MAEDICA – a Journal of Clinical Medicine
2021; 16(3): 493-498
https://doi.org/10.26574/maedica.2021.16.3.493

MÆDICA - a Journal of Clinical Medicine

REVIEW

Obstetric and Perinatal Complications Associated with Assisted Reproductive Techniques – Review

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ABSTRACT

Recently, the use of assisted reproductive techniques (ART) has witnessed a significant increase worldwide. Although most of these pregnancies have a good prognosis, studies show that ART is associated with a risk of obstetric and perinatal complications, compared to pregnancies conceived spontaneously. It is considered that the risk is directly proportional to the number of transferred embryos, thus multiple pregnancies are an independent risk factor that supports the large-scale implementation of single embryo transfer protocols. Simultaneously, studies report obstetric and perinatal complications in singleton pregnancies obtained after ART and it is not possible to establish whether parental or procedural factors are the causal determinants. The purpose of this article is to summarize the risk of maternal-fetal complications associated with ART.

Keywords: assisted reproduction technology (ART), obstetric complications, neonatal complications, elective single embryo transfer (eSET), cryopreservation.

INTRODUCTION

Infertility is a public health problem with major implications for the physical, mental and social condition of affected couples. For this reason, most patients diagnosed with infertility decide upon using assisted reproductive techniques (ARTs) and studies are demonstrating an increase in their efficiency and safety over time (1). In 2016, in Europe, 1.8 million children were conceived through assisted reproduction (2).

Studies have shown that the use of ART was associated with an increased risk of obstetric complications such as pregnancy-induced hypertensive disorders, placental abnormalities, gestational diabetes, but also perinatal complications such as prematurity, low birth weight, small for gestational age and congenital anomalies. These side effects have been attributed to the increased incidence of multiple pregnancies, especially in older women (3). However, studies have shown that the risk of complications was maintained in the case of singleton pregnancies obtained after ART compared to the general population (4).

Recently, ART pregnancies have a better prognosis compared to previous years due to imple-

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Article received on the 7th of June 2021 and accepted for publication on the 3rd of September 2021

mentation of single embryo transfer protocols, which have reduced the incidence of multiple pregnancies and their associated complications. In Europe, the transfer of a single embryo increased from 37.7% in 2015 to 41.5% in 2016, and the transfer of two embryos decreased from 53.9% to 51.9%. In 2016, two more countries, Slovenia and the United Kingdom, joined the single embryo transfer protocol, so that 10 European countries decided on this protocol (2).

Protocols using cryopreservation techniques increased the rate of single embryo transfer, which helped reduce the incidence of multiple pregnancies. According to statistics, cryopreservation techniques are beginning to gain significant importance, thus the transfer of cryopreserved embryos is increasing at European level (2). The implementation of the freeze-all protocol is currently taken into consideration because a reduction in the rate of multiple pregnancies and ovarian hyperstimulation syndrome has been observed. However, women should be carefully selected considering obstetric and perinatal risks associated with cryopreservation (5).

A study from the CoNARTaS group (6) demonstrated a decreasing trend of ART-associated complications compared to spontaneously obtained pregnancies. The increasing rate of single embryo transfer, use of cryopreservation techniques, as well as the shortening of the infertility period by early use of assisted reproduction can explain the improved prognosis in these pregnancies.

The current review provides a summary of data from the literature on maternal-fetal complications in pregnancies obtained through ART.

Obstetric complications

The results of studies in the literature show that pregnancies conceived through ART have an increased risk of obstetric complications such as pregnancy-induced hypertension, pre-eclampsia, placental abnormalities and gestational diabetes.

Pregnancy-induced hypertension and pre-eclampsia are common complications among women who get pregnant through ART (7-9). It has been observed that the risk of these complications is maintained also with cryopreservation (5, 10, 11) and in the case of using donated fresh oocytes (12-15). Although some studies support the widespread use of cryopreserved embryos, the results are not conclusive.

