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In Vitro Fertilization and Adverse Childhood Outcomes: What We Know, Where We Are Going, and How Will We Get There? A Glimpse into What Lies Behind and Beckons Ahead

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Abstract

The majority of perinatal morbidity after in-vitro fertilization is due to multiple pregnancy; however even singleton infants are at an increased risk for adverse outcomes. We have summarized data that evaluates adverse outcomes in IVF-infants and recent attempts to delineate the underlying etiologies that confer this risk. We submit that practitioners of reproductive medicine should remain at the forefront of this investigation.

The first live birth resulting from in-vitro fertilization (IVF), Louise Brown of the United Kingdom, was reported in 1978 by Edwards and Steptoe. In the three decades since her birth, in-vitro fertilization has steadily evolved, and millions of couples worldwide have started and completed their families utilizing this technology. Over the last decade in the United States alone, the use of assisted reproductive technology has doubled, with over 61,000 infants born in 2008, accounting for over 1% of all US births. (1). The medical subspecialty of reproductive medicine has been transformed by the success of in-vitro fertilization. As practitioners, we have the pleasure of treating subfertile couples and our ability to offer them successful treatment options has never been better.

In recent years, an emerging body of research has demonstrated adverse outcomes in infants born using assisted reproductive technologies (ART). There is no doubt that the vast majority of perinatal morbidity associated with IVF is attributable to the conception of multiple pregnancies. The most recent US data reported a 29% incidence of twin pregnancy, and a 3.7% incidence of triplet pregnancy following IVF, an approximate a 14-fold and 54-fold increase compared to unassisted conception, respectively (2,3). It is widely established that multiple pregnancy confers a much higher risk of adverse outcome; more than 60% of twins are born preterm, and more than 50% are low birth weight as compared to 14% and 9% of singletons (4). While revision of the ASRM guidelines (1998, 1999 and 2004) has ledto a reduction in high order multiple pregnancy, twin pregnancy is still an all too

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common event, and the rate has not decreased (5). Changes in the embryo transfer guidelines (2010) will hopefully result in a further reduction of multiple gestations. However, as many practices routinely exceed these guidelines (6), it is very possible that there will be no appreciable reduction in twin gestation without further action. Currently there is little incentive to decrease multiple birth rates as there is no “penalty” for a practice to have a high twin rate and, in fact, multiple birth is consisted a “success” when pregnancy rates are published. As a medical specialty we must do a better job of policing ourselves and reduce this rate, for the benefit of our patients. If we do not, in all likelihood, government or insurance mandates will be forced upon us.

Many of the multiple births conceived in the USA are due to ovulation induction; however, there is no precise estimate of this rate. This is unacceptable. An organ transplant center that does not know the rejection and survival outcome of its patients would be widely criticized, appropriately. Yet practices performing ovulation induction often do not know (or share) the pregnancy rate and multiple pregnancy rate in the population they serve. Trials such as Avoiding Multiple Gestation using Ovulation Induction (AMIGOS) sponsored by the NIH via the Reproductive Medicine Network are designed to objectively estimate the multiple gestation rates with clomid, letrozole and gonadotropins. However, a registry of outcomes for all who practice ovulation induction would be exceedingly valuable. The push back that the extra work added to a practice would be a burden is short sighted.

Adverse perinatal outcomes are not restricted to multiple pregnancies. 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 as compared to unassisted singleton conceptions (7,8,9). The paper published in 2002 by Schieve et al was one of the first to report the association between low birth weight (LBW: <2500 grams) and very low birth weight (VLBW: <1500 grams) (7). In this landmark study, observed rates of low birth weight in IVF conceptions were compared to expected rates based on birth registry data, and after controlling for parity and age, the odds of both LBW and VLBW in IVF singleton births was 1.8 times higher than the expected rate in unassisted singleton births. The findings of this initial study were corroborated by two subsequent meta-analyses (8,9). In 2004, Helmerhorst et al performed a systematic review of 25 studies, 17 of which were matched for maternal age and parity and demonstrated a similar increase in the relative risk of LBW (RR 1.7; 95% CI 1.5–1.9) and VLBW (RR 3.0, 95% CI 2.1–4.4) (8). In addition, this study also reported observed increases in IVF singleton births for small for gestational age (SGA: RR 1.4, 95% CI 1.2–1.7) and preterm delivery (PTD: RR 2.0, 95% CI 1.8–2.3) as compared to unassisted singleton births. A second meta-analysis by Jackson et al reported similar findings and point estimates (9).

The etiology of adverse outcomes in IVF- conceived singleton infants is not known. Some data have demonstrated that pathology linked to the underlying subfertility, or prolonged time to conception, may predispose these couples to adverse neonatal outcomes. One such study evaluated a historical cohort to determine if infants born to subfertile women who conceived without medical assistance had similar rates of very low birth weight (VLBW), low birth weight (LBW), very preterm delivery (VPTD) and preterm delivery (PTD) when compared to infants born to infertile women who conceived with the assistance of IVF (10). Importantly, the authors found that infants born to subfertile women following *IVF* were at higher risk for all adverse outcomes, concluding that the increased risk in these infants could not be solely attributed to underlying subfertility. Thus, the question remains, what aspect of IVF treatment confers increase in risk?

