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# Ovarian Stimulation and Low Birth Weight in Infants Conceived Through In Vitro Fertilization

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## Abstract

**Objective—**Singleton infants born after in-vitro fertilization (IVF) are at increased risk for low birth weight (LBW) and/or preterm delivery. We sought to assess if the alteration of the peri-implantation maternal environment due to ovarian stimulation may contribute to increased risk in in vitro fertilization (IVF) births.

**Methods—**The Society of Assisted Reproductive Technology database was used to identify IVF-conceived infants born in the United States between 2004-2006. Associations were assessed in infants born after fresh compared with frozen and thawed embryo transfer in women of similar ovarian responsiveness, in paired analysis of infants born to the same woman following both types of embryo transfer, and in infants born following oocyte donation.

**Results—**Of 56,792 infants identified, 38,626 and 18,166 were conceived following transfer of fresh and frozen embryos, respectively. In singletons, there was no difference in preterm delivery. However, the odds of overall low birth weight (LBW) (10% vs.7.2%; AOR 1.35, 95% CI 1.20-1.51), LBW at term (2.5% vs. 1.2%; AOR 1.73, 95% CI 1.31-2.29), and preterm LBW (34.1% vs. 23.8%; AOR 1.49, 95% CI 1.24-1.78) were all significantly higher following fresh embryo transfer. In singletons following either fresh or frozen embryo transfer in the same patient, this association was even stronger (LBW: [11.5% vs. 5.6%; AOR 4.66, 95% CI 1.18 – 18.38,). In oocyte donor recipients who do not undergo any ovarian hormonal stimulation for either a fresh or

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a frozen embryo transfer, no difference in LBW was demonstrated (11.5% vs.11.3%; AOR 0.99, 95% CI 0.82 – 1.18).

**Conclusions—**The ovarian stimulation-induced maternal environment appears to represent an independent mediator contributing to the risk of LBW, but not preterm delivery, in infants conceived following IVF.

## Introduction

More than 57,000 infants are born yearly in the United States using assisted reproductive technologies (1). Multiple gestation remains the main contributor to perinatal morbidity in IVF conceptions, but data have indicated that even singleton births are at increased risk for a number of adverse perinatal outcomes, including low birth weight and preterm delivery (2-11). The contributing factors underlying this association are not known, but may be due to an underlying inherent increased risk in subfertile couples or, alternatively, may be associated with ovarian stimulation and/or procedures specific to the IVF treatment (7, 12, 13). IVF involves a complex set of medical, surgical and laboratory manipulations. During a fresh IVF cycle, exogenous gonadotropins are administered to promote the development of multiple follicles resulting in estradiol levels that can be 10-20 times greater than physiologic (14, 15, 16). Often, IVF cycles result in the generation of more embryos than is appropriate to transfer during the initial fresh cycle and embryos are cryopreserved. In a frozen/thawed embryo transfer cycle, the endometrium is prepared by mimicking the endocrine environment of a normal, non-stimulated menstrual cycle (17). Thus, the study of births following fresh versus frozen embryo transfer provides an opportunity to isolate one aspect of the IVF process because the environment in which the egg was stimulated, retrieved, fertilized and cultured is the same in both types of transfer, while the main difference is in the maternal endocrine milieu at the time of transfer and implantation.

The goal of this study was to assess if the alteration of the peri-implantation maternal environment due to ovarian stimulation may independently contribute to low birth weight (LBW) and/or preterm delivery following IVF. Live births following a fresh embryo transfer were compared to live births following transfer of frozen-thawed embryos in patients with similar ovarian response. To enhance the robustness of this analysis the outcome of infants born after a fresh and a frozen transfer, in the same woman (in different cycles) were compared. Finally, we contrasted these findings to infants conceived following a fresh or frozen ET cycle using donated oocytes. During these cycles, the recipients do not undergo any ovarian hormonal stimulation and thus the maternal hormonal milieu is the same for both transfer types.

