Published in final edited form as:

Fertil Steril. 2011 February ; 95(2): 548–553. doi:10.1016/j.fertnstert.2010.05.049.

Perinatal morbidity after in vitro fertilization is lower with frozen embryo transfer

Suleena Kansal Kalra, M.D., M.S.C.E.[a], **Sarah J. Ratcliffe, Ph.D.**[b], **Lauren Milman, M.D.**[a], **Clarisa R. Gracia, M.D., M.S.C.E.**[a], **Christos Coutifaris, M.D., Ph.D.**[a], and **Kurt T. Barnhart, M.D., M.S.C.E.**[a,b]

[a]Division of Reproductive Endocrinology and Infertility, University of Pennsylvania, Philadelphia, Pennsylvania

[b]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania

Abstract

Objective—To study the association of perinatal outcome and IVF transfer type in a group of infertility patients with standardized treatment and similar prognosis.

Design—Retrospective cohort study.

Setting—University-based infertility center, January 1998 to June 2006.

Patient(s)—Two hundred eighteen IVF pregnancies after fresh embryo transfer (ET); 122 IVF pregnancies after frozen ET.

Intervention(s)—Assessment of perinatal outcome in fresh versus frozen ET pregnancies.

Main Outcome Measure(s)—Pregnancy outcomes after fresh versus frozen embryo transfer (ET). Primary outcome was a composite of three events: preterm delivery, intrauterine growth restriction, or low birth weight. Secondary outcomes were subtypes of pregnancy loss. Associations were assessed using multivariate logistic regression.

Result(s)—The final sample included 340 pregnancies: 218 fresh and 122 frozen ETs. Singleton pregnancy was less likely after transfer of fresh embryos (odds ratio [OR] 0.39, 95% confidence interval [CI] 0.23–0.67), and pregnancies after fresh ET were more likely to end in first-trimester loss (OR 1.82, 95% CI 1.05–3.13). Composite adverse outcome after transfer of fresh (44.0%) versus frozen (32.6%) embryos was higher (OR 1.52, 95% CI 0.90–2.56) and was strongly associated with twin gestation (OR 23.82, 95% CI 11.16–50.82).

Conclusion(s)—Perinatal morbidity is higher in IVF pregnancies conceived after a fresh ET compared with a frozen ET. Although some differences are related to conception with twin gestations, these findings suggest that adverse outcomes may be related to differences in IVF procedures.

Reprint requests: Suleena Kansal Kalra, M.D., M.S.C.E., 3701 Market Street, Suite 800, Philadelphia, PA, 19104 (FAX: 215-349-5512; skalra@obgyn.upenn.edu).

S.K.K. has nothing to disclose. S.J.R. has nothing to disclose. L.M. has nothing to disclose. C.R.G. has nothing to disclose. C.C. has nothing to disclose. K.T.B. has nothing to disclose.

Keywords

In vitro fertilization; adverse outcome; frozen embryo transfer; perinatal outcome; ovarian stimulation; hormonal environment

Since the first live birth resulting from in vitro fertilization (IVF), there has been a dramatic rise in the number of infants born as a result of this technology (1). However, there has been increasing concern regarding the potential health impact on infants conceived with the assistance of IVF. Studies have suggested that even singleton pregnancies are at increased risk for preterm birth, low birth weight, congenital anomalies, perinatal mortality and several other pregnancy-related complications (2–10). The etiology of these outcomes is as yet unknown.

We and others have hypothesized that dysfunctional placentation provides a biologically plausible explanation for these adverse outcomes (8, 9). The nonphysiologic hormonal milieu at the time of implantation and placentation during a fresh IVF cycle may modulate trophoblast invasion and lead to abnormal placentation. In contrast, hormonal parameters in a frozen-thawed embryo transfer (FET) cycle more closely resemble the endocrine environment at the time of an unassisted conception.

