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In Vitro Fertilization and Risk for Hypertensive Disorders of Pregnancy: Associations with Treatment Parameters

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Condensation

The risk for hypertensive disorders of pregnancy is increased with subfertility, frozen embryo transfer, and oocyte donation.

Short Title: Risk of hypertensive disorders of pregnancy by fertility status and in vitro fertilization (IVF) treatment parameters.

AJOG at a Glance:

A. Why was the study conducted?

To evaluate risks for hypertensive disorders of pregnancy by maternal fertility status and IVF treatment parameters.

B. What are the key findings?

Among IVF pregnancies, the risk of hypertensive disorders of pregnancy was increased with donor oocyte fresh and frozen transfer and autologous oocyte frozen embryo transfer.

C. What does this study add to what is already known?

Although IVF-conceived pregnancies have been previously shown to be at greater risk hypertensive disorders of pregnancy, this study refined the association demonstrating that risk is limited to pregnancies achieved via autologous frozen and oocyte donation fresh and frozen transfer.

Abstract

Background: Although in vitro fertilization (IVF) has been associated with an increased risk for hypertensive disorders of pregnancy, the association of risk with IVF treatment parameters is unclear.

Objective: To evaluate risk for hypertensive disorders of pregnancy by maternal fertility status, and IVF treatment parameters.

Study Design: Women in 8 States who underwent IVF resulting in a live birth during 2004 through 2013 were linked to their infant's birth certificates. A 10:1 sample of births from non-IVF deliveries were selected for comparison. Those with an indication of infertility treatment on the birth certificate were categorized as subfertile and omitted for the study population; all others were categorized as fertile. The IVF pregnancies were additionally categorized by oocyte source (autologous vs donor) and embryo state (fresh vs thawed). Both the fertile and IVF births were limited to singletons only, and the IVF pregnancies were limited to those using partner sperm. Hypertensive disorders of pregnancy (including gestational hypertension and preeclampsia) were identified from the birth certificate, modeled using logistic regression, and reported as adjusted odds ratios (AOR) and 95% confidence intervals. For analyses of IVF pregnancies from autologous oocytes-fresh embryos, the reference group was fertile women (subgroup analysis 1). For analyses within the IVF group, the reference group was autologous oocytes- fresh embryos (subgroup analysis 2).

Results: The study population included 1,465,893 pregnancies (1,382,311 births to fertile women and 83,582 births to IVF-treated women). Compared to fertile women, IVF women with autologous-fresh cycles did not have an increased risk for hypertensive disorders of pregnancy [AOR 1.04, 95% CI 0.99, 1.08]. Among IVF births (subgroup analysis 2), the risk for hypertensive disorders of pregnancy was increased for autologous-thawed, 1.30 [1.20, 1.40]; donor-fresh, 1.92 [1.71, 2.15]; donor-thawed, 1.70 [1.47, 1.96]. Excluding women with pregestational diabetes or chronic hypertension, and adjusting for body mass index and infertility diagnoses did not substantially change the results. When stratified by <34 weeks (early onset hypertensive disorders of pregnancy) versus ≥34 weeks (late onset hypertensive disorders of pregnancy), only the donor-fresh group had an increased risk for early-onset, but the risks for all other oocyte source-embryo state groups compared to autologous-fresh were increased for late-onset.

Conclusion: The risk for hypertensive disorders of pregnancy is increased for IVF-treated women ~~and~~ in pregnancies conceived via frozen embryo transfer (with both autologous or donor oocyte) and fresh donor oocyte embryo transfer. No increase in risk was seen with fresh autologous IVF cycles. Excluding women with pregestational diabetes or chronic hypertension, and adjusting for body mass index and infertility diagnoses did not substantially change the results.

