Published in final edited form as:

Fertil Steril. 2017 November ; 108(5): 784–790. doi:10.1016/j.fertnstert.2017.08.035.

Embryo cryopreservation and preeclampsia risk

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Abstract

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 [95% CI 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.

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C.K.S. has nothing to disclose. D.W. has nothing to disclose. M.B. has nothing to disclose. D.B. has nothing to disclose. I.M.B. has nothing to disclose. S.B. has nothing to disclose. Y.Z. has nothing to disclose.

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Presented at the Annual Meeting of the American Society for Reproductive Medicine, which was held on October 17–19, 2016, in Salt Lake City, Utah.

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.

Keywords

Preeclampsia; preterm delivery; embryo cryopreservation; singleton birth; twin birth

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 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 common practice in Massachusetts during this time period (P<.0001, Table 1).

The outcomes of singleton births from pregnancies conceived with autologous and donor eggs, comparing fresh and cryopreserved-warmed ETs, are shown in Table 2. Considering the pregnancies from the autologous egg group, the frequency of maternal diagnoses of preeclampsia of all types, including preeclampsia without severe features, preeclampsia with severe features, preeclampsia with preterm delivery, and chronic hypertension with superimposed preeclampsia, was higher after cryopreserved-warmed ET than after fresh transfer. Eclampsia was rare and did not differ between groups.

In pregnancies conceived with donor eggs resulting in singleton births, the mean gestational age at delivery was almost 1 week later after fresh transfer compared with cryopreserved transfer, although both were at term (>37 weeks, Table 2). The rate of preeclampsia did not differ between the cryopreserved transfer and fresh transfer groups (10.78% vs.12.13%, respectively, P=.56). Compared with births from pregnancies after fresh ETs, preterm birth and gestational hypertension were more frequent in births from pregnancies after cryopreserved-warmed transfers (11.82% vs. 17.10%, P=.04, and 6.69% vs. 10.78%, P=.05, respectively).

Twin birth outcomes after the transfer of embryos from autologous and donor eggs are depicted in Table 3. Greater than 50% of twins delivered preterm, but there was no difference in mean gestational age between fresh and cryopreserved transfers within these groups. Similar to singleton gestations from autologous eggs, preeclampsia with severe features and preeclampsia with preterm delivery were more frequent among twin pregnancies after cryopreserved warmed transfers than fresh ETs (9.26% vs. 5.70%, $P<.01$, and 14.81% vs. 11.74%, $P=.04$, respectively).

In contrast, the incidence of all types of preeclampsia was similar between cryopreserved and fresh transfer groups among births from donor egg twin pregnancies (Table 3). The number of embryos transferred did not affect risk for preeclampsia except for donor egg twin pregnancies (odds ratio [OR] = 3.25 [1.23–8.23], data not shown).

Multivariable model parameter estimates for singleton births from pregnancies conceived with autologous eggs are shown in Table 4. We considered both the entire group of autologous egg singletons (n = 8,505) as well as a subgroup restricted to mothers whose BMI was known (n = 3,368). For the entire group, the multivariate adjusted odds ratio for preeclampsia was 2.17 (1.67–2.82), and for preeclampsia with preterm delivery was 2.19 (1.43–3.35). Type of ET, any diabetes, any hypertension, and parity were predictive of preeclampsia in both groups; in the group with BMI data, BMI was also a predictor for preeclampsia. Furthermore, type of ET, hypertension, and BMI predicted preeclampsia with preterm delivery. We did not investigate other gestational categories due to limited power.

DISCUSSION

We report that embryo cryopreservation and warming, which are used commonly and sometimes preferentially for ET with ART cycles, increased the likelihood of preeclampsia with severe features among resulting births, compared with fresh ET, when using autologous eggs. Among singleton pregnancies, preeclampsia was associated with embryo cryopreservation after stratifying for diabetes, hypertension, infant sex, mother's race/ethnicity, and parity. In addition, preeclampsia occurring with preterm delivery was increased in both singleton and twin gestation pregnancies after cryopreserved-warmed transfer with autologous eggs. Among donor egg pregnancies, no difference was detected in preeclampsia rates between fresh and cryopreserved-warmed ETs. To the best of our knowledge, this is the largest report of a possible effect of embryo cryopreservation and warming on the incidence of preeclampsia in pregnancies conceived with both autologous and donor eggs and the first to include information on the severity of preeclampsia and concurrent preterm delivery, a clinically relevant finding.