## Methods and Materials

The data source for the study included data that is routinely recorded in a standardized fashion for reporting to the Society for Assisted Reproductive Technology (SART) and the United States Center for Disease Control and Prevention (CDC). Data collected included patient demographic characteristics, infertility diagnosis, medication, treatment methods (i.e. fresh versus frozen embryo transfer), and outcomes for each cycle. Live births of infants after conception with IVF were identified from the SART registry from 2004-2006 with 346, 345, and 343 clinics reporting for each year, respectively. Analysis was restricted to live births conceived following the transfer of fresh embryos only in similar ovarian response cycles in which supernumerary embryos were available for freezing, and compared to live births conceived after the transfer of thawed embryos. Three analyses were performed: 1) A comparison of live births resulting from fresh or frozen transfer in women with non donated oocytes, 2) a comparison of live births resulting from a fresh and a frozen

embryo transfer in the same woman (in different cycles), and 3) and comparison of live birth resulting from fresh or frozen transfer in women who conceived with donated oocytes. Where applicable,analyses were stratified by singleton and twin gestation.

Exposure was defined as live birth resulting from a fresh embryo transfer directly following hormonal ovarian hyperstimulation and ultrasound-guided oocyte retrieval. Comparison was made to live birth resulting from a frozen/thawed embryo transfer defined as transfer of embryos previously frozen after ovarian hyperstimulation and ultrasound guided oocyte retrieval and subsequently thawed for transfer in a separate cycle. Given that the frozen embryos were already created, hormonal ovarian hyperstimulation and ultrasound-guided oocyte retrieval were not performed during frozen ET cycles.

Information collected regarding the infants included date of birth, birth weight, and mode of delivery. Gestational age at delivery was calculated based on the date of the embryo transfer. Outcomes of this study include: preterm delivery (live born infant of gestational age of at least 32 weeks but less than 37 weeks), very preterm delivery (live born infant of gestational age of less than 32 weeks), low birthweight (LBW; infant weighing less than 2500 grams), term LBW (infant weighing less than 2500 grams and >=37 weeks gestation), preterm LBW (infant weighing less than 2500 grams and < 37 weeks gestation) and very preterm low birthweight (<2500 grams, <32 weeks). In addition, an analysis for small for gestational age (SGA: $<10^{th}$% for gestational age) was performed to assess the association with birthweight as a continuous variable corrected for gestational age. The study protocol was approved by the institutional review board of the University of Pennsylvania.

All data management and analyses were performed using STATA, version 11 (STATA Corp., College Station, USA). The assessment of the association between type of embryo transfer (fresh versus frozen) and risk of each type of adverse outcome was assessed using both univariable and multivariable analyses. In addition to our primary exposure of fresh as compared to frozen embryo transfer, the impact of other factors that have been demonstrated to be associated with adverse outcome were investigated, including: patient age at time of embryo transfer, prior parity, infertility diagnosis, number of embryos transferred, number of prior ART cycles, calendar year of treatment (2004,2005,2006), history of miscarriage and reduction in number of fetal hearts seen on initial ultrasound and number of infants born (i.e. vanishing twin) (18, 19). The adverse outcome of LBW was also stratified by preterm delivery. In these stratified analyses, preterm and very preterm deliveries were combined into one category when adjusting for the impact of other risk factors due to the low incidence of very preterm deliveries.

Patient and treatment characteristics in the fresh and frozen embryo transfer groups were compared using generalized estimating equations (GEEs) to account for correlation between groups because some women in the database underwent both fresh and frozen embryo transfers. Univariable analyses were performed on all variables to assess for potential association with adverse outcome. Variables with univariable p-value of <0.20 and variables of known clinical importance were selected for inclusion in the multivariable analysis. The adjusted odds ratios and 95% confidence intervals from the GEE models were reported. The significance level for all analyses was set at $p<0.05$. Sensitivity analyses were performed on data outside of expected norms including fresh embryo transfer after day 6 (n=79), non-oocyte donation cycle in patient greater than age 50 (n=704), a history of more than 5 full term births (n=48), transfer of greater than 6 embryos (n=98), and a total number of prior ART cycles that exceeded 6 cycles (n=642). Sensitivity analyses were performed on these outliers to assess if exclusion of these possible data entry errors significantly changed point estimates.

