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Original Research Article

Perinatal Outcomes in Children Born After Fresh or FET (Frozen Embryo Transfer) Using Donar Oocytes

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Abstract:

Background & Objective: To study whether children born after vitrified–thawed embryo transfers (ETs) using donated oocytes have worse perinatal outcomes when compared with fresh ET.

Methods: Patients with a first singleton live birth after single blastocyst transfer were compared using multivariable regression analysis to account for potential confounding factors. The primary outcome was birth weight. Secondary outcomes were birth weight z-scores and percentiles, small/large for gestational age, gestational age at delivery, gender, prematurity (<37 weeks and <32 weeks), neonatal morbidity (Apgar scores and need for neonatal intensive care) and maternal morbidity (gestational hypertensive disorders, gestational diabetes and caesarean delivery).

Results: There was no significant difference between the fresh ET and FET groups in terms of mean birth weight and birth weight z-scores, in both the unadjusted and confounder-adjusted models. However, artificial endometrial preparation was associated with a higher birth weight and birth weight z-scores when compared with a transfer in a natural cycle. Although a 1-day statistically significant difference in gestational age at birth was detected, premature birth rates (<37 weeks) did not vary significantly between groups. No other statistically significant differences were found in the remaining neonatal and maternal outcomes studies between the fresh ET and FET groups.

Conclusion: No significant difference in birth weight and prematurity rates between fresh or frozen embryo transfers (FETs) in new-borns after oocyte donation was found.

Keywords: ART / FET (frozen embryo transfer) / endometrial preparation / oocyte donation / birth weight / small for gestational age / prematurity / perinatal outcomes / gestational hypertension / caesarean delivery.

Introduction

Autologous singletons born after fresh ET have been previously associated with higher rates of preterm birth and low birth weight, while FETs seem to confer a higher risk of hypertensive disorders during pregnancy and macrosomia. However, studies comparing these outcomes using autologous oocytes are unable to adequately disentangle the putative detrimental consequences of embryo vitrification from the possible effects that ovarian stimulation and endometrial preparation may have on endometrial receptivity prior to ET. The oocyte donation model is, for this reason, a more appropriate setting to study these hypotheses; however so far, the information available regarding neonatal outcomes in this patient population is limited to either small and/or heterogeneous studies.

Materials and Methods

We performed a multicenter retrospective cohort study including 188 singletons born between 2019 and 2022 following oocyte donation and single blastocyst transfer, subdivided according to whether a fresh ET or FET was performed. We also performed two additional sensitivity analyses, subgrouping the sample according to the type of endometrial preparation and whether the donated oocytes had previously been vitrified or not.

Patients with a first singleton live birth after single blastocyst transfer were compared using multivariable regression analysis to account for potential confounding factors. The primary outcome was birth weight. Secondary outcomes were birth weight z-scores and percentiles, small/large for gestational age, gestational age at delivery, gender, prematurity, neonatal morbidity and maternal morbidity.

Main outcome measures: Perinatal data are routinely requested from all patients following birth by a questionnaire delivered with the support of our nursing staff by either phone or email.

The primary outcome of this study was birth weight. Secondary outcomes measured were birth weight z-score, small for gestational age, large for gestational age, gestational age at birth, prematurity under 37 weeks and under 32 weeks, gender of the offspring, neonatal morbidity and maternal morbidity [gestational diabetes and gestational hypertensive disorders, the latter including gestational hypertension, pre-eclampsia, eclampsia and haemolysis, elevated liver enzymes and low platelets, and caesarean deliveries].