In singleton gestations using autologous eggs, we report an increase in all categories of preeclampsia after cryopreserved-warmed transfers compared with fresh transfers. Our finding is similar to other reports that do not specify the methods used for embryo cryopreservation (10, 13). In the present study, it is likely that a variety of methods of embryo cryopreservation were employed including slow cooling and vitrification, as the study considered calendar years 2005–2010 in Massachusetts. At Baystate Medical Center, we reported that blastocyst vitrification exclusively as the method of embryo

cryopreservation increases preeclampsia in singleton gestations with autologous eggs by 3.1-fold (9). Thus, it appears that older methods of embryo cryopreservation and blastocyst vitrification (performed since 2009) (9) all may increase preeclampsia.

The mechanism for an effect of embryo cryopreservation on preeclampsia with autologous eggs is unknown. In a mouse model, rapid embryo freezing has been found to downregulate microRNA for the vascular endothelial growth factor signaling pathway in blastocysts, which could decrease the blastocyst's implantation potential and invasiveness (14). Alternatively, the endometrium itself may contribute. Low levels of E2 in early primate pregnancy allow for migration of extravillous trophoblasts into uterine spiral arteries with artery remodeling; elevation of E_2 later in pregnancy prevents further remodeling (15). If E_2 is elevated prematurely, extravillous trophoblast invasion of spiral arteries is suppressed (15, 16). With ART, E_2 is at pharmacologic levels early in gestation after injectable gonadotropins for ovarian stimulation in fresh cycles and after multiple E_2 transdermal patches in cryopreserved-warmed cycles. It is possible that prematurely elevated E_2 in ART pregnancies after both fresh and cryopreserved-warmed transfers may contribute to more frequent preeclampsia in ART pregnancies compared with spontaneous conceptions (6). Histological studies of preterm placentas after fresh and cryopreserved-warmed transfers of autologous eggs are needed to determine whether there is lower placental perfusion after cryopreserved-warmed transfers.

We found that preeclampsia was 2.69-fold more likely in singleton gestations when donor eggs were employed compared with autologous eggs, consistent with a meta-analysis (17). The reasons for an increase in preeclampsia risk with donor eggs are not well understood but could involve the maternal immune response. Preeclampsia occurs when the cytotrophoblast does not adequately penetrate the maternal decidual spiral arterioles to replace the endothelium, a process dependent on HLA-C expression by trophoblasts (2, 3). Anonymous donor eggs are, by definition, completely allogenic to the mother and likely express a different HLA-C pattern, which could result in failure of trophoblast invasion, leading to preeclampsia. The allogenic differences in donor egg pregnancies may be greater than whatever differences may be present between fresh and cryopreserved-warmed embryos, leading to increased preeclampsia after all donor egg transfers. Further research is needed to explain these findings.

The increased incidence of preeclampsia in twins compared with singletons has been recognized for many years and was confirmed in our study. This finding has been previously attributed to a larger placental mass or greater relative placental ischemia in twin gestations compared with singletons (18).