The SART database includes a unique patient ID field which allows for the identification of some patients who underwent more than one cycle at the same clinic. The database does not identify patients that transfer from one clinic to another. This unique patient ID allowed us to perform our second analysis, a paired analysis on a subset of patients who conceived a singleton pregnancy from at least one fresh and one frozen embryo transfer at the same institution at different points in time to control for the contribution from the host patient. Some patients delivered more than one singleton birth following a fresh and/or frozen embryo transfer, as such, more than two pregnancies were included for some women. Conditional logistic regression was used to analyze the paired data. Adjusted analyses potentially included the same covariates as in the primary analysis. However, categorical covariates with insufficient variability (<5% in one or more categories) in this subsample were either collapsed or excluded from the adjusted model, as appropriate.

The third analysis was restricted to singleton live births conceived following the transfer of fresh donor oocyte embryos, in cycles with supernumerary embryos available for freezing at the time of fresh oocyte collection, and compared to live births conceived following transfer of thawed embryos created with donor oocytes. This analysis used the same procedures as described above.

## Results

The SART database included a total of 368,833 cycles from 2004-2006. The analysis was restricted to only those cycles which resulted in live birth, thus excluding 238,616 cycles. To minimize the variability in prognosis for success, we further restricted the cohort of fresh embryo transfer births to those which resulted from transfer of fresh embryos only in cycles with excess embryos available for cryopreservation (best prognosis patients), thus excluding an additional 56,544 births. Also excluded from analysis were: births that resulted from simultaneous transfer of both fresh and frozen embryos (n=42), and those with missing live birth outcomes (n=471). For the primary analysis, oocyte donation births (n=16,368) were excluded, resulting in a total of 56,792 births eligible for inclusion; 38,626 followed transfer of fresh embryos and 18,166 followed transfer of frozen embryos.

Table 1 provides a comparison of patient and treatment characteristics in those who delivered a live birth following fresh compared to frozen embryo transfer in the overall cohort (with the exclusion of oocyte donor recipients Table 1 also demonstrates that pregnancies following frozen embryo transfer had a higher mean number of embryos transferred than pregnancies resulting from fresh embryo transfers (2.6 vs 2.4, respectively, $p<0.001$).

In patients with embryos available for cryopreservation, fresh embryo transfer was more likely to result in a clinical pregnancy than frozen embryo transfer, 52.1% versus 32.7%, respectively (data not shown in table). Despite the fact that fewer embryos were transferred, transfer of fresh embryos was more likely to result in a multiple birth than transfer of frozen embryos with an increased risk of twins following transfer of fresh embryos, 34.4% vs 21.9%, respectively (OR 1.93; 95% CI 1.85 – 2.02, $p<0.0001$). Triplets were also more likely following transfer of fresh versus frozen embryos, 2.4% vs 1.8%, respectively (OR 1.59, 95% CI 1.39-1.83, $p<0.0001$). There was no difference in infant gender with similar numbers of males and female infants born after fresh or frozen ET (Table 1).

Subsequent analyses were stratified by singleton and twin pregnancy. Table 2 presents the analysis of preterm delivery and low birthweight in singleton births following fresh versus frozen embryo transfer. Mean gestational age at delivery for singletons was the same for both fresh and frozen embryo transfer pregnancies, 38.0 +/- 2.7 weeks (p = NS).