Observation Chart

Table 1: Patient and donor baseline demographics and general characteristics of the treatment cycle

Fresh ET Vitrified–thawed ET. (N=94) (N=94) P-value			
Female recipient age (years, median, IQR) 42.0 (39.0, 44.0) 42.0 (39.0, 45.0) <0.01			
Female recipient BMI (kg/m^2, median, IQR)	22.6 (20.7, 25.2)	22.6 (20.7, 25.1)	0.83
Female recipient smoking status			<0.01
No	(67.5%)	(66.4%)	
Current/past	(21.0%)	(17.0%)	
Missing information	(11.6%)	(16.6%)	
Female factor infertility[a]	(19.8%)	(22.7%)	0.01
Male factor infertility	(23.1%)	(31.0%)	<0.01
Donor age (years, median, IQR)	25.0 (22.0, 29.0)	25.0 (22.0, 29.0)	0.11
Donor BMI (kg/m^2, median, IQR)	22.0 (20.1, 24.2)	22.1 (20.2, 24.5)	0.32
Oocyte status			<0.01
Vitrified–thawed	(46.3%)	(33.8%)	
Missing information	(3.7%)	(4.8%)	
Sperm source			<0.01
Autologous	(82.4%)	(86.1%)	
Donor	(17.5%)	(13.9%)	
Sperm preparation technique			<0.01
Combined/unrecorded	(8.5%)	(9.3%)	
Density gradient	(64.0%)	(56.0%)	
Swim-up	(27.4%)	(34.7%)	
Year of treatment			<0.01
Before 2010	(1.1%)	(2.9%)	
Between 2010 and 2015	(30.6%)	(37.7%)	
After 2015	(68.3%)	(59.4%)	
Type of endometrial preparation			<0.01
Natural cycle	(3.0%)	48 (17.2%)	
Artificial cycle	(97.0%)	(82.8%)	
Endometrial thickness, (mm, median, IQR)	8.5 (7.5, 9.8)	8.5 (7.5, 9.7)	0.55
E2 (pg/ml, median, IQR)	202.0 (146.0, 303.0)	221.0 (160.0, 316.0)	<0.01
P4 (ng/ml, median, IQR)	0.1 (0.1, 0.3)	0.2 (0.1, 0.3)	<0.01

Table 2: Obstetric and perinatal outcomes in the fresh versus vitrified–thawed embryo transfer model

Fresh ET (N=94) Vitrified–thawed ET (N=94) P-value (95% CI) P-value					
Birthweight (g, median, IQR) 3215 (2900, 3540) 3200 (2860, 3500) 0.08 10.35 (226.20, 46.90) 0.58					
Birthweight percentile (%, median, IQR)	51.4 (25.2, 76.8)	52.3 (27.7, 76.3)	0.54	0.93 (21.56, 3.41)	0.47
Birthweight z-scores (median, IQR)	0.0 (20.7, 0.7)	0.1 (20.6, 0.7)	0.53	0.02 (20.06, 0.11)	0.60
Small for gestational age	(10.2%)	(9.9%)	0.80	20.13 (20.43, 0.18)	0.41
Large for gestational age	(10.8%)	(9.3%)	0.16	20.24 (20.53, 0.05)	0.10
Gestational age (days, median, IQR)	275 (268, 283)	274 (266, 282)	<0.01	21.47 (22.50, 20.44)	<0.01
Premature birth rates (<37 weeks)	(9.9%)	(11.2%)	0.12	0.18 (20.05, 0.41)	0.12
Very premature birth rates (<32 weeks)	(1.4%)	(1.9%)	0.25	0.25 (20.28, 0.78)	0.35
Gender of the offspring Male	(54.5%)	(50.9%)	0.01	20.16 (20.27, 20.04)	<0.01
Gender of the offspring Female	(45.5%)	(49.1%)			
Apgar scores 5^{0a} (<7)	(1.4%)	(1.1%)	0.51	20.14 (20.45, 0.17)	0.37
Apgar scores 5^{0a} (7–10)	(99.4%)	(99.6%)			
Apgar scores 10^{0a} (<7)	(0.5%)	(0.3%)	0.68	0.38 (20.34, 1.10)	0.30
Apgar scores 10^{0a} (7–10)	(99.9%)	(100.0%)			
Need for neonatal intensive care	(10.5%)	(10.4%)	0.88	20.07 (20.45, 0.31)	0.71
Gestational hypertensive disorders	(6.5%)	(6.3%)	0.71	0.10 (20.20, 0.40)	0.50
Gestational diabetes	(7.0%)	(7.2%)	0.81	20.05 (20.28, 0.17)	0.66
Caesarean delivery	(57.4%)	(61.2%)	0.04	0.13 (20.09, 0.34)	0.25