Earlier studies of perinatal morbidity associated with IVF have been limited by potential bias and confounding, including potential differences in laboratory technique across centers and limitation of study outcomes to those gestations that reached the third trimester (2, 7, 10). In particular, earlier studies investigating the association of FET and subsequent perinatal outcomes have not been limited to a cohort of similar-prognosis patients, such as those who have excess embryos available for cryopreservation. It is possible that patients who conceive after FETare inherently different than those who conceive with fresh embryo transfer but do not have excess embryos available for cryopreservation.

To minimize potential bias and confounding, we conducted a retrospective cohort study of patients with similar prognosis at a single center. We compared women who conceived after fresh embryo transfer, in which two-pronuclear (2PN)–stage embryos were available to freeze, with women who conceived after transfer of 2PN previously frozen embryos to determine the association of adverse perinatal outcomes, including early pregnancy loss, preterm delivery, low birth weight, and/or intrauterine growth restriction.

METHODS AND MATERIALS

Population

Our cohort consisted of all pregnancies conceived with the assistance of IVF at a single university center from January 1998 to June 2006. The exposed population included pregnancies achieved after the transfer of fresh embryos in cycles in which supernumerary embryos were available for freezing at the 2PN stage. The unexposed population included pregnancies conceived after the transfer of thawed embryos previously frozen at the 2PN stage. Embryos created from donor eggs and donor embryos were excluded from this analysis.

Embryo Transfer

The standard ovarian stimulation protocol during fresh IVF cycles used pituitary down-regulation with leuprolide acetate and recombinant FSH. Luteal supplementation consisted of daily intramuscular 50 mg progesterone. Fresh embryo transfers were performed on day 3 (197/218, 90.3%), or day 5 (21/218, 9.6%). Transfer of previously frozen thawed embryos was performed after pituitary down-regulation and endometrial preparation. Embryos were frozen at the 2PN stage and replaced 1 day after thaw (day 2 transfer).

Data Collection

Data collection included demographic information, obstetric history, infertility diagnosis, clinical information regarding the assisted reproductive technologies procedure (number of embryos transfered), and pregnancy outcome. Pregnancy outcome information included infant's date of birth, birth weight, and mode of delivery. Gestational age at delivery was calculated based on the date of the embryo transfer. Data were entered into an electronic database checked for outliers and missing information before statistical analysis. Institutional Review Board approval was obtained at the University of Pennsylvania before data collection.

Study Outcomes

The primary outcome was a composite dichotomous outcome consisting of at least one of three adverse events in the third trimester: preterm delivery (delivery before 37 weeks), intrauterine growth restriction (IUGR; <10th percentile for gestational age), or low birth weight (<2,500 g) (12).

Secondary outcomes analyzed included specific subtypes of pregnancy loss and/or complications, including: 1) first-trimester loss (biochemical loss, clinical pregnancy loss, or ectopic pregnancy); 2) clinical pregnancy loss alone; and 3) any adverse outcome (first-trimester loss, clinical pregnancy loss, second-trimester loss, preterm delivery, IUGR, and/or low birth weight). These outcomes are defined as follows: biochemical pregnancy loss: decreasing β-hCG levels below the discriminatory zone for visualization of an intra-uterine pregnancy; ectopic pregnancy: absence of intrauterine pregnancy on ultrasound with β-hCG levels above the discriminatory zone and/or absence of villi in endometrial specimen following dilation and curettage; clinical pregnancy loss: pregnancy loss at ≤12 weeks gestation after ultrasound confirmation of an intrauterine gestational sac; second-trimester pregnancy loss: pregnancy loss at >12 weeks' gestation and <24 weeks gestation.

Power Calculation

We performed an a priori sample size calculation based on an estimated prevalence of the composite primary outcome of 15% in the FET group and 30% in the fresh embryo transfer group (12). We used a 2:1 ratio of fresh:frozen embryo transfer pregnancies to optimize efficiency.

Assuming a type I error rate of 0.05, our estimated sample size of 100 pregnancies after FET and 200 pregnancies after fresh embryo transfer demonstrated 83% power to detect a twofold increase in the risk of our composite adverse perinatal outcome.