Key words: autologous-fresh, autologous-thawed, donor-fresh, donor-thawed, embryo state, gestational hypertension, preeclampsia, in vitro fertilization, infertility, oocyte source

Introduction

The use of assisted reproductive technologies (ART) has risen steadily in the United States since the first in vitro fertilization (IVF) birth in 1981 due to several reasons, including childbearing at older maternal ages and increasing insurance coverage and availability of infertility treatments [1-4]. The number of ART cycles in the United States has more than tripled in the most recent 20-year period between 1997 and 2017 (from 71,826 to 248,385 cycles per year [196,850 with intent to transfer]), and currently 2.0% of all live births in the United States are the result of this technology [5-8]. In addition, over the past decade, there have been important changes in IVF treatment, with a growing proportion of cycles from cryopreserved oocytes or embryos [9-11]. In 2016, nearly 60% of ART cycles in the United States were categorized as either frozen embryo transfer (FET) or banking of eggs/embryos for future FET [9]. Data from the Society for Assisted Reproductive Technology Clinical Outcomes Reporting System (SART CORS) indicates that in the US the proportion of IVF cycles resulting in live births using donor oocytes paralleled increasing maternal age in both 2004 and 2015, accounting for about 16% of cycles in both years [6].

It is well-established that both ART and subfertility are associated with compromised maternal and infant perinatal outcomes [12-20]. In addition to being older and of lower parity, subfertile and IVF-treated women begin pregnancy with a higher prevalence of chronic disease (hypertension and diabetes) compared to their fertile counterparts, and are more likely to develop hypertensive disorders of pregnancy and diabetes, as well as placental complications [20,21]. IVF cycles and donor oocyte cycles are associated with increased risks for hypertensive disorders of pregnancy compared to spontaneously-conceived pregnancies [22-29]. FET and donor oocyte cycles in particular commonly employ protocols in which estradiol and progesterone are used to develop the endometrium, and there is no formation of the corpus luteum at the time that pregnancy begins [30]. Emerging data suggest that absence of the corpus luteum is associated with deficient maternal circulatory adaptations during early gestation [31-33] and increased risk for hypertensive disorders of pregnancy [32, 34].

A persistent, unresolved question is whether adverse outcomes such as the increased risk of hypertensive disorders in pregnancy among subfertile and IVF pregnancies are related to the treatment parameters or the underlying infertility diagnosis [35]. It is also not clear whether the increase in hypertensive disorders of pregnancy that has been associated with IVF is present for both fresh embryo transfer and FET, or is limited only to FET. The purpose of this analysis is to evaluate the risk of hypertensive disorders of pregnancy (including gestational hypertension and preeclampsia) by maternal fertility status, treatment parameters, and infertility diagnosis.

Materials and Methods

This study involved linking data from the national IVF database, SART CORS, to birth certificates as part of a larger study in 14 States (CA, CO, CT, FL, IL, MA, MI, NC, NJ, NY, OH, PA, TX, and VA) on ART and risk of childhood cancer (NIH grant R01 CA151973), with continuing analyses in four of the original States (NY, TX, MA, and NC) to evaluate subsequent child health (NIH grant R01 HD084377). The data for the current analysis was limited to live births (≥22 weeks' gestation and ≥300 grams birthweight) to mothers at least 18 years of age in study States in which the 2003 revision of the US Certificate of Live Birth had been implemented. The study States and years based on the 2003 revision of the US Certificate of Live Birth included: California, 2006-13; Colorado, 2007-13; Florida, 2004-13; Michigan, 2007-13; New York City, 2008-13; New York State, 2004-13; Ohio, 2006-13; Pennsylvania, 2004-13; and Texas, 2005-13.

SART CORS data

The Society for Assisted Reproductive Technology (SART) maintains Health Insurance Portability and Accountability Act of 1996 (HIPAA)-compliant Business Associate Agreements with its approximately 375

reporting clinics. In 2004, following a contract change with the Centers for Disease Control and Prevention, SART leveraged the SART CORS data system for the purposes of conducting research. SART makes data available for research to entities that have agreed to comply with SART research guidelines. Patients undergoing assisted reproductive technology at SART-associated clinics sign clinical consent forms that include permission to use their deidentified data for research. The database includes information on demographic factors, IVF diagnoses and treatment parameters, and pregnancy outcomes. The data in the SART CORS are validated annually with some clinics having on-site visits for chart review. During each visit, data reported by the clinic are compared with information recorded in the medical record; most data fields have discrepancy rates less than 2%, with discrepancy regarding diagnosis fields ranging from 2-5% [6].