Obstetric and perinatal outcomes of 188 first singleton livebirths after single blastocyst transfer using donated oocytes, subdivided according to type of embryo transfer (ET, fresh or vitrified–thawed) divided by fresh or frozen embryo transfers (ET). Multivariable linear, logistic or ordered logistic regression analysis was performed, as appropriate. Control variables were added to the regression models as potential confounding based on either purported or known previous clinical relevance .Apgar scores are subcategorized as a dichotomous outcome, the multivariable assessment presented used ordered logistic regression (with Apgar scores categorized from 1 to 10). aRC, adjusted regression coefficient; IQR, interquartile range. Statistically significant P-values (p<0.05) are highlighted in bold.

Table 3: Oocyte cryopreservation sub-analysis

Fresh oocytes (N=94)	Vitrified–thawed (N=94)	P-value	(95% CI)	P-value
Birthweight (g, median, IQR)	3200	3221	0.58	212.44	0.48
Birthweight percentile (%, median, IQR)	51.8	51.8	0.60	20.22	0.85
Birthweight z-scores (median, IQR)	0.0 (20.7, 0.7)	0.0 (20.6, 0.7)	0.60	20.02 (20.11, 0.06)	0.59
Small for gestational age	(9.9%)	(10.2%)	0.78	20.08 (20.43, 0.18)	0.41
Large for gestational age	(9.8%)	1 (11.0%)	0.23	20.00 (20.27, 0.26)	0.98
Gestational age (days, median, IQR)	275.0 (267.0, 283.0)	274.0 (267.0, 282.0)	0.45	20.10 (21.09, 0.88)	0.84
Premature birth rates (<37 weeks)	(10.3%)	252 (10.3%)	0.94	20.02 (20.24, 0.20)	0.84
Very premature birth rates (<32 weeks)	(1.5%)	(1.5%)	0.93	20.02 (20.56, 0.52)	0.95
Gender of the offspring			0.78	20.03 (20.014, 0.08)	0.61
Male	(46.7%)	(47.0%)			
Female	(53.3%)	(53.0%)			
Apgar scores 5^{0a}			0.02	20.03 (20.32, 0.26)	0.84
<7	(0.3%)	(0.8%)			
7–10	(99.7%)	(99.2%)			
Apgar scores 10^{0a}			0.21	20.29 (20.96, 0.39)	0.41
<7	(<1%)	(0.1%)			
7–10	(100.0%)	(99.9%)			
Need for neonatal intensive care	(9.7%)	(11.3%)	0.11	0.40 (0.05, 0.76)	0.03
Gestational hypertensive disorders	(7.5%)	(4.8%)	<0.01	20.43 (20.72, 20.13)	<0.01
Gestational diabetes	(8.0%)	(5.8%)	<0.01	20.32 (20.54, 20.11)	<0.01
Caesarean delivery	(59.0%)	(58.9%)	0.95	20.01 (20.22, 0.21)	0.95

Obstetric and perinatal outcomes of 188 first singleton livebirths after single blastocyst transfer using donated oocytes, subdivided according to whether oocytes used were fresh or vitrified–thawed. A multivariable linear, logistic or ordered logistic regression analysis was performed, as appropriate. Control variables were added to the regression models as potential confounding based on either purported or known previous clinical relevance,Apgar scores are subcategorized as a dichotomous outcome, the multivariable assessment presented used ordered logistic regression (with Apgar scores categorized from 1 to 10). aRC, adjusted regression coefficient; IQR, interquartile range.Statistically significant P-values (p<0.05) are highlighted in bold.

