ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Embryo cryopreservation and preeclampsia risk

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Objective: To determine whether assisted reproductive technology (ART) cycles involving cryopreserved-warmed embryos are associated with the development of preeclampsia.
Design: Retrospective cohort study.
Setting: IVF clinics and hospitals.
Patient(s): A total of 15,937 births from ART: 9,417 singleton and 6,520 twin.
Intervention(s): We used linked ART surveillance, birth certificate, and maternal hospitalization discharge data, considering resident singleton and twin births from autologous or donor eggs from 2005–2010.
Main Outcome Measure(s): We compared the frequency of preeclampsia diagnosis for cryopreserved-warmed versus fresh ET and used multivariable logistic regression to adjust for confounders.
Result(s): Among pregnancies conceived with autologous eggs resulting in singletons, preeclampsia was greater after cryopreserved-warmed versus fresh ET (7.51% vs. 4.29%, adjusted odds ratio = 2.17 [1.67–2.82]). Preeclampsia without and with severe features, preeclampsia with preterm delivery, and chronic hypertension with superimposed preeclampsia were more frequent after cryopreserved-warmed versus fresh ET (3.99% vs. 2.55%; 2.95% vs. 1.41%; 2.76 vs. 1.48%; and 0.95% vs. 0.43%, respectively). Among pregnancies from autologous eggs resulting in twins, the frequency of preeclampsia with severe features (9.26% vs. 5.70%) and preeclampsia with preterm delivery (14.81% vs. 11.74%) was higher after cryopreserved versus fresh transfers. Among donor egg pregnancies, rates of preeclampsia did not differ significantly between cryopreserved-warmed and fresh ET (10.78% vs. 12.13% for singletons and 28.0% vs. 25.15% for twins).
Conclusion(s): Among ART pregnancies conceived using autologous eggs resulting in live births, those involving transfer of cryopreserved-warmed embryos, as compared with fresh ETs, had increased risk for preeclampsia with severe features and preeclampsia with preterm delivery. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Preeclampsia, preterm delivery, embryo cryopreservation, singleton birth, twin birth

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Preeclampsia is a common condition of late pregnancy, characterized as maternal hypertension with end organ injury after 20 weeks' gestation. It often includes proteinuria and may include thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, and visual symptoms (1). As a primary cause of maternal and perinatal mortality, preeclampsia has increased by 25% in the last 20 years in the United States and has resulted in 50,000–60,000 maternal deaths each year worldwide (1).

Despite its high prevalence, the etiology of preeclampsia remains unclear. It is commonly associated with abnormal placentation and evidence of a maternal inflammatory response, which may contribute to its pathogenesis (2, 3). It is more common in women who are nulliparous, African-American, obese, carrying twins, or using an egg donor or who have a personal or family history of the disorder; however, it can affect any pregnancy (3).

Assisted reproductive technology (ART) accounted for approximately 1.6% of births in the United States in 2013 (4). Use of ART is known to increase preeclampsia compared with

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spontaneous conception (5, 6). ART often involves embryo cryopreservation, as it allows supplementary embryos not transferred into the uterus immediately in a fresh cycle to be reserved for later pregnancy attempts. Improved fetal outcomes after cryopreserved-warmed transfers compared with fresh transfers have been reported, including lower preterm delivery rates and a decrease in low birth weight (7, 8).

While limited information is available regarding the effect of embryo cryopreservation on maternal outcomes, results from a few studies suggest an increased risk for preeclampsia in cryopreserved-warmed versus fresh ET (6, 9, 10). Prior studies are limited by considering hypertensive disorders in general (6), small numbers of singletons only (9), or patients with polycystic ovary syndrome only (10). The aim of the present study was to use linked ART surveillance and maternal hospital discharge data to examine the association between cryopreserved-warmed ET and incidence of preeclampsia in a large group of singleton and twin births after both autologous and donor egg ETs in women with a variety of infertility diagnoses.