Birth Certificate Data

The 2003 revision of the birth certificate includes specific severe maternal morbidities occurring within 24 hours before or after delivery: maternal transfusion; third or fourth degree perineal laceration (vaginal births); ruptured uterus; unplanned hysterectomy; and admission to intensive care; gestational hypertension and preeclampsia. Also in the 2003 revision of the birth certificate, three checkboxes were added to indicate that: *1) the pregnancy resulted from infertility treatment, (worded as: if yes, check all that apply): 2) Fertility-enhancing drugs, artificial insemination, or intrauterine insemination; 3) Assisted reproductive technology (e.g., IVF [in vitro fertilization], GIFT [gamete intrafallopian transfer]).* Pregnancies which linked to the SART CORS cycles were categorized as IVF; pregnancies with an indication that it resulted from infertility treatment (via the infertility checkbox) but did not link to an IVF cycle were categorized as subfertile and omitted from the study population; the remaining pregnancies were categorized as fertile. The study population was limited to singleton births only. The data was further limited when diabetes reported on the birth certificate could be differentiated as pregestational versus gestational.

Linkage procedure

In the course of conducting a study on childhood cancer following IVF, we linked the SART CORS data and State Vital Records. Each State received a file of cycles of women who were residents of that State. To begin the linkage process, a limited data file was generated by Redshift Technologies, Inc., the organization which maintains the SART CORS on behalf of SART, containing only the following factors: study-specific patient ID and cycle ID, woman's first, middle name or initial, and last names, social security number, date of birth, zip code of residence, date of cycle outcome (live birth), plurality of the live birth, sex(es) and birthweight(s) of the infant(s). The State then performed a linkage to identify the IVF births; 84.4% of IVF-conceived births in the SART CORS were linked to their respective birth certificates. For each delivery identified as having been conceived by IVF, we requested that the subsequent 10 deliveries (all liveborn infants from a pregnancy) be selected as the non-IVF comparison group, although not all States implemented this request, providing the next 10 births (individual children) instead, and often only one infant from a twin or triplet+ pregnancy. The files of the study children were then linked to each State's vital records. Once all data were linked and complete, the files were stripped of all identifying elements (such as names, dates, social security numbers, and any other information that could identify an individual), but retaining the patient ID and cycle ID for the IVF group. The de-identified files were then transmitted to the investigators using secure file transfer methods. For the investigators, Redshift created a de-identified data file with the study-specific patient ID and cycle ID, and the IVF treatment parameters, and sent the file by secure transfer methods. We then merged the two deidentified data files using the patient ID and cycle ID. This study was approved by the Institutional Review Boards at Michigan State University, the University of Michigan, and each of the State Departments of Health. The Michigan State

University IRB determined that this research did not involve human subjects, as defined in 45 CFR 46.102 (f), in reviews dated June 23, 2011 and November 13, 2015.

Comparison groups

Women were classified as IVF-treated only if the State matched the subject to a record in the SART CORS; 84.4% of the women in the SART CORS were identified by the matching; a comparison of the matched and non-matched women and their pregnancies is shown in Supplemental Table 1. The matched and non-matched women were very similar in most characteristics. The IVF-treated women were then divided into 4 groups depending on the source of the oocyte (autologous or donor) and the state of the embryo (fresh or thawed). Subgroup analysis 1 included births to fertile, and IVF-treated women with autologous-fresh cycles. Subgroup analysis 2 included IVF births by the four oocyte source-embryo combinations.

