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Review

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Perinatal outcomes following assisted reproductive technology: A Review of the Literature

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Abstract

Nowadays, infertility affects approximately 8-12% of the population. Multiple causative factors are leading to the failure of subfertile couples to achieve a normal pregnancy, as well as various types of assisted reproductive techniques that have developed globally in order to confront infertility.

Over the past few years, especially after the birth of the world's first baby to be conceived by In Vitro Fertilization (IVF) in 1978, numerous studies have been conducted concerning the risk of obstetric and perinatal complications. In this review, we aimed to detail the perinatal outcomes in relation to the ART procedures routinely applied. Consequently, the above-mentioned procedures have been associated with the presentation of hypertensive disorders and gestational diabetes mellitus in women, multiple pregnancy, preterm birth and low birth weight. Furthermore, studies indicate that infants born from assisted reproductive technologies appear to suffer much more frequently not only by congenital or epigenetic abnormalities, but also by neurodevelopmental disorders and specific types of cancer.

Indisputably, artificial fertilization methods still continue growing worldwide with new medical technologies' evolvement. It becomes, therefore, evident that the possible long-term, adverse neonatal outcomes have not been completely clarified yet. Taking into consideration that the number of the couples that undergo fertility treatments is constantly rising, more research is of vital importance so that their potential impact of such exposure on maternal and neonatal health can be understood.

Key words: Infertility, in vitro fertilization, complications, morbidity, autism, cancer

Introduction

It is widely believed that the pioneers of IVF tried to introduce their innovative ideas in a still unprepared world, where social, political and scientific institutions were not able to embrace the development of assisted reproduction technologies. Until 1978, the process of reproduction was considered the work of nature and God, not of researchers. It is therefore easy to understand the harsh criticism that the latter faced until, over the years, the presence of assisted reproductive technologies became established as a modern and desirable, constantly evolving reality.

Undeniably, infertility has been recognized as a major public health issue. The reality is that, while the provision of treatment options to address infertility has increased at an impressive rate over the last two decades, its incidence rates have remained the same over the last century (10-13%). Overall estimates suggest that, globally, more than eighty million couples experience fertility problems, particularly in developing countries.[1]

Numerous factors can affect the complex process of normal conception, not only endogenous but also exogenous.[2] Among them, we could distinguish the age of the woman[3,4], the presence of disturbed anatomy in the female reproductive system, and the presence of endocrine disorders, while the male factor of infertility also plays a role.

Therefore, it was expected that the use of assisted reproductive technology (ART) would become widespread. Perinatal outcomes and long-term safety for the women and children are paramount. More specifically, 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.

Material and Method

The objective of our study was to provide a systematic review of perinatal outcomes among infants conceived with the use of assisted reproductive technology.

A search was performed through the database of PubMed and Scopus, including articles from 2012 to March 2020, with emphasis on the literature over the course of the last 5 years.

Review of the literature and Discussion

1. Obstetric risks

1.1. Gestational hypertension

Hypertensive disorders of pregnancy include gestational hypertension, pre-eclampsia, and eclampsia.[5] A meta-analysis[6] and a subsequent retrospective cohort study[7] showed a significantly increased likelihood of gestational hypertension in singleton pregnancies after using in vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI), compared with singleton pregnancies from natural conception. The risk of pre-eclampsia was also higher, but the difference did not reach the limits of statistical significance.[8] Similarly, no statistically significant difference was found in the incidence of hypertensive disorders of pregnancy between twin pregnancies by ART and by natural conception.[7]

1.2. Gestational diabetes mellitus

Studies have shown an increased incidence of gestational diabetes in pregnancies resulting from assisted reproductive technology compared to natural pregnancies.[7,9] Moreover, research suggests that the risk is likely due to the older age of women who tend to undergo infertility treatments.[10]

1.3. Premature birth

According to studies, pregnancies resulting from ART have an increased risk of preterm delivery.[6,10,11] However, this risk has been described to be lower when the technique used is IVF involving the transfer of cryopreserved rather than fresh embryos.[12]

2. Morbidity and outcome of newborns by assisted reproductive technology (ART)

2.1. Low birth weight (<2500g)

According to the MOSART study[12], a longitudinal cohort study, singleton pregnancies from IVF have a higher risk of low birth weight (LBW) newborns, compared to infants born of infertile and fertile couples, while this difference does not seem to be evident in the case of multiple pregnancy.

According to further studies, a lower incidence of low birth weight newborns is noticeable in the case of IVF using the transfer of cryopreserved embryos.[13-16]

2.2. Neonatal prematurity

Preterm birth is a significant factor related to perinatal morbidity and mortality. According to the literature, premature birth is more frequently as-

sociated with singleton pregnancies resulting from IVF techniques.[17] There seems to be no distinction depending on the method chosen in each case.[18] No statistically significant difference has been found in terms of prematurity in multiple pregnancy, probably because it consist already an independent risk factor for preterm birth.

Studies also show an increased risk of preterm delivery in pregnancies carried out by assisted reproductive technology with reported use of fertility drugs, for example ovarian stimulation treatments.[19,20]

2.3. Multiple pregnancy

With the increasing use of assisted reproduction methods, twin pregnancies are now estimated to represent 20% of all twin pregnancies in Europe, while the percentage for multiple pregnancy is around 3%.[21] Multiple pregnancies are known to be associated with several obstetric complications (gestational hypertension, pre-eclampsia, gestational diabetes mellitus, prematurity). In other words, infants born from such pregnancies have increased morbidity and mortality.

