomes of singletons born after IVF/ICSI to outcomes of spontaneously conceived singletons showed higher morbidity in the IVF/ICSI group, with higher risk of Caesarean section (1.56, 1.51-1.60), low birthweight (1.65, 1.56-1.75), perinatal mortality (1.87, 1.48-2.37), preterm delivery (1.54, 1.47-1.62) and small for gestational age (1.39, 1.27-1.53)(26). These findings are in accordance with 3 previous meta-analyses and systematic reviews which showed similar higher morbidity in IVF singletons compared to spontaneously conceived singletons (21, 27, 28). It has moreover been reported that among singleton infants born at 37 weeks of gestation or later, those conceived with assisted reproductive technology had a risk of low birth weight that was 2.6 times that in the general population (95 % confidence interval, 2.4 to 2.7)(29).

II. Congenital malformations and genetic disorders

Since the first child conceived by assisted reproductive technology (ART) was born, concern has risen as to the safety of the methods. From the literature it is well known that ART children are at increased risk of congenital malformations even after adjustment for known confounders such as maternal age (30). A recent meta-analysis including 45 cohort studies showed that ART infants (n = 92 671) had a higher risk of birth defects [Relative risk (RR), 1.32, 95% confidence interval (CI), 1.24-1.42] compared with naturally conceived infants (n = 3 870 760). The risk further increased when data were restricted to major birth defects (RR, 1.42, 95% CI, 1.29-1.56) or singletons only (RR 1.36, 95% CI 1.30-1.43). The results for ART multiples were less clear. When all data for multiples were pooled the RR estimate was 1.11 (95% CI, 0.98-1.26) but this increased to 1.26 (0.99-1.60) when the analysis was restricted to studies of ART twins where some adjustment was made for differences in zygosity distribution between ART and non-ART multiples (31). On the other hand, the first large-scale report of birth defects in 15,405 offspring conceived by ART in China found that infants born after IVF/ICSI have a birth defect frequency comparable to that in the general Chinese population (32).

Among the pathologies which have been found to be more specifically associated with ARTs are hypospadias, congenital heart diseases and imprinting disorders. Hypospadias is the only organ system in which Odds Ratio (OR) has been consistently shown to be increased. An

odds ratio of 3.0 (95% CI: 1.09-6.50) was reported by Wennerholm et al. (33) and 1.5 (95% CI: 1.0-2.1) by Ericson and Kallen (34). Klemetti et al. (35) also showed increased hypospadias. A potential explanation for increased hypospadias in ART is heritable low testosterone, also adversely affecting spermatogenesis (36). With ICSI the frequency of sex chromosomal abnormalities appears increased in prenatal samples (amniocentesis) as well as hypospadias (33-35).

The only other organ system seriously implicated is cardiac. Sala et al. (37) found a significant increase, but in general other authors have found no increase. Special pitfalls exist in assessing cardiac anomalies. A patent ductus arteriosus is normal at birth, but soon closes in full-term infants; in premature infants persistence is normal, and surgical ligation is routine(36). Specific associations have been found to exist between ART and subcategories of Congenital Heart Defects (CHD) (38). Tararbit et al. (39) found that ARTs (all methods combined) were associated with a 2.4-fold higher odds of Tetralogy of Fallot (TOF) after adjustment for maternal characteristics, paternal age and year of birth [adjusted odds ratios (OR): 2.4, 95% confidence interval (CI): 1.5–3.7] with the highest risk associated with ICSI (adjusted OR: 3.0, 95% CI: 1.0–8.9). No statistically significant associations were found for the other CHDs investigated, which included hypoplastic left heart syndrome, transposition of great arteries, and coarctation of the aorta. The same group of researchers later investigated the potential confounding role of multiple pregnancies on the occurrence of TOF in ART-conceived neonates but found that by far, most of the higher risk of TOF associated with ART is a direct effect and only a small proportion of the effect may be mediated by multiple pregnancies (40).

Many factors have been suggested to explain the higher incidence of congenital malformations in ART-conceived offspring. A plethora of variables in ART technology (vicissitudes of culture media; ovulation stimulation) could perturb embryonic differentiation through altered gene expression (36). Parental subfertility has however been suggested to be the most likely cause of increased frequency of birth defects in ART (41). This implication is based on several studies showing higher frequency of birth defects in subfertile couples who conceived naturally (42-44).