Data Analysis

All data management and analyses were performed using Stata version 8 (Stata Corp., College Station, TX). Some patients underwent both fresh and frozen embryo transfers (n = 58), and thus our two groups were correlated. Excluding successive patient cycles from the sample would have resulted in the exclusion of only frozen cycles, potentially biasing the results. Generalized estimating equations (GEEs) were performed to account for the inherent correlation among cycles from the same patient (13). Patient and treatment characteristics in the fresh and frozen embryo transfer groups were compared by using GEEs. The assessment of the association between type of embryo transfer (fresh vs. frozen) and risk of each type of adverse outcome was assessed using both bivariate and multivariate analyses.

Bivariate analyses were performed on all variables to assess for potential association with adverse outcome. Variables with a bivariate *P* value of <.20 and variables of known clinical importance were selected for inclusion in the multivariate analyses. The adjusted odds ratios (ORs) and 95% confidence intervals (CIs) from the GEE models were reported. The significance level for all analyses was set at $P<.05$.

RESULTS

A total of 368 pregnancies were eligible for inclusion; 238 followed transfer of fresh embryos, and 130 followed FET. Required information was unavailable for 20/238 (8.4%) conceptions after fresh embryo transfer and 8/130 (6.2%) conceptions after FET.

The final sample of 340 pregnancies, in 282 women, consisted of 218 conceptions after fresh and 122 after frozen embryo transfer. Table 1 presents patient and treatment characteristics in both groups. There were no statistically significant differences in most paramaters. Patients who conceived after FETwere more likely to be parous. The maximum E_2 levels were over tenfold higher and the endome-trial stripe was thicker in fresh embryo transfer cycles. There were significantly more frozen embryos transferred compared with fresh embryos.

Fresh embryo transfer was more likely to result in a multiple pregnancy and, correspondingly, less likely to result in a singleton. There were a total of eight triplet pregnancies in our entire cohort, six after transfer of fresh embryos and two after FET.

Table 2 presents the results of unadjusted and adjusted analyses for adverse outcome by trimester in fresh versus frozen transfer cycles, as well as adjusted analyses for twin gestation. There were a total of 12 second trimester losses: seven after transfer of fresh embryos and five after frozen embryo transfer. Because second-trimester loss occurred so infrequently (4.5%) in our cohort, we were unable to use statistical methods to analyze this outcome independently.

Our primary outcome was a third-trimester adverse outcome incorporating the risk of any one of the following: preterm birth, IUGR, and low birth weight. In unadjusted analysis, there were increased odds of adverse third-trimester outcome after fresh transfer compared with FET, but this did not reach statistical significance. There was a statistically significant

increase in total adverse outcome (any one of first-trimester loss, second-trimester loss, or adverse third-trimester outcome) in pregnancies after a fresh embryo transfer compared with FET.

Bivariate analyses of treatment and patient characteristics associated with the risk of each adverse outcome were performed, and variables that met a prespecifed cutoff of $P<.20$ were selected for inclusion into final multivariate analyses. In addition to fresh versus frozen embryo transfer, other variables hypothesized or proved to be associated with adverse outcome were analyzed, including twin gestation, ovarian hyperstimulation syndrome (OHSS), intracytoplasmic sperm injection (ICSI), age, endometrial stripe thickness, maximum E_2 level, percentage fertilization, and parity. Compared with singletons, twins were 23 times more likely to experience a third-trimester adverse outcome (OR 23.17, 95% CI 11.07–48.51; $P<.001$) and 8.5 times more likely to experience any adverse outcome (OR 8.52, 95% CI 4.45–16.30; $P<.001$). Increasing maternal age was associated with an increase in the likelihood of clinical pregnancy loss (OR 1.18, 95% CI 1.06–1.32; $P=.004$). OHSS in the source cycle met the prespecified criteria for inclusion in multivariate analysis ($P=.10$), and parity was included because it was considered to be clinically important. The remainder of the variables were not included in the final model.