The odds of low birthweight was significantly higher in IVF singletons following transfer of fresh embryos for all analyses; when low birthweight was analyzed as an overall variable (Overall LBW: AOR 1.35, 95% CI 1.20 – 1.51, p<0.001), and when low birthweight was stratified by term and preterm delivery (term low birth weight: AOR 1.73, 95% CI 1.31 – 2.29, p=0.001; preterm low birth weight: AOR 1.49, 95% CI 1.24 – 1.78, p<0.001). The subanalysis restricted to primiparous patients demonstrated consistent results with LBW more likely in singleton first births following fresh as compared to frozen embryo transfer (OR 1.23, 95% CI 1.06-1.42, p=0.007; AOR 1.25, 95% CI 1.06-1.46, p=0.007). In addition, a higher odds of SGA in singleton infants conceived after fresh vs. frozen ET was demonstrated (6.73% vs 3.5%, respectively; AOR 1.71, 95% CI 1.46 - 2.00, p <0.001). Mean birthweight was 156 grams lower in singleton infants following fresh as compared to frozen ET (3215.7 +/- 627.4 grams vs. 3371.9 +/- 653.3 grams, respectively, p<0.001).

Table 3 presents the analysis of preterm delivery and low birth weight in twin births following fresh versus frozen embryo transfer. There was no difference in the risk of preterm delivery in twins based on fresh versus frozen embryo transfer. Low birth weight, however, was significantly more likely to occur in twin pregnancies conceived following fresh as compared to frozen embryo transfer for all analyses.

Two important control analyses are presented in Tables 4 (pregnancies in the same patient) and 5 (pregnancies in donor-egg cycles). The results of the paired analysis of singleton pregnancies resulting from either a fresh and a frozen embryo transfer in the same patient are presented in Table 4. There were 680 singleton births following fresh embryo transfer and 676 singleton births following frozen embryo transfer in the same patient at two different times. Paired analysis demonstrated no association between transfer type and preterm delivery. However, low birthweight was strongly and significantly associated with fresh embryo transfer in both crude and adjusted analyses (AOR 4.66, 95% CI 1.18 – 18.38, p=0.03).

Table 5 presents the results of the analysis of 8,768 singleton live births resulting from oocyte donation. There was no association between transfer type and preterm delivery(AOR 0.96, 95% CI 0.84 – 1.09, p=0.50). There was also no association between transfer type and low birth weight (Overall LBW: AOR 0.99, 95% CI 0.82 – 1.18, p =0.87).

## Discussion

The elucidation of the contribution of treatment on the perinatal morbidity of children conceived with in vitro fertilization is of both scientific and public health importance. In this study, we isolate one aspect of the complex process of IVF to determine if ovarian hormonal stimulation is associated with adverse outcome. Using a large contemporary database, we have demonstrated that low birth weight is higher in children conceived following a fresh as compared to a frozen embryo transfer cycle. This finding, in conjunction with the results of the analyses in the same woman and in oocyte donor recipients, suggests an independent association between one aspect of IVF and perinatal morbidity. We hypothesize that the mechanism of this observation may be the non-physiologic peri-implantation maternal hormonal environment of a fresh IVF cycle following hormonal ovarian stimulation.

A major strength of our study is the size of the SART database, including more than 50,000 births, which allowed for restriction of the cohort to live births from women of similar ovarian responsiveness. Exposure was restricted to women with a live birth resulting from fresh embryos in cycles with excess embryos available for cryopreservation to limit potential selection bias and confounding present in previous studies (20, 21, 22). The large sample size also allowed appropriate power after controlling for important confounders of

adverse outcome, and in analyses restricted to singleton and twin deliveries. In addition, the paired analysis of women with live birth after both a fresh and a frozen ET, and the study of birth outcomes of infants conceived with donated oocytes in a fresh or frozen ET cycle further strengthen the current study design. Our conclusions are supported by the consistency of findings noting an association of fresh embryo transfer and low birth weight in term infants, preterm infants, singletons, and in twin gestations. Interestingly, we also consistently do not demonstrate an association of preterm delivery and transfer type.