The most recent meta-analysis comparing the use of freeze-all strategy with the transfer of fresh embryos did not report significant differences in the cumulative rate of live births. However, it was observed that the transfer of cryopreserved embryos increased the risk of hypertensive complications in pregnancy (16). Researchers assessed whether this effect was influenced by women's response to the ovarian stimulation protocol. Thus, two meta-analyses showed that, although the elective transfer of cryopreserved embryos was associated with an increased cumulative live birth rate only for the hyperresponsive population, it increased the risk of pre-eclampsia. This is the reason why women who can benefit from this procedure should be carefully selected (17, 18). The transfer of cryopreserved embryos is performed in the context of programmed cycles, in which estrogen and progesterone are administered to prepare the endometrium. In these cycles, ovulation is suppressed, so the luteal body is absent. Corpus luteum also secretes vasoactive hormones in addition to estrogen and progesterone. The role of these vasoactive hormones is to influence the development of the placenta, but they are not exogenously administered in programmed cycles (19). Because arterial compliance increases physiologically in pregnancy, von Versen-Höynck *et al* evaluated the velocity of the carotid-femoral pulse wave depending on the presence or absence of the luteal body. The results show that the absence of the luteal body decreases aortic compliance and increases the risk of pre-eclampsia in pregnancies obtained by *in vitro* fertilization (IVF) (20). This encourages the use of natural cycles when using cryopreservation techniques.

Beside that advanced maternal age and multiple pregnancies are independent risk factors for gestational diabetes (GD), ART use increases this risk by 28% (21). A meta-analysis compared singleton pregnancies obtained through ART with those obtained spontaneously and showed that assisted reproduction was associated with an increased risk of GD. This risk is higher in the IVF group compared to the intracytoplasmic sperm injection (ICSI) group and for fresh embryo transfer, compared to cryopreserved embryo-transfer (22). In a meta-analysis of 29 studies, Sha *et al*

demonstrated that the risk of GD is higher in women diagnosed with polycystic ovary syndrome who obtain a pregnancy through IVF (23).

The risk of placental abnormalities, such as placenta previa and placental abruption, is increased in singleton pregnancies obtained through ART. A meta-analysis performed by Vermey *et al* demonstrates that this risk is also maintained in the population of subfertile women (24). Given the increased risk of pregnancy complications associated with multiple pregnancies, Karami *et al* performed a meta-analysis and demonstrated the association between ART use and the risk of placenta previa for both singleton and multiple pregnancies (25). The stage of embryo-transfer can also influence the risk of placental abnormalities. It is considered that the transfer of a blastocyst stage embryo increases the incidence of placenta previa (26). This can explain why the incidence of prematurity is higher in pregnancies obtained after transferring a day 5-embryo (27). Spangmose *et al* also demonstrated that the placenta previa rate was reduced if cryopreservation techniques were used compared to the transfer of fresh embryos. This result can be due to reduced endometrial stimulation in the case of cryopreservation (26).

Perinatal complications

A recent review by Madrazo-Cabo *et al* showed that pregnancies obtained through ART had an increased risk of preterm birth, low birth weight, small for gestational age, admission in neonatal intensive care unit (NICU) and congenital anomalies compared to the general population (28). A meta-analysis from 2013, which included 65 articles and analyzed the risk of prematurity, low birth weight and perinatal mortality, showed that the incidence of perinatal complications was lower in the ICSI group compared to the IVF group (29). Pregnant women in the ICSI group are considered reproductively healthier, as the primary indication for ICSI use is male infertility. Other studies claim that there are no significant differences between the two techniques in terms of the risk of complications (4). Cavoretto *et al* demonstrated in a meta-analysis that pregnancies obtained through IVF/ICSI had an increased incidence of spontaneous preterm birth compared to those obtained by spontaneous conception (10.1% *versus* 5.5%), even after adjustment for potential confounders (30).

The use of blastocysts is considered to allow high-quality self-selection of embryos and thus increase the success rate of pregnancy and the rate of live births (31). However, Levi-Setti *et al* did not demonstrate any significant differences between the two groups (32). Simultaneously, Dar *et al* have shown that blastocyst embryo transfer was associated with an augmented risk of prematurity and low birth weight (27). To prevent the increased rate of prematurity and its complications in ART pregnancies, researchers analysed whether this risk was influenced by cryopreservation techniques. Maheshwari *et al* performed a meta-analysis showing that the transfer of a cryopreserved embryo was associated with a reduced risk of prematurity, compared to pregnancies obtained after transferring fresh embryos (10).