Variables

Independent variables included maternal age at delivery (continuous and as 18-24, 25-29, 30-34, 35-37, 38-40, 41-43 and ≥44 years), race (white, black, Asian, other) and Hispanic ethnicity, education (less than 8th grade, some high school, high school graduate or GED, some college or associate degree, bachelor's degree, or post-graduate education), parity (nulliparous, primiparous, or multiparous prior to the index pregnancy), pregestational diabetes and gestational diabetes, chronic hypertension, length of gestation (continuous and as 22-27 weeks, 28-32 weeks, 33-36 weeks, and ≥37 weeks), body mass index (BMI), and infant sex. IVF treatment parameters included the number of prior IVF cycles and infertility diagnoses (male factor, endometriosis, ovulation disorders, diminished ovarian reserve, tubal ligation, tubal hydrosalpinx, tubal other, uterine factor, unexplained, and other-RFA [immunologic, chromosomal, or other serious disease]). BMI (weight/height squared) was calculated from height and pregnancy weight reported on the birth certificate for subanalysis 1, and from height and prepregnancy weight reported in the SART CORS for subanalysis 2. Dependent variables included gestational hypertension or preeclampsia as a single outcome of hypertensive disorders of pregnancy, as identified on the birth certificate.

Statistical Methods

There were two subgroup analyses: 1) births among the fertile and IVF autologous-fresh groups, with the fertile group as the reference and 2) births within the IVF groups, by oocyte source-embryo state categories, with the autologous-fresh group as the reference. We modeled the risk of hypertensive disorders of pregnancy using logistic regression as adjusted odds ratios (AOR) and 95% confidence intervals controlling for fertility group, maternal age, race and ethnicity, education, parity, State of residence, year of birth, and infant sex, overall and by early-onset (<34 weeks) hypertensive disorders of pregnancy, and by late-onset (≥34 weeks). Four models were generated based on further adjustments and exclusions: Model 1 adjusted for pregestational diabetes and chronic hypertension; model 2 excluded pregestational diabetes and chronic hypertension, model 3 excluded pregestational diabetes and chronic hypertension and adjusted for pregestational BMI, and model 4 excluded pregestational diabetes and chronic hypertension and adjusted for infertility diagnoses. All analyses were performed using the SAS software, version 9.4 (SAS Institute).

Results

The study population included 1,437,065 pregnancies in subgroup analysis 1 and 83,582 pregnancies in subgroup analysis 2. A description of the total study population is shown in Table 1. Women in the fertile group were more likely to be younger, Hispanic, and multiparous, and less likely to be college graduates compared to the IVF groups, which for most characteristics tended to be similar. Within the IVF groups, women who used donor oocytes were substantially older than those using autologous oocytes, and those using fresh embryos were more likely to be nulliparous and have fewer prior cycles compared to women

using thawed embryos. Otherwise IVF-treated women did not vary by other characteristics. The rates of hypertensive disorder of pregnancy were 3.6% for fertile women, 4.5% with autologous-fresh pregnancies, 5.3% with autologous-thawed, 9.3% with donor-fresh, and 7.1% with donor-thawed.

The results of the logistic regression models by subgroup analyses are shown in Table 2. Compared to fertile women, IVF-treated women in the autologous-fresh group (subgroup analysis 1) did not have an increased risk of hypertensive disorders of pregnancy in any of the models, for all gestations, and in pregnancies limited to <34 weeks or ≥34 weeks; the adjusted odds ratios (AORs) ranged from 1.03 to 1.05 for all gestations, 0.84 to 0.86 for gestations <34 weeks, and 1.01 to 1.03 for gestations ≥34 weeks. Within the IVF group (subgroup analysis 2), for all gestations, the results were consistent similar for each of the four models, with significantly increased risks of hypertensive disorders of pregnancy compared to the autologous-fresh group for the autologous-thawed group (AOR 1.30), the donor-fresh group (AORs from 1.91 to 1.96), and the donor-thawed group (AORs from 1.51 to 1.70). For gestations ≥34 weeks, the results were similar, with significantly increased risks in the autologous-thawed group (AORs from 1.32 to 1.37), the donor-fresh group (AORs from 1.90 to 1.94), and the donor-thawed group (AORs from 1.43 to 1.65). Among gestations <34 weeks, only the risks for the donor-fresh group were significantly increased, for model 1 and model 3, with AORs of 1.54 and 1.92, respectively.