It is likely that multiple factors contribute to low birth weight and preterm delivery, many of which are unknown and their mechanism(s) may differ. Our analysis of pregnancy outcome in the same women was expected to minimize unrecognized confounding. The paired analysis of women with a live birth after both a fresh and a frozen transfer demonstrated an almost 4 fold increase in the strength of association of transfer type and low birth weight and no association with preterm delivery. The increase in the strength of association for low birth weight with no change in the association for preterm delivery in this analysis adds validity to our overall conclusions.

Because embryos generated from donor oocytes are exposed to a similar endocrine milieu at the time of either a fresh or a frozen embryo transfer, we hypothesized that there should be no association between transfer type and low birth weight in the donor egg recipient patient population. As predicted, we found no difference in low birth weight (or preterm delivery) in this patient population. This observation lends further strong support to our conclusion that the non physiological maternal environment following ovarian hormonal stimulation may be one of the potential contributors leading to low birth weight in infants conceived during a fresh IVF cycle. Our findings are supported by several smaller European publications in which infants born after transfer of frozen embryos demonstrated higher birth weight than those born after transfer of fresh embryos (23, 24, 25). Furthermore, a Danish study reported that the risk of low birth weight was no different in singleton births after frozen embryo transfer as compared to singleton unassisted conceptions (20). The strength and novelty of our study, due to the large sample size and ability to perform subanalyses, was the ability to isolate the maternal hormonal milieu at the time of transfer as an underlying mechanism that contributes to this association.

The cellular mechanism(s) responsible for the association of adverse perinatal outcomes with IVF cannot be determined from the present study. A physiologically plausible hypothesis is that this adverse outcome may be the result of alterations in implantation and placentation. These processes depend on both embryonic factors regulating the adhesive and invasive properties of the trophoblasts and maternal uterine and immunologic factors that play permissive and regulatory roles modulating trophoblast invasion (26). It is conceivable that some of these interactions are altered in the setting of ovarian hyperstimulation (27-34). Modulation of endometrial cell function may alter regulatory processes and modify the implantation process. This hypothesis is supported by the demonstration of differential expression of more than 200 endometrial genes in stimulated versus natural cycles during the window of implantation (35). Unfortunately, no data are available in the SART database in order to correlate specific hormonal measurements with outcomes in this cohort of patients.

Alternatively, the altered endocrine milieu may directly affect the peri-implantation embryo and thus affect the implantation process by modulating directly the differentiation and invasive activity of the trophoblast cells. It is noteworthy that the reported increase in low birth weight is independent of preterm birth and/or gestational age at delivery. No difference in preterm delivery was noted in our study. In addition, the clinical significance of the absolute difference of a 156 gram decrease in mean birthweight of singleton infants born

after fresh ET as compared to frozen ET is unclear. However, the increased *proportion* of low birth weight infants following fresh ET may have significant clinical relevance due to the reported association of low birth weight and adult onset disease states (36, 37, 38).

Alternate mechanisms cannot be excluded. It is possible that the freezing and thawing processes may act as a natural stress test with only the fittest frozen embryos surviving, thus resulting in pregnancies with reduced adverse outcomes. However, the higher proportion of multiple pregnancies in fresh embryo transfer cycles, despite transfer of fewer embryos, would argue that the fittest embryos were probably transferred in the fresh cycles. Moreover, if the decreased risk of low birth weight was associated with a natural selection process due to the freezing and thawing of embryos, one would have expected to observe the association of transfer type in donor oocyte recipients as well. In fact, we demonstrated no association of perinatal morbidity and, specifically, low birth weight with transfer type (fresh vs. frozen) in recipients of embryos generated from donor oocytes. It is noteworthy, however, that the incidence of overall low birth weight in singleton infants after frozen embryo transfer in donor oocyte recipients was higher than that in autologous IVF cycles. This increase was predominantly due to a relative increase in preterm low birth weight, perhaps reflective of the reported increase in the incidence of antepartum complications in this older group of patients (39).