Table 4: Type of endometrium preparation sub-analysis

Natural cycle	Artificial cycle	P-value	(95% CI)	P-value
Birthweight (g, median, IQR)	3105 (2800, 3450)	3220 (2900, 3540)	<0.01	101.02 (39.81, 162.24)	<0.01
Birthweight percentile (%, median, IQR)	45.0 (23.4, 72.4)	52.5 (26.4, 76.9)	<0.01	6.77 (2.60, 10.95)	<0.01
Birthweight z-scores (median, IQR)	0.1 (20.7, 0.6)	0.1 (20.6, 0.7)	<0.01	0.24 (0.09, 0.38)	<0.01
Small for gestational age	(13.5%)	(9.8%)	0.03	20.50 (20.95, 20.05)	0.03
Large for gestational age	(7.5%)	(10.5%)	0.07	0.20 (20.32, 0.71)	0.46
Gestational age (days, median, IQR)	275.0 (267.0, 281.0)	275.0 (267.0, 283.0)	0.22	0.07 (21.75, 1.89)	0.94
Premature birth rates (<37 weeks)	(11.1%)	(10.3%)	0.60	20.13 (20.52, 0.26)	0.52
Very premature birth rates (<32 weeks)	(1.1%)	(1.6%)	0.38	0.54 (20.67, 1.75)	0.38
Gender of the offspring			0.97	20.07 (20.014, 0.08)	0.48
Male	(46.9%)	(46.8%)			
Female	(53.1%)	(53.2%)			
Apgar scores 50a			0.33	20.12 (20.69, 0.45)	0.679
<7	(0.2%)	(0.6%)			
7–10	(99.8%)	(99.4%)			
Apgar scores 100a			0.56	0.43 (21.27, 2.13)	0.620
<7	(0.0%)	(0.1%)			
7–10	(100.0%)	(99.9%)			
Need for neonatal intensive care	(9.7%)	(10.5%)	0.67	0.35 (20.35, 1.04)	0.331
Gestational hypertensive disorders	(3.0%)	(6.7%)	<0.01	0.68 (0.01, 1.35)	0.05
Gestational diabetes	(8.7%)	(6.9%)	0.15	20.40 (20.77, 20.04)	0.03
Caesarean delivery	(46.8%)	(60.0%)	<0.01	0.76 (0.43, 1.09)	<0.01

Obstetric and perinatal outcomes of 188 first singleton livebirths after single blastocyst transfer using donated oocytes, subdivided according to the type of endometrial preparation (natural or artificial cycle). A multivariable linear, logistic or ordered logistic regression analysis was performed, as appropriate. Control variables were added to the regression models as potential confounding based on either purported or known previous clinical relevance,Apgar scores are subcategorized as a dichotomous outcome, the multivariable assessment presented used ordered logistic regression (with Apgar scores categorized from 1 to 10). aRC, adjusted regression coefficient; IQR, interquartile range. Statistically significant P-values (p<0.05) are highlighted in bold.

Results

Patients and donor baseline demographics and general characteristics of the treatment cycle A total of 188 singleton deliveries were included in the analysis (94 after fresh ET and 94 following FET), as described. The baseline demographic and cycle characteristics for each group are shown. The

distribution of the following characteristics varied significantly among the two groups: patient age and infertility diagnosis, patient and donor smoking status, year of treatment, type of endometrial preparation, serum E2 and P4 levels, oocyte status, sperm source and sperm preparation technique.

Obstetrics and perinatal outcomes: Birth weight There was no significant difference between the fresh ET and FET groups in terms of birthweight versus 3200 g, IQR [2860 g, 3500 g], respectively) in both the unadjusted and confounder-adjusted models . Moreover, there was no association between type of ET (fresh ET and FET) and birthweight z-scores (0.0, IQR [0.7, 0.7]; versus 0.1, IQR [0.6, 0.7], respectively), small for gestational age and large for gestational age, in both the unadjusted and confounder-adjusted models

Gestational age: The mean gestational age at delivery was 275 days, IQR (268, 283) and 274 days, IQR (266, 282) in the fresh ET and FET groups, respectively, which remained significant even after confounder adjustment. The premature birth rates (<37 weeks) were, respectively, 9.9% (8.9–10.8%) and 11.2% (9.8–12.6%) for fresh ET and FET, while the very premature birth rates (<32 weeks) were 1.4% (1.0–1.8%)

Gender of the offspring: Male children represented 53.2% of all newborns included in the study. There were significantly more male newborns in the fresh cycles (54.5%) compared with the FET cycles (50.9%).

