Reproductive outcomes after assisted conception

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Abstract

Question Increasingly my patients are undergoing assisted conception. These patients are excitedly anticipating pregnancy, but are there risks to the fetus when using assisted reproductive technology (ART)?

Answer The current medical literature suggests only a mild increase in preterm deliveries, low birth weight, birth defects, and genetic imprinting defects. These results might, in part, be related to the indication for ART, rather than the ART itself.

Issues de la procréation assistée

Résumé

Question Mes patientes ont de plus en plus recours à la procréation assistée. Ces patientes anticipent leur grossesse avec beaucoup d'excitation, mais y a-t-il des risques pour le fœtus quand on utilise la technologie de reproduction assistée (TRA)?

Réponse Les ouvrages médicaux actuels font valoir qu'il n'y a qu'une légère augmentation des accouchements avant terme, des faibles poids à la naissance, des déficiences congénitales et des déficiences de l'empreinte génétique. Ces issues peuvent, en partie, être reliées aux raisons de recourir à la TRA plutôt qu'à la TRA elle-même.

Subfertility, which affects 10% to 15% of individuals in the western world,[1] is commonly defined as the inability to conceive for 1 year or more. It precedes up to 25% of pregnancies in the United States.[2] Female subfertility, without treatment, might be related to adverse pregnancy outcomes such as preeclampsia, placenta previa, and others.[3]

Assisted reproductive technology (ART) is handling oocytes, sperm, or both outside the human body. Assisted reproductive technology includes in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI), fresh or frozen embryo transfer, and intrauterine insemination, with or without ovarian stimulation.[4]

Pregnancy outcome and ART

Assisted reproductive technology dramatically increases the risk of multiple pregnancies and the related maternal and fetal morbidity and mortality.[5,6] However, there are also concerns about the procedures themselves. In particular, ICSI, which practically bypasses the natural selection of sperm and involves physical manipulation of the oocyte with a needle, is thought to increase the risk of damaged embryos.[7] Assessing the actual risk related to the ART itself is challenging owing to high variability of techniques and cotherapies, heterogeneity in the parent population (eg, age differences, background morbidities), and inconsistent criteria for defining congenital abnormalities in different registries.[7]

Much of the older published data demonstrated an increased risk of obstetric, perinatal, and neonatal abnormalities; however, many of these studies were marred by the lack of adjustment for potential confounders such as parental age and background illness, and the specific type of ART.[4,7,8]

Numerous studies have suggested an association between ART and DNA modifications related to genetic imprinting disorders such as Beckwith-Wiedemann and Angelman syndromes, which were found in a higher proportion in children conceived with ART compared with the general population.[9-11] However, these are very rare disorders, and therefore determining the true odds ratio (OR) for risk is difficult. Nevertheless, the biological plausibility for these imprinting defects is robust, and surveillance is essential.

Risks of ART

In 2006, a systematic review of the effect of ART on perinatal outcomes and guidelines for the use of ART were approved and published in Canada.[4] In the systematic review, intrauterine insemination without other treatments was not found to increase the risk of congenital malformations. After adjusting for maternal age and parity, ovarian stimulation was found to be associated with an increased risk of preterm birth (1-fold to 2-fold) and low birth weight (1-fold to 3-fold) among singletons. Singleton pregnancies after IVF, with or without ICSI, were found to have increased risk of gestational

hypertension and diabetes (2-fold); placenta previa (3-fold to 6-fold); placental abruption (2-fold); induction of labour and cesarean delivery (2-fold); stillbirth or neonatal death (2-fold); preterm delivery (2-fold); low or very low birth weight (2-fold to 3-fold); small size for gestational age (1-fold to 2-fold); neonatal intensive care unit admission (1-fold to 2-fold); major congenital malformations, particularly cardiac and musculoskeletal malformations (2-fold to 3-fold); chromosomal anomalies in IVF-ICSI (1-fold to 2-fold); and a probable increased risk of genetic imprinting disorders such as Beckwith-Wiedemann and Angelman syndromes. However, the considerable methodologic problem in this review was the comparison of outcomes in ART pregnancies with those of spontaneously conceived pregnancies in fertile women, rather than in subfertile women. Therefore, substantial confounders such as the reason for infertility (eg, parental underlying disease) might have confounded the results.[4]

Between 2009 and 2012, several systematic reviews and meta-analyses looked at the outcomes of pregnancies conceived with ART.[12-15] All of them have shown that singleton ART pregnancies (especially with IVF-ICSI) are associated with a statistically significant increased risk of placenta previa or placental abruption (OR range 1.6 to 2.13), preterm birth (OR range 1.8 to 2.1), low birth weight (OR approximately 1.6), and birth defects (in particular, cardiovascular, musculoskeletal, genital, and gastrointestinal; OR approximately 1.4). Most, but not all, of the reviewed studies adjusted the analysis for maternal age. The important limitations discussed in all of these studies were the lack of control for important confounding factors, such as the reason for infertility, and comparison with fertile women rather than subfertile untreated women.[12-14] Some of the systematic reviews also looked at the outcomes of IVF alone (total n=12 816) compared with IVF-ICSI (total n=5395), showing no statistically significant differences between the 2 groups in terms of the rates of birth defects.[13,15]

A recent large Australian population-based cohort compared IVF or ovulation induction pregnancies to untreated infertile women who spontaneously conceived; after adjusting for factors such as multiple pregnancies, body mass index, and smoking habits, the risk of low birth weight infants, premature deliveries, or defects was not significantly increased. However, data regarding the reason for infertility were lacking.[16]

A recent large Australian observational study looked at the associations between birth defects and conceptions using different types of ART, and compared such associations with those in spontaneous conceptions in fertile women. After multivariate adjustment for maternal age and background illnesses, the association between IVF and any type of birth defect was no longer significant (OR 1.07, 95% CI 0.90 to 1.26), whereas the increased risk for any birth defect associated with ICSI remained significant (OR 1.57, 95% CI 1.30 to 1.90). Specific defects included cardiovascular, musculoskeletal, urogenital, and gastrointestinal defects, and cerebral palsy. All types of ART were related to stillbirths, preterm deliveries, cesarean sections, and infants with low birth weights. The authors concluded that with ART (specifically ICSI), the risk of obstetric complications and birth defects is increased, albeit to a lesser extent, even after multivariate adjustments for important confounding factors.[17]

Several studies,[18-23] including a systematic review,[23] have looked at long-term neurologic sequelae at different ages (1 to 10 years) for

children conceived with ART; no significant differences were found in the rates of neurodevelopmental disorders, or when comparing IVF alone to IVF-ICSI. Maternal age, level of education, and other demographic factors had more important effects on the children's neurocognitive development than the mode of conception did.[18-23]

Conclusion

The current medical literature suggests only a mild increase in preterm deliveries, low birth weight, birth defects, and genetic imprinting defects. These results might, in part, be related to the indication for ART, rather than the ART itself. Mothers receiving ART and their children should receive periodic screening and follow-up both prenatally and postnatally, with long-term developmental follow-up on a regular basis.

Competing interests
None declared

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