Finally, we were unable to assess for the impact of prolonged embryo culture on outcome, as number of days in embryo culture prior to cryopreservation was not recorded in the database. In addition, we were not able to assess the impact of embryo quality or morphology on subsequent outcome. Unfortunately, a prospective study of appropriate power to definitively answer this question via randomization of women to a fresh or frozen transfer cycle after IVF, in a trial of similar size, is not feasible.

Multiple pregnancy remains the strongest determinant of perinatal morbidity and should not be overlooked (40). In the present study, over 80% of singletons were delivered full term compared to only 23% of twins. Additionally, low birth weight complicated approximately 7-10% of singleton pregnancies compared to 60-70% of twin pregnancies. Continued adoption of more conservative embryo transfer guidelines, including elective single embryo transfer (eSET) in selected patients will decrease multiple births and increase the number of subsequent frozen embryo transfer cycles (41, 42, 43). In both instances perinatal morbidity associated with IVF will likely be reduced.

Prevention of low birth weight is important as it has been linked to adult disease, including diabetes and cardiovascular disease (36,37,38). We consistently demonstrated that a fresh embryo transfer is associated with low birth weight in singleton and twins born preterm or at term, but is not associated with preterm delivery. The complementary analyses strongly suggest that the mechanism for this association may be the potentially modifiable supraphysiologic hormonal maternal environment resulting from ovarian stimulation and multifollicular development during a fresh IVF cycle.

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## Table 1

Demographic Information of Patients with Live Birth Following Fresh versus Frozen Embryo Transfer (N=56,792)

| Variable | Fresh Embryo Transfer N=38,626 | Frozen Embryo Transfer N=18,166 | P-value |
|---|---|---|---|
| Maternal age | 33.4 +/- 3.9 | 34.4 +/- 4.1 | <0.001 |
| Prior gravidity | 0.96 +/- 1.3 | 1.30 +/- 1.3 | <0.001 |
| Prior full term birth | 48.5% | 61.7% | <0.001 |
| Number of prior ART cycles | 0.51 +/- 0.9 | 1.38 +/- 1.0 | <0.001 |
| Number of embryos transferred | 2.4 +/- 0.8 | 2.6 +/- 1.0 | <0.001 |
| Implantation rate | 62.6% | 51.3% | <0.001 |
| Infertility Diagnosis | | | |
| Male factor | 39.4 | 37.4 | <0.001 |
| Endometriosis | 13.6 | 13.3 | NS |
| Polycystic Ovarian Syndrome | 19.0 | 20.6 | <0.001 |
| Diminished Ovarian Reserve | 5.8 | 6.3 | 0.033 |
| Tubal factor | 20.2 | 20.5 | NS |
| Unexplained | 14.2 | 12.1 | <0.001 |
| Other | 11.5 | 11.8 | NS |
| Pregnancy Plurality | | | |
| Singleton | 63.2% | 76.3% | |
| Twin | 34.4% | 21.9% | OR 1.93 (1.85 – 2.02) <0.001 |
| HOMP (≥ triplet) | 2.4% | 1.8% | OR 1.59 (1.39 – 1.83) <0.001 |
| Gender of singleton infant | | | p=0.709 |
| Male | 49.6% | 49.8% | NS |
| Female | 48.8% | 48.6% | NS |
| Unknown | 1.7% | 1.5% | NS |