The complexity of IVF makes it a challenge to answer this question. Currently it is unclear if risk is associated with medication, surgical procedures, culture and manipulation of gametes and embryos, the altered hormonal environment at the time of implantation, or a combination of these factors. Moreover, what is paramount is to determine which aspects of treatment are modifiable in order to reduce risk, and not to simply implicate IVF as “unsafe” in general. Identification and isolation of one process is difficult due to confounding and bias, but is one way to assess its contribution to adverse neonatal outcome.

The effect of the supraphysiologic hormonal milieu resulting from ovarian stimulation can be assessed using a comparison of singleton infants born following transfer of fresh embryos to infants born following transfer of frozen/thawed embryos (in women of similar prognosis and response to treatment). Our group assessed this association using a large retrospective cohort study evaluating over 31,000 singleton infants born after IVF as reported to the United States Society of Assisted Reproductive Technology (SART) registry. The odds of overall LBW (AOR 1.35, 95% CI 1.20–1.51, p<0.001), LBW at term (AOR 1.73, 95% CI 1.37–2.03, p<0.001), and preterm LBW (AOR 1.49, 95% CI 1.24–1.78, p<0.001) were all significantly higher in singleton infants conceived following fresh ET as compared to those after frozen embryo transfer (11). In paired analysis of singleton births following conception with fresh and frozen/thawed ET in the same patient (in different cycles), as expected, the association was even stronger (LBW: AOR 4.66, 95% CI 1.18 – 18.38, p =0.03). As a control, we also evaluated infants born to oocyte donor recipients, in whom the endometrial preparation protocols are similar and more physiologic, regardless if a fresh or frozen/thawed embryo is transferred We found no difference in LBW (AOR 0.99, 95% CI 0.82 – 1.18), when comparing outcome in infants conceived with a fresh or frozen/thawed embryo using with a donor egg, which lends support to the hypothesis that the environment at the time of embryo transfer may be, in part, mediating this risk. These finding are consistent with several smaller European publications that have reported that infants born after transfer of frozen embryos demonstrate higher birth weight than those born after transfer of fresh embryos (12,13,14). Furthermore, a recently published Australianstudy reported that the risk of low birth weight was no different in singleton births after frozen embryo transfer as compared to singleton unassisted conceptions (15).

The increased risk conferred by IVF is unlikely to be solely due to the endocrine environment at the time of implantation. Other studies have assessed the potential contribution of the laboratory, specifically that of extended embryo culture. Two separate studies have reported that singleton infants born after transfer of blastocyst stage (day 5/6) embryos have higher rates of preterm delivery as compared to infants born after transfer of cleavage stage (day 3) embryos (16,17). An initial study evaluated Swedish birth register data and found that infants born after blastocyst stage transfer were at higher risk for both preterm birth (OR 1.35, 95% CI 1.07–1.71) and congenital malformations (OR 1.4, 95% CI 1.14–1.81) as compared to infants born after cleavage-stage transfer (16). A subsequent larger study of the US SART registry confirmed the increased risk of preterm delivery and extended embryo culture with a similar point estimate (OR 1.38, 95% CI 1.29 – 1.48) (17). The exact mechanism underlying the association of increased preterm delivery and extended embryo culture is not yet clear, but should be of concern and active investigation given the movement of our field toward extended embryo culture.

Finally, other evidence has suggested increased risk in IVF-conceived children conceived utilizing micromanipulation of gametes such as intracytoplasmic sperm injection (ICSI), including an increased risk of congenital and sex chromosome abnormalities. (18,19) It is unclear if this elevated risk is due to manipulation of the egg and sperm, or due to genetic information transferred from a man with severe male factor. However, ICSI is now used in up to 50% of all IVF cases, including many cases without abnormal semen parameters or

male factor. Recent evaluation of SART data presented at ASRM has questioned the efficacy of ICSI, demonstrating a lower pregnancy rate when ICSI was used in many different diagnostic categories including women with unexplained and tubal factor infertility (20). Clearly it is prudent to minimize manipulation of gametes in a situation where risk has been identified and efficacy has not been established.

The objective of summarizing these data is to call for action and responsibility. These findings need to be a source of continued investigation in our field. We have already begun to incorporate elective single embryo transfer into our armamentariumto reduce multiple pregnancy, the strongest determinant of adverse outcome in IVF births. However, we can not overlook that there may be other factors that contibute to morbidity in IVF-conceived children. Many in the reproductive community consider it an act of self - sabotage to pursue the association of adverse outcomes and in-vitro fertilization. We suggest it is the opposite. The continued thoughtful and methodologically sound pursuit of the answer to these questions will preserve the sanctity of our field. If we do not ask these difficult questions, and seek these challenging solutions, investigators from other disciplines will do so, potentially without an understanding of the complexity and rapid changes that have ledto the practice of IVF today. As such, it is possible that negative findings may be exaggerated or misinterpreted. Such reports are quickly disseminated by media, often superficially, resulting in harm to the field of reproductive medicine, and cause anxiety and confusion in the couples we treat.

It is a privilege to care for couples seeking assistance with conception. With privilege, comes responsibility. It is paramount that, as a field, we be at the forefront of this investigation to facilitate our common goal: to improve the care of our patients and the safe delivery of their dreams.

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