The significant results of multivariate analyses are presented in Table 2. Fresh embryo transfer was significantly more likely than FET to result in first-trimester loss. Twin gestation was associated with a 24-fold increase in odds of a third-trimester composite adverse outcome and an ~8-fold increase in the development of any adverse outcome. Parity and OHSS in source cycle had no association with any of the adverse outcomes (data not shown, *P* value nonsignificant). Increasing age was significantly associated with clinical pregnancy loss (OR 1.16, 95% CI 1.04–1.30; $P=.01$) but not with any other adverse outcome.

Given the association between twin pregnancy and adverse outcome in the multivariate model, we performed an unadjusted subanalysis restricted to the cohort of singleton pregnancies (Table 3). The direction of the association was consistent with the previous bivariate analysis and the multivariate analyses.

DISCUSSION

The purpose of this study was to isolate one aspect of the in vitro fertilization process to potentially identify components that may be associated with the increased perinatal morbidity noted in other studies (2–10). Previous studies reporting an increase in low birth weight in IVF infants who were conceived with a fresh embryo transfer compared with FET are limited by the inherent variability resulting from differences in treatment protocols at multiple sites and by the potential for differences in the risk of perinatal morbidity in women who do and do not have embryos available to cryopreserve. Our purposeful restriction to women of similar prognosis, treated in standardized fashion, allowed a more precise evaluation of the isolated effect of fresh versus frozen embryo transfer on subsequent perinatal outcomes in IVF pregnancies. In addition, we performed subanalyses of different

types of pregnancy loss to ascertain whether transfer of fresh embryos may be more likely to result in pregnancy loss.

Overall, this study found that the odds of first-trimester loss after fresh embryo transfer were nearly twice that after FET (OR 1.89, 95% CI 1.08–3.33; *P*=.027). Our data also demonstrated that adverse outcome beyond the first trimester is strongly associated with twin gestation but likely also independently associated with fresh embryo transfer. The odds of total adverse outcome after fresh embryo transfer were also increased, although they failed to reach statistical significance (OR 1.54, 95% CI 0.96–2.44; *P*=.08). Subanalyses restricted to singletons resulted in point estimates of similar magnitude and direction. When singleton pregnancies were analyzed separately, the rate of third-trimester adverse was considerably lower (19.6% after fresh ET, 16.9% after frozen ET), highlighting the major contribution of twin gestation on the subsequent development of adverse outcome. Thus, one important finding of this study is that there were significantly more twin pregnancies after fresh embryo transfer (29.8%) than after FET (13.9%). Together, these findings suggest that the independent negative contribution of fresh embryo transfer on perinatal morbidity is weaker than the contribution of multiple gestation.

The exact mechanism of the increased vulnerability of embryos to pregnancy loss after fresh embryo transfer is not known. Data have suggested that normal maintenance of pregnancy requires tonic suppression of uterine prostaglandin synthesis and that a defect in this inhibition can be associated with early pregnancy loss (14, 15). It is possible that this inhibition is altered in the setting of OHSS and retrieval (11, 16). The potential impact of inflammation and the nonphysiologic steroid milieu of a fresh IVF cycle on the expression of many of these processes is unknown. Therefore, transfer of fresh embryos into a supraphysiologic endocrine uterine environment may be associated with more risk.

Alternatively, it is possible that uncontrolled confounders, such as the difference in fresh versus frozen embryo cleavage stage on day of transfer, may have contributed to an increased risk of first-trimester loss. Frozen embryos were transfered on day 2, whereas the majority of fresh embryos were transfered on day 3. It has been previously suggested that transfer on day 2 may be associated with a lower rate of miscarriage (17–19). It has also been hypothesized that prolonged in vitro culture may compromise early development and predispose to increased risk of miscarriage (20). Finally, it is possible that embryos that survive the freeze thaw process are less likely to be aneuploid and, therefore, less likely to result in miscarriage (21). This finding may reflect an early natural selection process, because the most vulnerable frozen embryos do not survive the freeze-thaw process, and only the most competent frozen embryos survive the thaw and subsequently implant. A future study may better elucidate the mechanism underlying our findings.