## Table 2

Preterm Delivery and Low Birthweight in Singleton Live Births Following Fresh vs. Frozen Embryo Transfer

| **Preterm Delivery N=32,065** | **Fresh Embryo Transfer** | **Frozen Embryo Transfer** | **OR (95% CI)** | **AOR (95% CI)*** |
|---|---|---|---|---|
| Fullterm | 81.1% (17,099/21,083) | 81.5% (8,947/10,982) | Reference | Reference |
| Preterm Delivery (32 – 37 weeks) | 16.0% (3,377/21,083) | 15.8% (1,737/10,982) | 1.01 (0.95-1.08) p=0.65 | 1.06 (0.98 - 1.14) P=0.16 |
| Very Preterm (<32 weeks) | 2.9% (607/21,083) | 2.7% (298/10,982) | 1.05 (0.91-1.21) p=0.46 | ** |
| Low Birthweight N=31,822 | Fresh Embryo Transfer | Frozen Embryo Transfer | OR (95% CI) | AOR (95% CI)* |
| Overall LBW (<2500 grams) | 10.0% (2,094/20,916) | 7.2% (782/10,906) | 1.44 (1.33-1.57) p<0.001 | 1.35 (1.20 – 1.51) p<0.001 |
| Term LBW^ (≥ 37 weeks, <2500 gms) | 2.5% (422/16,962) | 1.2% (107/8,877) | 2.10 (1.69-2.60) p<0.001 | 1.73 (1.31 - 2.29) p=0.001 |
| Preterm LBW^ (<37 weeks, <2500 gm) | 34.1% (1,138/3,341) | 23.8% (407/1,714) | 1.66 (1.45 – 1.89) p<0.001 | 1.49 (1.24 – 1.78) p<0.001 |

* Adjusted for reporting year, patient age, parity, infertility diagnosis, number of embryos transferred, number of prior ART cycles, prior miscarriage, reduction in fetal heart, multiple pregnancy, implantation rate, and infant gender

** For adjusted analysis, preterm and very preterm delivery combined

^ Only subjects with recorded data for both gestational age and birthweight were included in analysis.

## Table 3

Preterm Delivery and Low Birthweight in Twin Live Births Following Fresh vs. Frozen Embryo Transfer

| **Preterm Delivery (n=14,598)** | **Fresh Embryo Transfer** | **Frozen Embryo Transfer** | **OR (95% CI)** | **AOR (95% CI)*** |
|---|---|---|---|---|
| Fullterm | 23.5% (2,689/11,454) | 23.7% (745/3,144) | Reference | Reference |
| Preterm Delivery (32 - 37 wks) | 62.8% (7,196/11,454) | 63.3% (1,989/3,144) | 1.00 (0.91 - 1.10) p=0.96 | 1.03 (0.91 - 1.16) p=0.64 |
| Very Preterm (<32 weeks) | 13.7% (1,569/11,454) | 13.0% (410/3,144) | 1.06 (0.93 - 1.21) p=0.40 | ** |
| Low Birthweight N=14,450 | Fresh Embryo Transfer | Frozen Embryo Transfer | OR (95% CI) | AOR (95% CI)* |
| Overall LBW (<2500 grams) | 69.9% (7,924/11,339) | 61.5% (1,912/3,111) | 1.46 (1.34 - 1.58) p<0.001 | 1.36 (1.22 – 1.52) p<0.001 |
| Term LBW^ (≥ 37 weeks, <2500 gms) | 32.7% (873/2,670) | 26.1% (192/737) | 1.38 (1.15 - 1.66) p = 0.001 | 1.35 (1.10 - 1.64) p=0.004 |
| Preterm LBW^ (< 37 weeks, <2500 gms) | 77.6% (5,536/7,132) | 67.2% (1,324/1,971) | 1.69 (1.52 – 1.89) p<0.001 | 1.59 (1.38 – 1.84) p<0.001 |

* Adjusted for reporting year, patient age, parity, infertility diagnosis, number of embryos transferred, number of prior ART cycles, prior miscarriage, reduction in fetal heart, multiple pregnancy, implantation rate

** For adjusted analysis, preterm and very preterm delivery combined

^ Only subjects with recorded data for both gestational age and birthweight were included in analysis.