MATERIALS AND METHODS

We used linked data from the States Monitoring ART (SMART) Collaborative, a project coordinated by the Centers for Disease Control and Prevention's (CDC) Division of Reproductive Health and the departments of health in the states of Connecticut, Massachusetts, and Michigan. Details about this linked data set have been described elsewhere (11, 12). Briefly, data from the National Assisted Reproductive Technology Surveillance System (NASS) are probabilistically linked with state-level vital records, hospital discharge, and other registry data. The linkage rate was 90%. At the time of this analysis, only Massachusetts had linked hospital discharge data; therefore, data from Connecticut and Michigan were excluded. Resident singleton and twin live births to women occurring in Massachusetts at >20 weeks of estimated gestational age from 2005 through 2010 were included. This study was approved by the Institutional Review Boards of the CDC and the Massachusetts Department of Public Health; it was determined exempt by the Institutional Review Board at Baystate Medical Center.

Among singleton and twin live births, we compared the distribution of demographic and clinical characteristics for births resulting from fresh ET with those from cryopreserved-warmed ET, stratified by use of autologous or donor eggs. Demographic and clinical variables were derived from the NASS database (gravidity, parity, body mass index at the start of the IVF cycle [BMI], infertility diagnosis, and ET type), birth certificates (pleurality, gestational age, infant sex, and mother's age and race/ethnicity), and maternal hospital discharge data. Chronic hypertension and pregestational diabetes were ascertained from maternal records using International Classification of Diseases, 9th Revision (ICD-9) codes (401.90 and 648.00), respectively. The proportion of missing data was 0.1%–16%, except for maternal BMI, which was missing in >50% of cases.

For both singleton and twin births resulting from fresh and cryopreserved-warmed ETs, we also compared the distribution of gestational age, infant sex, preterm birth, gestational diabetes, preeclampsia, and eclampsia, stratified by use of autologous or donor eggs. Information on gestational age was obtained from the birth certificate. ICD-9 codes from maternal hospital discharge data were used to identify gestational diabetes (648.8), gestational hypertension (642.0–642.04), and types of preeclampsia and eclampsia (preeclampsia without severe features [642.40–642.44], preeclampsia with severe features [642.50–642.54], chronic hypertension with superimposed preeclampsia [642.7], and eclampsia [642.60–642.64]). Criteria used to define preeclampsia were updated and expanded by the American Congress of Obstetricians and Gynecologists (ACOG) in 2013 (1), but anyone who met the ACOG criteria for preeclampsia before 2013 would still meet the criteria after 2013. Each subject in our study met the ACOG criteria for preeclampsia that were active at the time of her diagnosis and would meet the criteria today. An additional variable to indicate preeclampsia with preterm birth was created to indicate the presence of any of the above preeclampsia ICD-9 codes for infants with a gestational age at birth <37 weeks.

Chi-square and Fisher's exact tests were used for bivariate comparisons. Continuous variables such as age were compared with unpaired *t*-tests. For the multivariable logistic regression analyses, models with generalized estimating equations were fit using preeclampsia and preeclampsia with preterm birth as the outcomes and type of ET as the predictor of interest. Covariates included in the models were birth year, infant sex, maternal age, maternal race, diabetes (pregestational or gestational), hypertension (chronic or gestational), and parity. Due to the high proportion of missing BMI data, separate models were constructed with and without BMI as a covariate. Two-tailed probabilities of $<.05$ were considered statistically significant.

RESULTS

Baseline maternal demographic and clinical characteristics for 9,417 singleton births from pregnancies achieved with autologous eggs and donor eggs and for 6,520 twin births from pregnancies achieved with autologous eggs and donor eggs are shown in Table 1. Overall, women using donor eggs were approximately 7 years older than those using autologous eggs, and male factor infertility was more frequent among those using autologous eggs than donor eggs for both singletons and twins, while diminished ovarian reserve was most commonly reported for donor egg cycles.

Among all gestations, women having fresh ETs were more likely to be nulliparous compared with those having cryopreserved-warmed transfers. For twin births, a greater percentage occurred among non-Hispanic white women with fresh ETs compared with those with cryopreserved-warmed ETs; no differences in maternal race/ethnicity were observed for singleton births. The frequency of maternal chronic hypertension and pregestational diabetes mellitus diagnoses did not differ significantly between fresh and cryopreserved-warmed transfers. With both autologous and donor egg pregnancies, women having cryopreserved-warmed transfers were more likely to have had a prior ET compared with those having a fresh transfer, which was