Earlier literature has focused on the potential detrimental impact of cryopreservation due to the freeze-thaw process and subsequent adverse outcomes (22, 23). However, it is noteworthy that in our cohort, FET appeared to be, at the very least, as safe as fresh embryo transfer regarding the subsequent adverse perinatal outcomes, and it possibly conferred benefit. A potential reason for our conflicting results is that our cohort was limited to only those women who conceived after transfer of fresh embryos and had embryos to freeze at the

2PN stage. By restricting our cohort to this similar-prognosis population, we attempted to minimize potential bias and confounding.

These data provide potential insight into adverse outcomes associated with IVF-conceived pregnancies. In our cohort of similar-prognosis patients, IVF pregnancies that followed fresh embryo transfer appeared to be associated with an increased likelihood of first-trimester loss compared with pregnancies that followed FET. In addition, these data confirm earlier reports that FET may be associated with decreased fetal and perinatal morbidity independent of multiple gestation. Mechanisms underlying this association warrant further investigation.

References

1. [Accessed February 8, 2010] Assisted Reproductive Technology Report: Home. Available at: http://www.cdc.gov/ART/
2. Schieve LA, Meikle SF, Ferre C, Peterson HB, Jeng G, Wilcox LS. Low and very low birth weight in infants conceived with the use of assisted reproductive technology. N Engl J Med. 2002; 346:731–7. [PubMed: 11882728]
3. Klemeti R, Gissler M, Hemminki E. Comparison of perinatal health of children born from IVF in Finland in the early and late 1990s. Hum Reprod. 2002; 17:2192–8. [PubMed: 12151458]
4. Hansen M, Kurinczuk JJ, Bower C, Webb S. The risk of major birth defects after intracytoplasmic sperm injection and in-vitro fertilization. N Engl J Med. 2002; 346:725–30. [PubMed: 11882727]
5. Ericson A, Kallen B. Congenital Malformations in infants born after IVF: a population-based study. Hum Reprod. 2001; 16:504–9. [PubMed: 11228220]
6. Jackson R, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. Obstet Gynecol. 2004; 130:551–63.
7. Schieve LA, Ferre C, Peterson HB, Macaluso M, Reynolds MA, Wright VC. Perinatal outcome among singleton infants conceived through assisted reproductive technology in the United States. Obstet Gynecol. 2004; 103:1144–53. [PubMed: 15172846]
8. Shevell T, Malone FD, Vidaver J, Porter TF, Luthy DA, Comstock CH, et al. Assisted reproductive technology and pregnancy outcome. Obstet Gynecol. 2005; 106:1039–45. [PubMed: 16260523]
9. Chung K, Coutifaris C, Chalian R, Lin K, Ratcliffe SJ, Castelbaum AJ, et al. Factors influencing adverse perinatal outcomes in pregnancies achieved through use of assisted reproductive technology. Fertil Steril. 2006; 86:1634–41. [PubMed: 17074345]
10. Wang YA, Sullivan EA, Black D, Dean J, Bryant J, Chapman M. Preterm birth and low birth weight after assisted reproductive technology–related pregnancy in Australia between 1996 and 2000. Fertil Steril. 2005; 83:1650–8. [PubMed: 15950632]
11. Papanikolaou EG, Tournaye H, Verpoest W, Camus M, Vernaeve V, Van Steirteghem A, et al. Early and late ovarian hyperstimulation syndrome: early pregnancy outcome and profile. Hum Reprod. 2005; 20:636–41. [PubMed: 15576388]
12. Cannon CP. Clinical perspectives on the use of composite endpoints. Control Clin Trials. 1997; 18:517–29. [PubMed: 9408715]
13. Hanley JA, Negassa A, Edwardes MD, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. Am J Epidemiol. 2003; 157:364–75. [PubMed: 12578807]
14. Abel MH, Smith SK, Baird DT. Suppression of concentration of endometrial prostaglandin in early intra-uterine and ectopic pregnancy in women. J Endocrinol. 1980; 85:379–86. [PubMed: 7411005]
15. Jaschevatzky OE, Shalit A, Grunstein S, Kaplanski J, Danon A. Increased decidual prostaglandin E concentration in human abortion. Br J Obstet Gynaecol. 1983; 90:958–60. [PubMed: 6626492]
16. Simón C, Mercader A, Frances A, Gimeno MJ, Polan ML, Remohí J, et al. Hormonal regulation of serum and endometrial IL-1 alpha, IL-1 beta and IL-1ra: IL-1 endometrial microenvironment of