It has been demonstrated that both parental factors and assisted reproductive techniques could increase the risk of neonatal complications. However, the subfertile population of women remains uncontrolled in some studies as they are frequently included in the cohort of pregnancies obtained by spontaneous conception. In this case, sibling-control studies are needed to demonstrate the contribution of parental and obstetrical factors, regardless of the use of ART (33). Thereby, Romundstad *et al* analyzed the group of "sibling pairs" women who obtained a pregnancy both spontaneously and through ART. The results showed a similar rate of prematurity, suggesting that maternal factors and the etiology of infertility can influence this risk (34).

Among the perinatal complications, it has been shown that newborns obtained by ART have an increased risk of low birth weight and macrosomia compared with spontaneous births. Low birth weights are three times more commonly associated with ART. Multiple pregnancies and prematurity are independent risk factors, but the culture medium used and the ovarian stimulation protocol can also be responsible for the weight differences in these newborns (35). Castillo *et al* observed in a multicenter cohort study a trend of increasing birth weight of newborns from pregnancies obtained through IVF. In their study, the authors observed an increase in birth weight by 13.4 grams *per*

year during the study period (36). Simultaneously, it was observed that newborns obtained after ART were at risk of large for gestational age and macrosomia, especially if cryopreservation techniques were used (10, 11, 37). By transferring cryopreserved embryos, the selection of high-quality embryos is made and these pregnancies are considered to have a better prognosis because they do not require ovarian stimulation. However, adverse reactions associated with cryopreservation, such as pregnancy-induced hypertensive disorders, large for gestational age and perinatal mortality, have also been described in the literature. For this reason, the implementation of "freeze-all" protocols should be performed after carefully selecting the population of women who can benefit from this technique (38).

A meta-analysis from 2018 regarding congenital anomalies showed an increased risk in the ART pregnancy group with significant differences globally, depending on the procedure used and the time of diagnosis (39).

Congenital anomalies have been reported for the central nervous system, auditory and visual as well as cardiovascular, gastrointestinal and genitourinary systems. Even if these anomalies are frequently associated with multiple pregnancies obtained after ART (40), some studies show opposite results (41). Giorgione *et al* demonstrated that congenital heart defects were common in pregnancies obtained through ART (1.30%) compared to those obtained spontaneously (0.68%) for both singleton and multiple pregnancies (42).

Given that ICSI is more frequently associated with congenital anomalies than IVF (43), its use beside the indication of male infertility should be limited. That is the reason why it is recommended to properly select couples who can benefit from the use of ICSI.

Studies have shown that azoospermia or oligozoospermia was associated with an increased incidence of de novo chromosomal abnormalities compared with the normozoospermia group. An increased incidence of autosomal translocations and Y-chromosome microdeletions was observed too (33, 44).

Also, ART has been associated with the risk of diseases caused by gene hypomethylation such as Angelman syndrome, Beckwith-Weidermann syndrome, Prader Willi syndrome and Silver Russell syndrome (45). However, given the rarity of these pathologies, most studies do not have sufficient statistical power to demonstrate a correlation with assisted reproductive procedures. ❑

CONCLUSIONS

Data from the literature show that ART has an increased safety and efficacy for treating infertility and it also increases the chances of obtaining a pregnancy in this population. It has been shown that the implementation of single embryo transfer protocols had significantly contributed to reducing the risk of obstetric and perinatal complications compared to multiple pregnancies.

Simultaneously, it has been shown that certain reproductive techniques were associated with an increased risk of pregnancy complications. Thus, the transfer of a blastocyst stage embryo allows the selection of high-quality embryos, but it increases the incidence of prematurity and low birth weight in this group. Cryopreservation techniques reduce the risk of ovarian hyperstimulation syndrome and allow an effective synchronization between the embryo and endometrium, thus reducing the incidence of prematurity. However, it has been observed to increase the risk of hypertensive complications in pregnancy, large for gestational age, macrosomia and perinatal mortality. For this reason, it is necessary to limit the use of freeze-all protocols to specific groups of patients who can truly benefit from this technique. Regarding the use of ICSI, it has been shown that it increases the risk of congenital anomalies compared with IVF.

Studies have also shown that for certain complications in pregnancy, parental characteristics, the etiology of infertility and population of subfertility women could influence the prognosis. According to relevant studies, ART is not a direct causal factor of pregnancy and perinatal complications, but it is an additional risk factor for this population of women. This is why ART should become an important observational marker for clinicians, to include these pregnancies in risk categories and establish a standardized methodology for the follow-up of the mother and newborn. ❑

Conflicts of interest: none declared.
Financial support: none declared.

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