Particularities of ICSI conceptions with regards to birth defects

With the introduction of ICSI in 1992, even severe male subfertility could be treated successfully (45). From the very beginning, ICSI was considered a more risky procedure. From the point of view of perinatal health, there are major differences between IVF and ICSI in both patient selection and the techniques themselves. Two types of risks are to be considered: ICSI procedure-dependent and ICSI procedure-independent risk factors (46, 47). Procedure dependent risks are caused by the procedure itself, involving the penetration of the zona pellucida and oocyte cytoplasm. Procedure-independent risks are related to the cause of infertility, leading to the use of spermatozoa that normally cannot achieve fertilization (48).

The incidence of Y-chromosome deletions and other chromosomal anomalies is increased in males with poor semen quality (49). Several studies have shown that children conceived by ICSI are at increased risk of inherent and de novo chromosomal aberrations (50-52). Further, a higher rate of urogenital malformations, primarily hypospadias, which has been related to paternal infertility, has been reported (46, 53).

When considering overall birth defects, 2 meta-analyses have raised the question of whether birth defects are more common in ICSI versus IVF infants but showed no statistically significant differences (54, 55). Lie et al. included four studies and reached a pooled estimate of 1.12 (95% CI, 0.97–1.28) (55). Wen et al.(54) reported a pooled estimate of 1.05 in IVF versus ICSI after including 24 studies and a reverse pooled estimate of 0.95 (95% CI, 0.83–1.10) in ICSI compared with IVF infants. In conclusion, sex chromosomal abnormalities and hypospadias are considered increased in ICSI compared with IVF alone (36).

Imprinting disorders

Genomic imprinting is a specialized epigenetic mechanism that silences one parental allele, while enabling gene expression from the other parental allele (56). Genomic imprinting is required for normal development, and disrupted imprinting is associated with significant pathologies including Angelman syndrome, Prader–Willi Syndrome (PWS), and Beckwith–Wiedemann Syndrome (BWS) (57, 58).

Within the last decade, several studies have raised concerns that assisted reproductive technologies (ARTs) may result in abnormal genomic imprinting, leading to an increased frequency of imprinting-related disorders in children born as a result of infertility treatment (57).

ART-related manipulations to oocytes and embryos, such as follicular stimulation, intracytoplasmic sperm injection (ICSI), and embryo culture, coincide with the timing of epigenetic reprogramming and sex-specific imprint acquisition. ART procedures may affect methylation status of imprinted regions in the DNA, leading to imprinting disorders (57).

Several reviews have noted the correlation of an increased incidence of some normally very rare imprinting disorders in the babies born after ART, including Beckwith– Wiedemann syndrome, Angelman syndrome and Silver–Russell syndrome, but not Prader–Willi syndrome (59-61).

In a case–control study in the USA, BWS was found to be six fold more frequent in patients born after ART than after natural conception (61). This has also been reported in an Australian study, in which it was 10-fold more frequent (62).

A recent meta-analysis furthermore showed that the combined odds ratio (95%confidence intervals) of any imprinting disorder in children conceived through ART was 3.67 (1.39, 9.74) in comparison with spontaneously conceived children, leading the authors to the conclusion that there was an increase in imprinting disorders in children conceived though IVF and ICSI but insufficient evidence for an association between ART and methylation in other imprinted genes (63).

Conclusion

While it is clear that IVF pregnancies are at increased risk of adverse perinatal outcomes, it is also the case that the majority of the children born following IVF will have a good outcome. For those with poorer outcomes this inevitably reflects aspects of the treatment but also the interplay with the underlying features that the couple bring to the pregnancy. Further research is needed to untangle this complex relationship to allow effective targeted interventions. Using large datasets, it should be possible to start disentangling the inter-related effects of different types of infertility, the multiple aspects of ART treatment and parental characteristics, as well as investigating risks of individual birth defects. There are

still many gaps in our knowledge of the consequences of current ART practice and further research is required to examine mechanisms of epigenetic modification in human embryos.

Given the known risks associated with IVF pregnancies, risk assessment is required during antenatal care with appropriate referral. Assisted reproductive technology is associated with a small (OR: 1.3) increase in birth defects. This should be communicated to patients prior to undergoing ART. The consensus to be communicated is that both traditional IVF as well as ICSI/IVF show the same increased risk, except for increased sex chromosome abnormalities and hypospadias in ICSI. The adoption of elective single embryo transfer provides a clear example of how treatment strategies can be altered to improve outcomes.

At present the long-term follow-up studies on children born following IVF are largely reassuring once the confounding factors of prematurity and multiple gestation are removed. However, with the continued refinement of the technical process and clinical application of novel developments, continued surveillance is a prerequisite.

Conflict of interest: None.

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