the human embryo at the apposition phase under physiological and supraphysiological steroid level conditions. J Reprod Immunol. 1996; 31:165–84. [PubMed: 8905550]

17. Shen S, Rosen MP, Dobson AT, Fujimoto VY, McCulloch CE, Cedars MI. Day 2 transfer improves pregnancy outcome in in vitro fertilization cycles with few available embryos. Fertil Steril. 2006; 86:44–50. [PubMed: 16730718]
18. Edwards RG, Rishel SB, Cohen J, Fehilly CB, Purdy JM, Slater JM, et al. Factors influencing the success of in vitro fertilization for alleviating human infertility. J In Vitro Fert Embryo Transfer. 1984; 1:3–23.
19. Oatway C, Gunby J, Daya S. Day three versus day two embryo transfer following in vitro fertilization or intracytoplasmic sperm injection. Cochrane Database Syst Rev. 2004; (2):CD004378. [PubMed: 15106249]
20. Rinaudo P, Schultz RM. Effects of embryo culture on global pattern of gene expression in preimplantation mouse embryos. Reproduction. 2004; 128:301–11. [PubMed: 15333781]
21. Hassold T, Hall H, Hunt P. The origin of human aneuploidy: where have we been, where are we going. Hum Mol Genet. 2007; 16:203–8.
22. Salumets A, Suikkari AM, Makinen S, Karro H, Roos A, Tuuri T. Frozen embryo transfers: implications of clinical and embryological factors on the pregnancy outcome. Hum Reprod. 2006; 9:2368–74.
23. Aytoz A, van den Abbeel, Bonduelle M, Camus M, Joris H, van Steirteghem A, et al. Obstetric outcome of pregnancies after the transfer of cyropreserved and fresh embryos obtained by conventional in-vitro fertilization and intracytoplasmic sperm injection. Hum Reprod. 1999; 14:2619–24. [PubMed: 10527997]

TABLE 1

Comparison of patient and treatment characteristics in fresh versus frozen embryo transfer cycles.

	Fresh (n = 218)	Frozen (n = 122)	*P* value[a]
Source cycle			
Infertility diagnosis			.680[b]
Tubal	46 (21.1)	25 (20.5)	
Male factor	33 (15.1)	24 (19.7)	
Anovulation	39 (17.9)	25 (20.5)	
Unexplained	67 (30.7)	37 (30.3)	
Endometriosis	27 (12.4)	11 (9.1)	
Other[c]	4 (1.8)	0 (0)	
Unknown	2 (0.9)	0 (0)	
Fertilization rate	67.21 ± .14	68.04 ± .16	.621
ICSI	36 (16.5)	16 (13.1)	.404
OHSS	49 (22.5)	26 (21.3)	.804
Embryo transfer cycle			
Parity	46 (21.1%)	47 (38.5%)	<.001
Age	33.53 ± 3.59	33.71 ± 3.70	.663
Maximum E_2 before embryo transfer	4921.8 ± 1503.6	335.3 ± 141.8	<.0001
EMS thickness at transfer	11.21 ± 2.30	10.31 ± 2.21	.0006
No. of embryos transfered	2.68 ± 0.78	2.90 ± 0.97	.022
Implantation rate			
Pregnancy plurality			.002
Singleton	122 (56.0) OR 0.39	93 (76.2) 95% CI 0.23–0.67	.0002
Twin	65 (29.8) OR 2.63	17 (13.9) 95% CI 1.43–5.00	.001
Triplet	6 (2.7) OR 1.69	2 (1.6) 95% CI 0.3–20.00	.52

Note: Continuous variables presented as mean ± SD, other values as n (%). CI = confidence interval; EMS = endometrial stripe; ICSI = intracytoplasmic sperm injection; OHSS = ovarian hyperstimulation syndrome; OR = odds ratio.