Perinatal morbidity: There were no statistically significant differences in Apgar scores at 5^0 and 10^0 in the fresh ET and FET groups, as well as the need for admission to the neonatal intensive care unit .

Maternal mortality: There were no statistically significant differences in terms of hypertensive disorders during pregnancy or the rate of gestational diabetes. The rate of caesarean delivery was higher in the FET group (61.2% versus 57.4%, P ¼ 0.04), although this difference no longer remained statistically significant following potential confounding adjustment (adjusted regression coefficient (aRC) 0.13, 95% CI (0.09;

The rate of caesarean delivery was also higher in the artificial group (60.0% versus 46.8%, P < 0.01), even following potential confounding adjustment (aRC 0.76, CI (0.43; 1.09), P < 0.01). On the contrary, there was a lower rate of gestational diabetes in artificial cycles following confounder adjustment (aRC 0.40, CI (0.77; 0.04), P ¼ 0.03). Additionally, we performed a four-arm confounder adjusted sub-group analysis (cryopreservation of the embryo plus endometrial preservation) that showed overall similar point estimates. Although, it should be noted that for the comparisons with the fresh ET after a natural cycle subgroup, the Bonferroni-adjusted P-values were non-significant, possibly owing to the limited size of this subgroup

Statistical Analysis: Baseline patient and cycle characteristics were summarized, with categorical data presented using frequencies and percentages, and continuous values using median and interquartile range (IQR). To compare the groups, we used Chi-square test for categorical variables, and the Mann–Whitney for continuous variables. In order to compare the main outcome measures between fresh and vitrified–thawed single ETs, multivariable linear, logistic or ordered logistic regression analysis were performed, as appropriate, with the addition of relevant control variables in the model to reduce the risk of bias due to confounding. Confounding factors were selected based on their clinical relevance and previous knowledge for each main outcome measure, as described. The variables considered as potential confounders included female and male infertility diagnosis, maternal and donor ages, BMI and smoking status, whether the oocytes were previously vitrified or not, sperm source and preparation technique, year of treatment, type of endometrial preparation (natural cycle or artificial cycle), endometrial thickness, recipient serum E2 and progesterone (P4), occurrence of gestational diabetes and/or hypertension disorders during pregnancy, offspring gender, and gestational age at birth. Endometrial thickness and serum E2 and P4 of the recipient were measured in the last ultrasound appointment prior to ET planning.

Two additional sensitivity analyses were also performed. In the first, the cohort was divided in two study groups according to whether fresh or vitrified–thawed oocytes were used. Second, we subdivided the sample based on type of endometrial preparation performed, natural or artificial cycle. Multivariable regression analysis was applied as described previously, to address the same main outcomes measures. Stata Software version 13.1 was used for statistical analysis. A P-value below 0.05 was considered as statistically significant.

Discussion

We found that embryo cryopreservation appears to have little effect on ART outcomes, namely on prematurity and abnormal birthweight. If this is the case, other mechanisms beyond embryo cryopreservation may be responsible for the altered birthweight described in the literature. There is growing evidence that ovarian stimulation significantly impacts birthweight of infants conceived with ART. Another meta-analysis compared stimulated IVF with natural/modified natural cycle IVF and reported a significantly higher risk of pre-term delivery and low birthweight in the former.

Likewise, there also seems to be an increased risk of preterm birth and low birth weight after fresh ET

with very high numbers of oocytes collected. Moreover, the recently reported inverse correlation between E2 levels and birthweight both in fresh ET and FET cycles further underlines the likely involvement of hyperoestrogenaemia in the process of implantation and foetal development. If endometrial function is altered owing to the hyperoestrogenaemia caused by ovarian stimulation, then this could explain the lower birthweight related to fresh ET in autologous cycles. It has also been suggested that FET results in a shift of the distribution curve of newborn weights, consequently leading to a higher group of infants having macrosomia, in proportion to the reduction of low birth weight.

