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Assisted Reproductive Technologies and Perinatal Morbidity: Interrogating the Association

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Abstract

Interrogating the association between ART and perinatal outcome is complicated but very important. The article introduces a series of articles that review this potential association with an eye toward etiology of risk, and what aspects of IVF can be modified to reduce this risk. When an association is not due to chance (i.e. statistically significant), one must also consider how the association may be affected due to bias or confounding. Despite lack of the perfect study, perinatal consequences of ART are apparent, even though the vast majority of children conceived with ART are healthy. Pregnancy after IVF is altered as evidenced by risk of preterm delivery, low birth weight among infants, and an alerted prevalence of preeclampsia. The long-term clinical implications of ART such as childhood development and metabolism have not been established and ongoing study is proceeding. The risk attributed to multiple births is iatrogenic and needs to be minimized. Optimizing the environment at the time a woman conceives will likely have an effect on gestation as well as the health of children. Reproduction effects health and health effects reproduction.

Keywords

IVF; ART; Perinatal outcomes; Obstetrical outcomes

Introduction

Since the birth of the first infant conceived in the USA with Assisted Reproductive Technology (ART) in 1981, use of advanced technologies to overcome the problem of infertility has increased steadily. In 2009, (the most recent data available from the CDC) a total of 146,244 ART procedures resulted in 45,870 live-birth deliveries and 60,190 infants, or 1.4 % of U.S. births (1). The proportion of conception assisted with IVF in some European countries is even higher. Among infants conceived with ART (in the USA), 33.4% were born preterm, compared with 12.2% of the general birth population, and 6.1% of ART infants were very preterm births, compared with 2% among the general birth population (1). The majority of this risk is due to the preterm delivery rates of multiple births. Among infants conceived with ART, 47% were born as multiple-birth infants compared with only

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3% of infants among the general birth population (1). These are real world data and represent a true iatrogenic health risk.

While every effort should continue to promote single embryo transfer, where feasible, it should also be recognized that conception with IVF increases maternal and perinatal morbidity even in a singleton conception. While the majority of singleton pregnancies following IVF are uncomplicated, multiple studies have suggested that IVF singleton pregnancies are independently associated with an increased risk of preterm birth, low birth weight, congenital anomalies, and perinatal complications compared with unassisted singleton conceptions (2–5). This article introduces a series of articles that review this potential association with an eye toward etiology of risk and what aspects of IVF can be modified to reduce this risk (6–9). Clearly the goal of all who practice reproductive medicine is to provide safe care to those in need, while minimizing risk and complications.

Understanding the literature with an evidence based filter

When assessing an association that has been demonstrated repeatedly, one must interrogate the reason(s) for the association. This is particularly true for the association between conception with IVF and increased perinatal morbidity. If the association is not due to chance (i.e. statistically significant), one must also consider how the association may be affected due to bias or confounding. One consideration is how any innate complications of those who undergo ART may affect the association. Do women with infertility have an elevated risk of perinatal risk compared with those who conceive without medical assistance (confounding by indication)? Is the medical care received by those who conceive with IVF different from those who conceive without assistance (bias due to health care access)? Is there a greater surveillance of infants conceived by ART (surveillance bias)? Do women recall treatment and outcome differently (recall bias)? Is the association due to difference in age and socioeconomic status of women who undergo ART (confounding)?

Bias

Bias is defined as a systematic difference in the way information is collected or analyzed such that it may result in an incorrect estimate of association. Bias cannot be corrected with statistical analysis or quantitated. When considering bias, the goal is to assess the direction and potential magnitude of its influence. For example, there is evidence that women with infertility (or with a longer time to conceive) are at higher risk of perinatal morbidity even without the use of ART. A Finnish study demonstrated an increased rate of preterm birth, small for gestational age, and “poor neonatal health” as the time to conception (without medical assistance) increased beyond 6 months (10). An Australian study noted that there was a higher risk of delivering a low birth weight infant and a higher risk of perinatal mortality in women with infertility who conceived without IVF while awaiting treatment (11). Finally, increased risks of preterm delivery, small for gestational age, and perinatal mortality have been noted in women who conceive with ovulation induction (and not IVF) (12.)

There is also evidence of surveillance bias in the data regarding women who conceived with IVF. In the meta-analysis assessing perinatal outcomes in singleton births following IVF, marked differences in obstetrical and neonatal care are noted (4). Women who used IVF to conceive were twice as likely to undergo an elective cesarean section, and their infants were 60% more likely to be observed in the NICU overnight (4).

The comparison population of women who use ART is also of paramount importance. When assessing the risks in children after conception with or without assisted reproductive technologies, it is important to understand the comparison groups. Before one can make the

conclusion that in vitro fertilization, ICSI, or even the use of fertility medications are associated with untoward outcomes, one must be able to compare that risk to an unbiased control group. The definition and identification of an unbiased control group is a very difficult task. A proper comparison group is a population of women including those who used ART. While it is clearly understood that an “unfair comparison” may lead to spurious results, it does not make agreement upon or identification of the appropriate control group easier. However, the potential of bias does not invalidate all data on the subject.