[a] Generalized estimating equation adjustment for correlations.

[b] Calculated after exclusion of other (n = 4) and unknown (n = 2), owing to small number of observations precluding use of chi-squared.

[c] Other (n = 4): two with recurrent pregnancy loss, two with uterine abnormalities (bicornuate, fibroid).

TABLE 2

Analysis of adverse outcomes in fresh versus frozen embryo transfers and twin gestation.

	Fresh, n (%)	Frozen, n (%)	Fresh ET, OR[e] (95% CI)	*P* value	Fresh ET, AOR[f] (95% CI)	*P* value	Twin gestation, AOR[g] (95% CI)	*P* value
First-trimester loss[a]	52/218 (23.9)	22/122 (18.0)	1.82 (1.05–3.13)	.03	1.89 (1.08–3.33)	.027	n/a	xxx
Clinical pregnancy loss	27 (12.4)	12 (9.8)			1.85 (0.77–4.35)	0.172		
Ectopic	3 (1.4)	2 (1.6)						
Biochemical loss	22 (10.1)	8 (6.6)						
Clinical pregnancy loss	27/193 (14.0)	12/112 (10.7)	1.35 (0.63–3.03)	0.41			n/a	xxx
Second-trimester loss[b]	7/166 (4.2)	5/100 (5.0)	xxx	xxx				
Third-trimester adverse outcome[c]	70/159 (44.0)	31/95 (32.6)	1.52 (0.90–2.56)	0.12	0.88 (0.43 – 1.72)	0.675	24.13 (11.2 – 51.6)	<.001
Preterm delivery	50 (31.4)	21 (17.2)						
IUGR	39 (24.5)	12 (12.6)						
LBW	53 (33.3)	17 (17.9)						
Any adverse outcome[d]	129/218 (67.9)	58/122 (47.5)	1.72 (1.12–2.63)	.01	1.54 (0.96–2.44)	.075	7.98 (4.2 – 15.2)	<.001

Note: AOR = adjusted odds ratio; CI = confidence interval; ET = embryo transfer; IUGR = intrauterine growth restriction; LBW = low birthweight; OR = odds ratio; xxx = insufficient numbers for statistical analysis.

[a] Any one of clinical pregnancy loss, biochemical loss, or ectopic pregnancy.

[b] Second-trimester pregnancy loss.

[c] Preterm delivery, IUGR, and/or low birth weight.

[d] Any one of clinical pregnancy loss, biochemical loss, ectopic pregnancy, second-trimester loss, preterm delivery, IUGR, and low birth weight.

[e] Generalized estimating equation adjustment for correlations.

[f] Adjusted for fresh embryo transfer, twin gestation (although first-trimester loss was not adjusted for twin gestation, because plurality was not known), maternal age at transfer, ovarian hyperstimulation syndrome in source cycle, and parity.

[g] Adjusted for fresh embryo transfer, maternal age at transfer, ovarian hyperstimulation syndrome in source cycle, and parity.

TABLE 3

Unadjusted analysis of pregnancy outcomes in singletons only.[a]

	Fresh	Frozen	OR (95% CI)	*P* value
Clinical pregnancy loss	23/122 (18.9)	13/94 (13.8)	1.41 (0.61–3.23)	.41
Third-trimester adverse outcome	19/97 (19.6)	13/77 (16.9)	1.23 (0.57–2.70)	.59
Total adverse outcome	44/122 (36.1)	30/94 (31.9)	1.30 (0.75–2.27)	.35

Note: CI = confidence interval; OR = odds ratio.

[a]Unadjusted bivariate analysis restricted to singleton births.