ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Are intracytoplasmic sperm injection and high serum estradiol compounding risk factors for adverse obstetric outcomes in assisted reproductive technology?

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Objective: To evaluate whether intracytoplasmic sperm injection (ICSI) use and E_2 on the final day of assisted reproductive technology (ART) stimulation are associated with adverse obstetric complications related to placentation.
Design: Retrospective cohort study.
Setting: Large private ART practice.
Patient(s): A total of 383 women who underwent ART resulting in a singleton live births.
Intervention(s): None.
Main Outcome Measure(s): Adverse placental outcomes composed of placenta accreta, placental abruption, placenta previa, intrauterine growth restriction, preeclampsia, gestational hypertension, and small for gestational age infants.
Result(s): Patients with adverse placental outcomes had higher peak serum E_2 levels and were three times more likely to have used ICSI. Adverse placental outcomes were associated with increasing E_2 (odds ratio 1.36, 95% confidence interval 1.13–1.65) and ICSI (odds ratio 3.86, 95% confidence interval 1.61–9.27). Adverse outcomes increased when E_2 was >3,000 pg/mL and continued to increase in a linear fashion until E_2 was >5,000 pg/mL. The association of ICSI with adverse outcomes was independent of male factor infertility. Interaction testing suggested the adverse effect of E_2 was primarily seen in ICSI cycles, but not in conventional IVF cycles. Estradiol >5,000 pg/mL was associated with adverse placental events in 36% of all ART cycles and 52% of ICSI cycles.
Conclusion(s): The ICSI and elevated E_2 on the day of hCG trigger were associated with adverse obstetric outcomes related to placentation. The finding of a potential interaction of E_2 and ICSI with adverse placental events is novel and warrants further investigation. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Elevated E_2, adverse obstetric outcomes, IVF, ICSI

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Received February 7, 2016; revised April 8, 2016; accepted April 13, 2016.
G.D.R. has nothing to disclose. K.K. has nothing to disclose. J.M.C. has nothing to disclose. B.J.Y. has nothing to disclose. R.J.C. has nothing to disclose. A.H.D. has nothing to disclose. E.F.W. received an unrelated grant from OvaScience. M.J.H. has nothing to disclose.
Supported, in part, by Intramural research program of the Program in Reproductive and Adult Endocrinology, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland.
The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of Defense, Department of Health and Human Services or the US Government.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.04.023

Assisted reproductive technology (ART) use in the United States has continued to increase from 2004 to 2013, with the number of infants more than doubling. More than 66,000 infants were born in 2013 with the use of ART, approximately 1% of all live births in the United States (1). However, ART is not without risks. It is known that ART is associated with increased risk of chromosomal abnormalities, small for gestational age (SGA), and low birth weight infants, preterm labor, preterm delivery, preterm premature rupture of membranes, intrauterine growth restriction (IUGR), gestational hypertension, preeclampsia, placenta previa, placental abruption, gestational diabetes, and cesarean delivery. Most of these complications are primarily attributed to the increased risk of multiple gestations with ART (2–15). However, studies have shown that most of these risks remain elevated compared with spontaneously conceived pregnancies, even when there is a singleton pregnancy conceived through ART (12, 21, 33).

Many factors contribute to the success or failure of ART cycles, but most end points of studies on ART parameters in our current literature examine clinical pregnancy or live birth. Unfortunately, there are very few studies on the effect of ART parameters on clinical obstetric complications as well as a dearth of knowledge at the molecular level of these parameters on the developing placenta. There are many ART parameters that could adversely affect implantation (all or nothing effect) or placentation (exaggerated or insufficient invasion of the trophectoderm).

Insufficient trophoblastic invasion at the time of implantation has been implicated as a possible cause of later obstetric complications such as preeclampsia, premature preterm rupture of membranes, preterm delivery, and IUGR resulting in SGA infants (16). There is evidence that abnormal placentation occurs due to decreased trophoblastic invasion of the decidual and myometrial spiral arteries and aberrant cell survival and apoptosis (17, 18). If severe enough, the continued insult to the placenta can lead to IUGR, SGA, preeclampsia, and/or placental abruption (18). On the other hand, excessive trophoblastic invasion is thought to be associated with placenta accrete, placenta increta, placenta percreta through the decidua or the absence of an adequate decidua formation (16, 19).

One theory to explain the increased risks is that abnormal placentation is mediated by elevated E_2 levels at the time of implantation, thus adversely affecting trophoblastic invasion of the endometrium. Bonagura et al. (20) demonstrated suppressed extravillous trophobastic spiral arterial invasion in the presence of elevated E_2 levels during the first trimester of baboon pregnancies. A study by Kalra et al. (10) showed that supraphysiologic levels of sex steroid hormones before embryo implantation appeared to contribute to the risk of low birth weight and other disorders of abnormal placentation. In addition, recent studies by Farhi et al. (12) and Imudia et al. (21) suggest that elevated peak E_2 levels during ART, even in singleton pregnancies, increased the risk of abnormal placentation without adversely affecting embryo implantation, pregnancy, or abortion risk.

However, a fundamental objective of controlled ovarian hyperstimulation (COH) is supraovulation with a coincident supraphysiologic hormonal milieu. The highest ovarian responses are often seen in the most fertile women (e.g., male factor infertility and oocyte donors). We examined whether E_2 was associated with obstetric outcomes to better understand the mechanism of the elevated risks for adverse pregnancy outcomes.

MATERIALS AND METHODS

Study Design

A retrospective cohort study was conducted at the largest US military academic medical center with Institutional Review Board approval. All fresh ART cycles from January 2010 to December 2013 were reviewed. Data were collected to include age, baseline levels for FSH, peak E_2 on the final day of ART stimulation, infertility diagnosis, and the number of embryos transferred. Pregnancy outcomes were collected to include preterm delivery, birth weight, presence of gestational hypertension or preeclampsia, preterm premature rupture of membranes, intrauterine growth restriction, placental abruption, placenta previa, placenta accrete, placenta increta, and placenta percreta. Adverse obstetric events were defined as follows: preterm delivery was a birth <37 weeks gestation; small for gestational age was birth weight <10th percentile for gestational age using standard curves; gestational hypertension was elevated systolic blood pressures ≥ 140 mm Hg or diastolic blood pressures ≥ 90 mm Hg after 20 weeks gestation; preeclampsia was hypertension with presence of proteinuria or clinical features; intrauterine growth restriction was an overall estimated fetal weight <10th percentile or abdominal circumference of fetus <10th percentile calculated from ultrasound evaluation using standard curve for gestational age; placental abruption was diagnosed clinically from medical records and placental pathology; and placenta previa, placenta accreta, placenta increta, or placenta percreta were diagnosed by ultrasound and confirmed after delivery.

The primary outcome was the composite risk of any adverse obstetric outcomes related to placentation. This included gestational hypertension, preeclampsia, IUGR/SGA, preterm premature rupture of membranes, placental abruption, placenta previa along with placenta accrete, placenta increta, or placenta percreta. Secondary outcomes measures were rates of implantation, live birth rates, and preterm delivery rates.

Patients

The ART records from 2010 to 2013 were evaluated for a singleton live birth. Patients with a singleton pregnancy noted by one gestational sac and fetal pole present during first trimester ultrasound were included after a fresh ART cycle with records available in the electronic medical record. Patients were only included one time during the study period. Exclusion criteria were as follows: any factors that could potentially affect implantation such as a fibroid uterus; hydrosalpinx or any other congenital uterine anomalies; any chronic diseases that could affect the course of the pregnancy such as diabetes mellitus, autoimmune diseases, or hypertension; any history of pregnancy complications in previous