## Table 4

Preterm Delivery and Low Birthweight in Singleton Live Births Following Fresh vs. Frozen Embryo Transfer in Same Patient at Different Times: Paired Cycle Analysis

| **N= 1,356** | **Fresh Embryo Transfer n= 680** | **Frozen Embryo Transfer n=676** | **OR (95% CI)** | **AOR* (95% CI)** |
|---|---|---|---|---|
| Fullterm | 81.1% (550/678) | 82.2% (555/675) | Reference | Reference |
| Preterm Delivery (32 - 37 wks) | 14.9% (101/678) | 15.9% (107/675) | 1.03 (0.73 - 1.46) p=0.49 | 1.86 (0.73 – 4.71) p=0.19 |
| Very Preterm (<32 weeks) | 4.0% (27/678) | 1.9% (13/675) | 2.44 (1.14-5.20) p=0.02 | ** |
| Overall LBW (<2500 grams) | 11.5% (78/680) | 5.6% (38/676) | 2.52 (1.59 - 4.00) p<0.001 | 4.66 (1.18 – 18.38) p = 0.03 |
| Term LBW^ (≥ 37 weeks, <2500 gms) | 2.4% (13/550) | 1.1% (6/555) | 3.33 (0.92 – 12.11) p=0.07 | N/A ¥ |
| Preterm LBW^ (<37 weeks, <2500 gm) | 50.8% (65/128) | 26.7% (32/120) | 1.86 (0.74 - 4.65) p=0.19 | N/A ¥ |

*Adjusted for reporting year, patient age, parity, infertility diagnosis, number of embryos transferred, number of prior ART cycles, prior miscarriage, reduction in fetal heart, multiple pregnancy, implantation rate

**For adjusted analysis, preterm and very preterm delivery combined

^Only subjects with recorded data for both gestational age and birthweight were included in analysis.

¥AOR for term LBW not applicable due to it being an extremely rare event.
AOR for preterm LBW not applicable due to insufficient power to adjust for important covariates.

## Table 5

Preterm Delivery and Low Birthweight in Singleton Live Births Following Fresh vs. Frozen Embryo Transfer in Oocyte Donor Recipients

| **Singletons N=8,768** | **Fresh Embryo Transfer** | **Frozen Embryo Transfer** | **OR (95% CI)** | **AOR (95% CI)*** |
|---|---|---|---|---|
| Fullterm | 76.6% (4,328/5,648) | 75.7% (2,361/3,120) | Reference | Reference |
| Preterm Delivery (32 - 37 wks) | 19.3% (1,091/5,648) | 20.7% (646/3,120) | 0.93 (0.83 - 1.03) p=0.16 | 0.96 (0.84 - 1.09) p=0.50 |
| Very Preterm (<32 weeks) | 4.1% (229/5,648) | 3.6% (113/3,120) | 1.08 (0.86 - 1.36) p=0.48 | ** |
| Overall LBW | 11.5% (644/5,595) | 11.3% (346/3,072) | 1.03 (0.90 - 1.18) p=0.65 | 0.99 (0-82 - 1.18) p=0.87 |
| Term LBW^ (≥ 37 weeks, <2500 gms) | 2.2% (93/4,286) | 1.7% (39/2,325) | 1.30 (0.89 - 1.89) p=0.17 | 1.41 (0.82 - 2.42) p=0.22 |
| Preterm LBW^ (<37 weeks, <2500 gm) | 32.7% (352/1,078) | 33.1% (211/638) | 0.98 (0.80 - 1.21) p=0.87 | 0.94 (0.71 - 1.24) p=0.67 |

*Adjusted for reporting year, patient age, parity, infertility diagnosis, number of embryos transferred, number of prior ART cycles, prior miscarriage, reduction in fetal heart, multiple pregnancy, implantation rate

**For adjusted analysis, preterm and very preterm delivery combined

^Only subjects with recorded data for both gestational age and birthweight were included in analysis.