Confounding

Confounding involves the possibility that any observed association is due, in total or in part, to effects of differences between the study groups other than exposure. Multivariate analysis allows for a measure of association while controlling for a number of confounding factors simultaneously. However, adjustment for confounding can only be made if data regarding the confounding factors are available. In many studies important data are missing or simply not collected. As examples, any study of an association of ICSI with congenital abnormalities should control for length of childlessness, as prolonged time to conceive is independently associated with anomalies (13). The study of childhood development must control for gestational age of delivery and co-morbidity. Even when proper information is available and collected on issues like demographics, the differences in race, age, socioeconomic status, insurance coverage, and pregnancy plurality may be too great to allow for proper adjustment. It is difficult to find a large number of 40-year-old women with twins who conceived without medical assistance.

Finally one needs to consider the specificity of any association found. What is it about IVF that contributes risk to children. Is it the medications, the laboratory procedures, the manipulations of embryos, or perhaps the maternal physiology? The practice of IVF has changed over the years. Broad generalizations regarding the “dangers” of ART are not helpful to furthering the cause of modifying practice to optimize success and reduce risk.

What is the optimal study design?

Many of these limitations would be overcome with a randomized clinical trial. However, such a trial would be at the very least impractical and may be unethical. Thus, we must depend on observational studies to assess this association. There is a debate regarding the best methodology to assess the effects of conception with ART on children. Longitudinal studies are very expensive, take a long time to complete, and can be affected by large dropout or lost-to-followup rate, especially if the loss is differential between the two study groups. Studies that recruit women to a tertiary care medical center for evaluation of a potential illness (such as developmental delay) may not be generalizable because those who agree to participate may suspect pathology in their children (whether or not they conceived with ART).

The use of administrative data can also be problematic. If data already exist, the time required to perform a study is much shorter. However, assessing exposure and outcomes in an administrative database can be completed and is dependent on the quality of data. Not all data in clinical registries or national databases are research quality. Often data from administrative databases do not agree with that of prospective studies or validation (14). Such an example is that a meta-analysis of individual research studies indicates a lower pregnancy rate with IVF in women with endometriosis (15), while the SART database notes a higher success rate for such women. Administrative data may also suffer from poor validation and lack of specificity. For example, there are likely many women who conceive with ART who do not have assisted conception checked off on a birth certificate (or noted in

birth registries). Moreover, if it is checked off, the type of infertility treatment received is not always clear.

Despite limitations the association appears real

While one must be wary of methodological limitations, one cannot dismiss the consistency of the findings. Despite the specific limitations of each study, the association of IVF with perinatal morbidity does appear to be real. It has been consistently confirmed in many situations, in diverse populations, and using many different study designs. What remains to be elucidated is the magnitude of the risk and what aspects of IVF contribute to the risk. There is data that suggested ICSI may contribute an independent risk factor for congenital anomaly (13) and that extended embryo culture may increase the risk for preterm delivery (16). However, the most consistent association is that there is a greater risk of perinatal morbidity, and in particular a greater incidence of low birth weight, in children conceived with a fresh embryo transfer compared with that of a frozen embryo transfer (17–23). The association of IVF with longer term clinical events has not been fully resolved.

Why the risk?

The observation that there is higher risk of perinatal morbidity in a fresh embryo transfer than a frozen transfer is intriguing as it may reflect an isolated aspect of IVF that confers risk. The risk of low birth weight is apparent in term and preterm singletons, as well as in term and preterm twins. The risk is higher in the paired comparison of the same women who conceived with fresh and frozen transfer (at different times) and is not apparent in women who use donor eggs, where preparation of the endometrium is the same in fresh and frozen transfer (23). The theorized mechanism of action is an “alteration of early placentation” due to “supra-physiological” environment. However, the specific aspects of “altered placentation or supra-physiological” environment is unknown. Investigation continues into endometrial receptivity, alternation in trophoblast growth, or function and/or epigenetic alteration (24). Further demonstration of an altered physiologic state is the association of fresh embryo transfer with preeclampsia (25,26). Again the molecular mechanism(s) of this risk are not yet known.

Summary

Interrogating the association between ART and perinatal outcome is complicated but very important. Despite lack of the perfect study and numerable individual identifiable methodological flaws with the current literature, the risk is apparent and cannot be dismissed. The short-term (perinatal) consequences of ART are apparent even though the vast majority of children conceived with ART are healthy. Pregnancy is altered even in singletons as demonstrated by risk of preterm delivery, low birth weight infant (even when delivered at term), as well as data demonstrating alerted prevalence and severity of preeclampsia. The longer term clinical implications of ART such as childhood development and metabolism have not been established and ongoing study is proceeding. Even as data continues to become available it should be viewed with care, as the practice of IVF continues to evolve including: changes in embryo culture, oxygen tension, freezing techniques, biochemical and/or metabolic selection of embryos, and patient demographics.

The etiology of risk associated with ART is likely multifactorial and the magnitude of this risk has not been precisely identified for all women or specific subgroups. Many questions still remain including the magnitude of risk of ICSI in non-male factor infertility, the affect of prolonged embryo culture, the affect of embryo biopsy, and elucidation as to why risk is lower after a frozen embryo transfer.

All patients considering ART should be clearly informed of the risk. The risk cannot be blamed on the patient. The risk attributed to multiple births is iatrogenic and needs to be minimized. Practicing ART is a privilege, but also carries responsibility. As scientists and physicians, it is our responsibility to provide safe care. Optimizing the environment at the time a woman conceives will likely have an effect on gestation as well as the health of children. Reproduction effects health and health effects reproduction.

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