Our study has both strengths and limitations. We report a large sample of fresh and cryopreserved-warmed ETs with autologous and donor eggs, linking data from ART cycles to birth certificates and hospital discharge data in a single state. To the best of our knowledge, our study is unique in reporting an increase in severe preeclampsia occurring with preterm delivery after cryopreserved-warmed ETs with autologous eggs, even after controlling for confounders. However, our study is retrospective and did not involve randomization of ET type. We cannot determine which methods of cryopreservation were

used or what protocols were used for endometrial preparation, and BMI data were missing from a large number of cycles. When considering only women whose BMI was known, our findings remained consistent. In addition, we did not have data on the method of fertilization used (conventional vs. intra-cytoplasmic sperm injection) and embryo stage at transfer because these variables are not collected consistently for cryopreserved embryos in NASS. We do not have information about numbers of pregnancies using donor sperm or pregnancies with a prior history of preeclampsia. Embryo biopsy for preimplantation genetic diagnosis is unlikely to affect our results, as it occurred in <4.5% of cases (19). Future studies are needed to determine the mechanism of increased preeclampsia with embryo cryopreserved cycles. Patients having cryopreserved-warmed transfers should be counseled about and monitored more carefully for preeclampsia.

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TABLE 1

Baseline maternal demographic and clinical characteristics: singleton and twin autologous, singleton, and twin egg donor gestations.

	Singleton birth						Twin birth					
	Autologous eggs			Donor eggs			Autologous eggs			Donor eggs		
Variable	**Fresh (n = 7,453)**	**Cryopreserved (n = 1,052)**	***P* value**	**Fresh (n = 643)**	**Cryopreserved (n = 269)**	***P* value**	**Fresh (n = 5,196)**	**Cryopreserved (n = 540)**	***P* value**	**Fresh (n = 684)**	**Cryopreserved (n = 100)**	***P* value**
Age (y), mean ± SD	35.28 ± 4.08	35.01 ± 3.88	.04	41.78 ± 4.35	42.00 ± 5.04	.53	34.51 ± 3.91	34.61 ± 3.90	.58	41.08 ± 4.73	42.72 ± 4.26	.001
Gravida ≥1, %	53.70	32.89	<.0001	54.90	33.83	<.0001	28.43	22.96	.009	27.92	16.00	.01
Parity 0, %	64.62	41.06	<.0001	69.83	45.72	<.0001	33.64	27.22	.003	34.80	21.00	.001
BMI (kg/m^2), %												
<18.5	1.02	0.95	NA	0.62	0.37	NA	1.33	0.74	NA	0.88	2.00	NA
18.5–24.9	24.37	18.44		23.17	20.07		24.25	23.52		19.44	18.00	
25–25.9	8.96	9.32		7.31	10.78		8.18	7.22		7.31	6.00	
>30	6.24	5.70		4.67	2.97		6.62	5.19		2.63	4.00	
Missing	59.41	65.59		64.23	65.80		59.62	63.33		69.74	70.00	
Race/ethnicity, %												
White	84.74	84.32	.22	87.09	90.71	.52	85.16	82.96	<.0001	91.52	78.00	<.0001
Black	3.02	4.18		2.18	2.60		2.52	5.56		2.05	6.00	
Hispanic	3.37	3.61		3.42	2.60		3.87	5.56		1.46	2.00	
Native American	1.05	0.67		0.78	0.37		1.23	1.30		0.88	0.00	
Asian/Pacific Islander	7.74	7.22		6.07	3.72		7.10	4.26		3.51	14.00	
Unknown	0.08	0.00		0.47	0.00		0.12	0.37		0.58	0.00	
Chronic hypertension, %	1.27	2.00	.06	2.80	1.86	.49	1.66	1.11	.47	4.39	4.00	1.00
Pregestational diabetes, %	0.97	0.95	.96	0.62	1.49	.20	0.81	0.37	.43	0.58	2.00	.17
Infertility diagnosis, %												
Tubal	8.24	8.65	.0004	0.93	1.86	.0003	6.97	10.93	.003	0.58	2.00	.10
Ovulation	8.06	9.22		2.33	7.43		9.16	10.74		4.39	8.00	
Diminished ovarian reserve	3.74	0.95		41.68	31.97		3.23	1.11		39.47	26.00	
Endometriosis	4.33	4.09		1.24	0.74		4.35	4.07		2.05	2.00	