Comment

Main findings

These analyses demonstrate that the risk for hypertensive disorders of pregnancy is increased with ~~subfertility,~~ autologous frozen embryo transfer~~,~~ and donor oocyte fresh and frozen embryo transfer. Importantly, our analyses did not find an increased risk for hypertensive disorders of pregnancy with fresh autologous oocyte transfer. In analyses adjusted for potential confounding factors, the risk for hypertensive disorders of pregnancy was highest among pregnancies achieved with donor oocytes using fresh or thawed embryos.

Clinical implications

Our findings add to a growing literature regarding adverse outcomes associated with specific ~~subfertility and with particular~~ types of IVF treatment [12-29, 32, 34-36], including perinatal and maternal morbidity. For example, a recent analysis of the risk of severe maternal morbidity by our group reported a two-fold greater risk of unplanned hysterectomy among autologous-thawed and donor-thawed IVF pregnancies [36]. Our findings demonstrating an increased risk of hypertensive disorders with ooycte donation are similar to Blazquez et al who also noted a similar risk of preeclampsia for fresh compared with frozen embryo transfers using donor oocytes [37]. Our findings are also consistent with a recent meta-analysis reporting an increased risk of preeclampsia with oocyte donation [38]. Although autologous IVF-conceived pregnancies have been previously shown to be at greater risk hypertensive disorders of pregnancy, the current study refined the association demonstrating that the risk is limited to pregnancies achieved via autologous frozen transfers~~, and that the risk is present for most infertility diagnoses~~.

Subfertility and adverse pregnancy outcomes are associated with the development of cardiovascular risk factors later in life [39-43]. Population-based studies have shown that women who experience pregnancy complications characteristic of placental syndrome (placental complications or preeclampsia/eclampsia) have an increased risk of cardiovascular disease as soon as 3-5 years after their birth [40]. Studies with longer periods of follow-up (8.7-14.6 years) support these findings, as well as a greater risk of mortality from cardiovascular causes [42, 43]. Clinical studies of women with a history of preeclampsia have additionally documented that these women have more unfavorable cardiovascular risk profile, more

extensive carotid atherosclerosis, and more cognitive impairment later in life, consistent with vascular disease/white matter pathology [44, 45]. Given the long-term implications of hypertensive disorders of pregnancy, any potential actionable factor affecting that risk is important to identify.

Although it may not be possible to modify some patient-related risk factors, altering critical components of the IVF treatment protocol could reduce the risk for hypertensive disorders of pregnancy. One potential explanation for the increased risk of hypertensive disorders of pregnancy in autologous frozen and donor oocyte fresh and frozen transfer is absence of the corpus luteum. Autologous frozen embryo transfers and donor oocyte recipient cycles (both fresh and frozen) are typically performed in programmed cycles in which endometrial development occurs in response to exogenous estradiol and progesterone, with ovarian suppression. Recent data suggests that the absence of the corpus luteum may perturb the maternal cirulcation in early pregnancy [32, 33] and increase the incidence of preeclampsia [32. 34]. With oocyte donation cycles, it is possible that autoimmune factors associated with the use of donor gametes [38] as well as increased maternal age may also contribute to increased risk for hypertensive disorders. Even if there are multiple contributors to risk of hypertensive disorders of pregnancy, any modifiable factor, such as protocol choice, is important to consider.