2.4. Congenital abnormalities

An increased incidence of cardiovascular, musculoskeletal, and genitourinary disorders has been reported in neonates after the application of both classical IVF (8.6%) and ICSI (9%).[22] In particular, congenital heart disease, congenital hip dislocation, congenital talipes equinovarus, spina bifida, and esophageal atresia have been reported.[23] Similarly, increased numbers of congenital anomalies are described in infants born through the transfer of cryopreserved embryos.[24]

2.5. Imprinting disorders

Studies conclude that there is a correlation between assisted reproductive techniques and imprinting disorders.[25,26] These disorders include syndromes such as Beckwith-Wiedemann syndrome (BWS), Angelman syndrome (AS), Prader-Willi syndrome (PWS), and Russell-Silver syndrome (SRS). However, due to the rarity of the aforementioned syndromes, the knowledge of the scientific community regarding the impact of assisted reproductive techniques on the occurrence of imprinting disorders is incomplete, thus further research is needed.

2.6. Chromosomal abnormalities

It has been described that the rate of spontaneous abortions in the first trimester of pregnancies achieved using assisted reproduction methods reaches 22-63%, with the main cause being chromosomal abnormalities.[27] The risk of aneuploidy increases in women over 35 years of age who have achieved pregnancy using these methods.[28] It is also believed that the type of technique used in each case may determine the risk of chromosomal abnormalities in the fetus. In particular, in a study of a large series of embryos, chromosomal abnormalities occurred in 3% of those resulting from ICSI, a number significantly higher than the percentage in the general population (1%).[28]

The incidence of sex chromosome anomalies is , also, found to be increased 3-4-fold in ART pregnancies, with Klinefelter's syndrome being the most common.

2.7. Neurodevelopmental disorders

In ART-conceived neonates, both their short-term and long-term neurodevelopmental development may be affected with greater frequency.[5] A population-based retrospective cohort study demonstrated an increased risk of cerebral palsy in children from IVF.[29,30] The forms of cerebral palsy included spastic diplegia, spastic hemiplegia, and spastic quadriplegia. Data, however, remain inadequate due to the lack of long-term studies focusing on the neurological effects of ART methods.

2.8. Autism

The available data are conflicting regarding the impact of ART methods on the development of autism.[18] A Swedish study did not show an increased risk of autism in singleton pregnancies from IVF. However, an increased risk was found when ICSI was the method used.

2.9. Endocrine disorders

Thyroid gland function in children with ART is still a relatively unexplored field. Elevated serum TSH hormone levels in IVF children have been described, without this being due to the presence of antithyroid antibodies;[31,32] while other studies link ART methods to early insulin resistance.

2.10. Cardiovascular and metabolic profile

Assisted reproductive methods have been shown to carry a risk of cardiometabolic disorders, arterial hypertension, and high body fat in children.[33]

2.11. Body mass index and body fat

Children conceived by IVF appear to show an increased rate of weight gain in early childhood. This rapid weight regain, also known as "catch-up" growth, is associated with higher rates of central obesity.[34] In vitro fertilization, furthermore, has been documented to be responsible for increased rates of peripheral fat deposition, as well as significantly lower rates of lean mass.

2.12. Blood pressure in children conceived by ART

According to the dutch OMEGA cohort study,[33] children resulting from IVF pregnancies have twice the risk of developing high systolic or diastolic blood pressure, even after the elimination of confounding factors. indeed, higher arterial pressure has been recorded in prepubertal offspring of pregnancies resulting from ovarian stimulation followed by IVF or a combination of IVF and ICSI.

2.13. Serum lipids in children conceived by ART

There are reports of increased levels of total cholesterol and low-density cholesterol (LDL) and low levels of high-density cholesterol (HDL) in children from IVF pregnancies compared to children conceived naturally.[5] There is conflicting data regarding triglycerides in childhood. Several studies have shown their levels to be elevated in IVF conceived children. However, different studies have not found statistically significant differences in triglyceride levels between these two groups of children.

2.14. Serum glucose in children conceived by ART

Similarly, available data on fasting blood sugar and insulin levels in children from pregnancies achieved through ART remain limited and contradictory. Thus, some studies show these levels to be elevated in children from IVF, while others do not conclude a substantial difference between these children and those conceived naturally.[5]

2.15. Puberty in children conceived by ART

A cohort study comparing adolescents conceived through IVF and ICSI techniques and adolescents from natural conception showed delayed breast development, advanced bone age, and increased DHEAS and LH levels in females of the former category. Similarly, reduced testosterone was found in male offspring from ART methods.[18]

2.16. Cancer in children conceived by ART

A large number of studies have shown an increased risk of malignancy in children from ART. These appear to involve hematological malignancies, with leukemia and Hodgkin's lymphoma occurring with high frequency. Furthermore, same studies indicate high percentage of retinoblastoma, hepatoblastoma, as well as rhabdomyosarcoma.[35-38]

2.17. Psychoemotional and social behavior of children conceived by ART

According to five-year research conducted in two countries, females conceived through ART were more prone to depression and anxiety, while males were more prone to aggressive behavior. Ultimately,

however, no difference was found in terms of mental health and social development of these children.[39]

Conclusion

The modern era is characterized by a plethora of scientific advances aimed at improving the quality of human life. Medically assisted reproduction is part of this. Its role in society today is of crucial importance.

In general, the assisted reproductive methods that have been developed are considered safe, and the offspring of these methods are healthy. However, studies have shown an increased incidence of perinatal events. These include congenital and chromosomal abnormalities, epigenetic changes as well as neurodevelopmental disorders in children resulting from one of the ART techniques.

Of course, there are still many unanswered questions regarding the safety of ART techniques and the morbidity of newborns resulting from them. Thus, a greater number of well-designed studies are needed, with long-term follow-up, to draw sound conclusions.

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