	Singleton birth						Twin birth					
	Autologous eggs			Donor eggs			Autologous eggs			Donor eggs		
Variable	**Fresh (n = 7,453)**	**Cryopreserved (n = 1,052)**	***P* value**	**Fresh (n = 643)**	**Cryopreserved (n = 269)**	***P* value**	**Fresh (n = 5,196)**	**Cryopreserved (n = 540)**	***P* value**	**Fresh (n = 684)**	**Cryopreserved (n = 100)**	***P* value**
Uterine	0.99	1.33		0.31	1.12		1.12	0.93		0.29	0.00	
Male only	24.47	24.52		1.87	0.74		23.60	25.17		4.68	4.00	
Other	10.08	8.75		19.44	28.25		9.45	10.74		22.81	32.00	
Unknown	23.68	24.05		5.44	7.06		25.87	23.52		6.73	6.00	
Multiple female without male	5.18	6.75		11.66	9.67		4.85	3.70		10.23	14.00	
Multiple female + male	11.22	11.69		15.09	11.15		11.41	9.07		8.77	6.00	
Embryos transferred	2.23 ± 1.03	1.98 ± 0.79	<.01	1.89 ± 0.46	1.94 ± 0.72	.25	2.42 ± 0.84	2.43 ± 0.92	.65	2.07 ± 0.30	2.28 ± 0.57	<.01
First ET, %	50.82	13.69		39.81	7.06		51.14	10.19		38.89	4.00	

Note: NA = over 50% of data are missing.

Sites. Embryo cryopreservation and preeclampsia risk. Fertil Steril 2017.

TABLE 2

Outcomes of singleton births from pregnancies achieved through ART with fresh versus cryopreserved-warmed ET, by egg source.

	Autologous eggs			Donor eggs		
Outcome	**Fresh (n = 7,453)**	**Cryopreserved (n = 1,052)**	***P* value[a] (unadjusted)**	**Fresh (n = 643)**	**Cryopreserved (n = 269)**	***P* value[a] (unadjusted)**
Gestational age (wk), mean ± SD	38.67 ± 2.13	38.61 ± 2.25	.43	38.61 ± 2.33	37.95 ± 2.74	.0002
Infant sex (female), %	48.20	48.29	.98	48.21	51.67	.35
Preterm birth, <37 wk, %	9.58	10.27	.52	11.82	17.10	.04
Gestational diabetes, %	7.30	7.89	.49	9.33	8.55	.71
Gestational hypertension, %	4.70	5.13	.58	6.69	10.78	.05
Preeclampsia, any type, %	4.29	7.51	<.0001	12.13	10.78	.56
Preeclampsia without severe features	2.55	3.99	.007	7.31	5.58	.34
Preeclampsia with severe features	1.41	2.95	.0002	4.51	4.83	.83
Preeclampsia with preterm delivery	1.48	2.76	.002	3.89	4.83	.64
Chronic hypertension with superimposed preeclampsia	0.43	0.95	.03	0.62	0.74	1.00
Eclampsia	0.01	0.10	.23	0.16	0.00	1.00

[a]Categorical: χ^2 test; continuous: *t*-test.

Sites. Embryo cryopreservation and preeclampsia risk. Fertil Steril 2017.

TABLE 3

Outcomes of twin births from pregnancies achieved through ART with fresh versus crypreserved-warmed ET, by egg source.

	Autologous eggs			Donor eggs		
Outcome	**Fresh (n = 5,196)**	**Cryopreserved (n = 540)**	***P* value[a] (unadjusted)**	**Fresh (n = 684)**	**Cryopreserved (n = 100)**	***P* value[a] (unadjusted)**
Gestational age (wk), mean ± SD	35.67 ± 2.90	35.75 ± 2.79	.51	35.64 ± 3.00	35.60 ± 2.27	.88
Infant sex (female), %	48.85	46.48	.30	47.95	46.00	.71
Preterm birth, <37 wk, %	52.19	53.70	.50	54.09	62.00	.14
Gestational diabetes, %	9.33	6.67	.04	11.70	14.00	.51
Gestational hypertension, %	6.56	11.85	<.0001	9.06	2.00	.02
Preeclampsia, any type, %	16.44	19.63	.06	25.15	28.00	.54
Preeclampsia without severe features	10.20	10.74	.69	13.16	16.00	.44
Preeclampsia with severe features	5.70	9.26	.0009	9.65	6.00	.24
Preeclampsia with preterm delivery	11.74	14.81	.04	18.71	22.00	.44
Chronic hypertension with superimposed preeclampsia	0.89	0.37	.32	3.22	6.00	.16
Eclampsia	0.15	0.00	1.00	0.29	0.00	1.00

[a]Categorical: χ^2 test; continuous: *t*-test.