If further studies demonstrate an increased risk for hypertensive disorders associated with absence of the corpus luteum, it is possible that FET could be performed in the context of a natural cycle or in a cycle with ovulation induction for women who are anovulatory. For women who do not have functioning ovaries, such as a subset of women undergoing oocyte donation, it is possible that replacing missing products of the corpus luteum, such as relaxin, could potentially reduce the risk for development of hypertensive disorders of pregnancy, a hypothesis that would need to first be tested in the context of a randomized controlled trial. Further studies regarding the risk of hypertensive disorders associated with various protocols used for oocyte donation and autologous frozen embryo transfer are clearly warranted, given the increasing utilization of these treatment options.

Both small for gestational age birthweights and preeclampsia have been linked to abnormal placentation in early pregnancy, due to decreased trophoblastic invasion of the decidual and myometrial spiral arteries and apoptosis. Several research teams have reported a strong association between supraphysiologic hormonal milieu and a constellation of adverse outcomes related to abnormal placentation, including fetal growth restriction, pregnancy-induced hypertension, and abnormal implantation of the placenta [46, 47]. Imudia et al [47] demonstrated that elevated peak serum estradiol levels (>90th percentile) on the day of hCG administration during controlled ovarian hyperstimulation for IVF (singletons born from fresh embryos) increased the likelihood of both small for gestational age birthweight (AOR 9.40, 95% CI 3.22, 27.46) and preeclampsia (AOR 4.79, 95% CI 1.55, 14.84). It has been suggested that superovulation alters the expression of genes critical to endometrial modeling during early implantation [48, 49]. It has been postulated that preeclampsia results from an abnormal maternal immune response to novel paternally-derived antigens [50, 51].

Strengths and limitations

This study has several strengths. The study includes a very large samples size and the SART CORS data were collected prior to and separately from the vital statistics data. Therefore, we have no reason to expect differential misclassification of the primary outcome, hypertensive disorders of pregnancy. SART CORS contains reliable classification of oocyte source and embryo state. The analyses controlled for many potential confounders.

The study has limitations. An observational linkage analysis such as this one is unable to control for all factors that may affect outcome. Details about the specific treatment protocols used were also not available. In addition, validation of hypertensive disorders of pregnancy as reported on the birth certificate compared to the medical record has not been done. Also, postpartum preeclampsia may be under-reported on the birth certificate. The use of vital records for the outcome of gestational hypertension or preeclampsia most likely underestimated the actual prevalence of this complication. Although early validation studies of the 2003 revision of the US Certificate of Live Birth showed varying sensitivities, those analyses were based on only 600 births, and for gestational hypertension, the numerator included fewer then five records [52]. In contrast, recent analyses of the population-based Massachusetts Outcomes Study of Assisted Reproductive Technology (MOSART) [20, 21], which used similar methodology to this present study, as well as hospital discharge records, reported a higher prevalence of gestational hypertension or preeclampsia compared with the current study. Using the current definition of hypertensive disorders as defined by the American College of Obstetricians and Gynecologists, we included both gestational hypertension and preeclampsia within the definition of the primary outcome variable, hypertensive disorders of pregnancy [53]. But because the current study did not allow access to individual medical records, we were unable to validate the diagnoses as designated on the birth certificate. Despite this limitation, there is no clear reason to suspect that under-reporting of pregnancy outcome would vary depending on whether the IVF treatment included fresh or frozen embryo transfer, or autologous or donor oocytes. Lastly, this study may not have accurately identified individuals using IVF who were not fertile, although we did limit the IVF group to those who used partner sperm. An infertility diagnosis was listed for all couples in this analysis. Nationally, <5% of IVF cycles involve preimplantation genetic diagnosis (PGD) or preimplantation genetic screening (PGS) [54].

Conclusion and future research direction

These analyses demonstrate that the risk for hypertensive disorders of pregnancy is increased in IVF pregnancies achieved using autologous thawed embryos and donor oocyte fresh and thawed embryos. With the current growing utilization of thawed embryo transfers and freeze-only cycles, further research is needed to determine if modifiable treatment factors, such as absence of the corpus luteum, are associated with an increased risk for hypertensive disorders of pregnancy.

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