Another hypothesis is the possibility of epigenetic modifications after ART. Animal studies have shown different methylation patterns that can alter differentiation and growth of the embryo. The study in mice suggested that FET embryos are more similar to naturally conceived embryos regarding gene expression and epigenetic patterns, implying that the changes found in fresh embryos may be related to exogenous ovarian stimulation and not the cryopreservation technique. Also of note is that the true impact of these putative birthweight abnormalities after ART remains unknown found no difference between fresh ET versus FET regarding neonatal weight and childhood weight gain trajectory. Recently, reported that children born after FET grew similarly to naturally conceived children and ART-related differences in weight and height decreased with age, and dissipated by the age of 17 years. Albeit reassuring, further studies are needed to truly evaluate the long-term consequences of birthweight in ART children. Regarding gestational age, even though we detected a statistically significant difference, we argue that this 1-day difference is of limited clinical relevance. More importantly, there was no difference in prematurity rates. Similar results had previously been suggested by smaller studies also using the oocyte donation model. However, the major strength of this current study, beyond the considerably greater number of cycles included, was also an effort to reduce potential confounding by restricting the sample to singleton pregnancies following single blastocyst transfers in previously nulliparous women, while still accounting for an extensive amount of other cofounder variables

Our sub-group analysis of natural versus artificial cycles identified a difference in birthweight and birthweight z-scores, further underlying the important role of the endometrium in neonatal outcomes. Also, hypertensive disorders and caesarean deliveries were found to be higher in the artificial cycle group. These findings have been described previously in other studies. Recent evidence suggests that the lack of a corpus luteum could be the root of the issue, which would ultimately lead to an increase in hypertensive disorders. A recent study that compared endometrial preparation methods for FET describes an association between natural cycles and gestational diabetes, although without adjusting for BMI or smoking status. We found the same association in our adjusted model that included these variables. Even though anatomical or functional changes in the placenta, arising at implantation, could be at the genesis of gestation diabetes, knowledge on this subject is still lacking.In our study, there was no impact of the cryopreservation of oocytes on birthweight and birthweight z-scores. The need for neonatal intensive care was higher in the vitrified–thawed oocytes groups after adjustment. Conversely, we also found lower maternal morbidity in the frozen oocytes group. Given the high number of subjects included in our study, we may have been able to detect even small differences between groups, but which could be of limited clinical relevance. Further studies should aim to confirm these findings.

Weaknesses of this study include its retrospective design and the inherent risk of bias related to confounding. Even though a great effort was made to account for relevant confounders, not all may have been accounted for, including unreported diseases in the oocyte recipients, which may have affected perinatal outcomes. Moreover, although we did adjust for the year of treatment, we did not account for all changes in routine clinical practice which may have occurred over time within the centers included. There is also a risk of loss to follow-up or failure in the self-reporting of outcomes, which may have led to an underestimation of the parameters studied. However, it is important to note that this loss to follow-up is unlikely to have differed according to the type of ET performed. We also did not assess the effect of the type of ET on the occurrence of birth defects or placental disorders, given that our database failed to have this information systematically reported. Finally, our sample consisted mainly of nulliparous women of advanced maternal age. For this reason, consideration is needed when generalizing our results to younger populations.

Conclusion

In conclusion, embryo cryopreservation was not associated with changes in birthweight or prematurity rates in donor oocyte recipients. Future studies should focus on the potential effect that ovarian stimulation and endometrial preparation may have on endometrial receptivity to better understand the true impact of ART on perinatal outcomes

What Do We Learn from the Study perinatal: Outcomes did not seem to be affected significantly by the embryo vitrification process in an oocyte donation model. Hence, other factors may contribute to the hindered perinatal outcomes described in ART, particularly the potential effect that ovarian stimulation and endometrial preparation may have on endometrial receptivity.

Limitations of the Study

this study is limited by its retrospective design and lack of information regarding congenital malformations. Moreover, the sample selection criteria that were used may limit the generalizability of our results.

Declarations:

Availability of data and material: Department of Pediatrics and Department of Obstretrics & Gynaecology LN Medical College, Bhopal,

Code availability: Not applicable.

Consent to participate: Consent taken.

Ethical Consideration: There are no ethical conflicts related to this study.

Consent for publication: Consent taken

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