Sites. Embryo cryopreservation and preeclampsia risk. Fertil Steril 2017.

TABLE 4

Multivariable model results, singleton births from pregnancies conceived with autologous eggs (n = 8,505).

Variable	Level	OR	95% Confidence limits		*P* value
Preeclampsia					
Embryo cycle	Cryopreserved	2.17	1.67	2.82	<.0001
Birth year (ref = 2010)	2005	1.05	0.75	1.47	.79
	2006	0.84	0.60	1.19	.34
	2007	0.94	0.67	1.31	.71
	2008	0.85	0.60	1.20	.36
	2009	0.98	0.70	1.35	.88
Infant sex	Male	1.22	0.99	1.50	.06
Mother's age		0.99	0.96	1.02	.50
Mother's race	Nonwhite	0.87	0.65	1.17	.35
Diabetes, any	Present	1.93	1.44	2.59	<.0001
Hypertension, any	Present	2.54	1.88	3.42	<.0001
Parity	1+	0.43	0.33	0.55	<.0001
Preeclampsia with preterm birth					
Embryo cycle	Cryopreserved	2.19	1.43	3.35	.0003
Birth year (ref = 2010)	2005	1.21	0.70	2.09	.49
	2006	0.96	0.55	1.69	.90
	2007	0.71	0.39	1.30	.27
	2008	1.10	0.63	1.89	.74
	2009	0.90	0.51	1.59	.73
Infant sex	Male	1.11	0.79	1.57	.54
Mother's age		1.03	0.98	1.07	.24
Mother's race	Nonwhite	1.03	0.65	1.65	.89
Diabetes, any	Present	1.77	1.08	2.91	.02
Hypertension, any	Present	2.96	1.85	4.72	<.0001
Parity	1+	0.51	0.34	0.76	.001
Restricted to records with nonmissing BMI (n = 3,368) Preeclampsia					
Embryo cycle	Cryopreserved	2.27	1.49	3.46	.0001
Birth year (ref = 2010)	2007	1.59	0.49	5.18	.44

Variable	Level	OR	95% Confidence limits		P value
	2008	0.86	0.52	1.44	.57
	2009	1.08	0.76	1.54	.65
Infant sex	Male	1.14	0.82	1.58	.43
Mother's age		0.99	0.95	1.03	.61
Mother's race	Nonwhite	0.83	0.52	1.30	.41
Diabetes, any	Present	1.84	1.20	2.81	.005
Hypertension, any	Present	3.09	1.93	4.95	<.0001
Parity	1+	0.53	0.36	0.78	.001
BMI (ref = under/normal)	Overweight/obese	1.97	1.41	2.75	<.0001
Preeclampsia with preterm birth					
Embryo cycle	Cryopreserved	2.33	1.14	4.76	.02
Birth year (ref = 2010)	2007	1.33	0.16	10.79	.79
	2008	0.83	0.35	1.97	.68
	2009	1.00	0.55	1.82	1.00
Infant sex	Male	0.93	0.54	1.62	.80
Mother's age		1.06	0.99	1.13	.11
Mother's race	Nonwhite	1.33	0.67	2.64	.41
Diabetes, any	Present	1.58	0.70	3.54	.27
Hypertension, any	Present	3.13	1.37	7.16	.007
Parity	1+	0.64	0.34	1.21	.17
BMI (ref = under/normal)	Overweight/obese	1.94	1.07	3.50	.03

Sites. Embryo cryopreservation and preeclampsia risk. Fertil Steril 2017.