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Vitrified-warmed embryo transfer is associated with mean higher singleton birth weight compared to fresh embryo transfer

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ABSTRACT

Objective: To test for differences in birth weight between singletons born after IVF with fresh embryo transfer vs. vitrified-warmed 2PN embryo transfer (vitrification protocol).
Design: Retrospective analysis of 464 singleton live births after IVF or ICSI during a 12 year period.
Setting: University hospital.
Interventions: Fresh embryo transfer, vitrified-warmed 2PN embryo transfer (vitrification protocol).
Main outcome measures: Birth weight standardized as a *z*-score, adjusting for gestational week at delivery and fetal sex. As a reference, birth weight means from regular deliveries from the same hospital were used. Multivariate regression analysis was used to investigate the relationship between the dependent variable *z*-score (fetal birth weight) and the independent predictor variables maternal age, weight, height, body mass index, RDS prophylaxis, transfer protocol, number of embryos transferred, indication for IVF treatment and sperm quality.
Results: The mean *z*-score was significantly lower after fresh transfer (-0.11 ± 92) as compared to vitrification transfer (0.72 ± 83) ($p < 0.001$). Multivariate regression analysis indicated that only maternal height and maternal body mass index, but not type of cryopreservation protocol, was a significant predictor of birth weight.
Conclusions: In this analysis focusing on 2PN oocytes, vitrified-warmed embryo transfer is associated with mean higher birth weight compared to fresh embryo transfer. Maternal height and body mass index are significant confounders of fetal birth weight and need to be taken into account when studying birth weight differences between ART protocols.

Introduction

Cryopreservation of embryos or 2 PN oocytes and later transfer have become important tools in modern assisted reproductive techniques. During the last years, US and European registries report increasing numbers of babies delivered after cryopreservation of embryos [1–3]. Therefore, the evaluation of the safety of cryopreservation in terms of child health is utterly important.

A variety of freezing and thawing protocols have been reported in literature. Additionally, the type of cryopreserved tissue differs between countries as cryopreservation of embryos is not allowed everywhere. These facts highlight the difficulties in judging safety aspects of cryopreservation in literature as protocols differ from each other.

Several systematic reviews and cohort studies have indicated similar or even better neonatal outcomes for singletons born after cryopreservation compared to singletons born after fresh transfer [4–7]. However, also higher rates of large for gestational age (LGA) and/or macrosomic infants were observed after cryo-transfer compared to singletons after spontaneous or fresh transfer. Of note, most studies have analyzed data on embryo cryopreservation and not 2PN oocyte cryopreservation [8,9].

The aim of the present study therefore was to explore differences in birth weight of singleton deliveries after fresh embryo transfer and vitrified-warmed 2PN embryo transfer (vitrification protocol), respectively.

Materials and methods

The present study is a retrospective exploratory analysis based on data logged in the local IVF and labour ward software databases

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(Recdate Advance©; View Point® 6.0, GE Healthcare). The data were retrieved in January 2014. Approval from the Institutional Review Board was obtained before data collection, and the protocol was prospectively registered (NCT 01088425). The study included data on singleton deliveries after fresh embryo transfer in IVF or ICSI cycles and embryo transfer after vitrification. Inclusion criteria were defined: IVF or ICSI treatment and singleton delivery at Luebeck University. Exclusion criteria were defined as: in-vitro maturation cycles and/or cycles involving assisted hatching; delivery <24 + 0 weeks p.m.; cycles with incomplete data. Parental and fetal parameters were analyzed according to pregnancy age at delivery and fetal sex.

Outcome measure

Fetal birth weight was recorded in grams with information on fetal sex and gestational age at delivery. It was decides to customize birth weight of each case by comparison with a reference population of spontaneous conceived singleton live births. This was done by calculating *z*-scores [10]. The *z*-score of each individual case was calculated using the following formula: (weight of individual case at given gestational age-mean weight of reference population at same gestational age)/standard deviation in the reference population [11]. The *z*-scores indicate how many standard deviations an observation is below or above the reference population mean. The reference population consisted of 3385 singleton male neonates and 3385 singleton female neonates born at Luebeck University and registered in the View Point® software.

Power calculation

The a-priori sample size assessment was based on the assumption that the mean *z*-score in neonates after fresh transfer would be 0.2 standard deviations below the reference population. Sample sizes of 143 and 143 observations achieve 80% power to detect a difference of 0.2 standard deviations from the neonates on the fresh transfer group assuming a standard deviation of 0.9 for both groups and using alpha 0.05 and beta 0.2 (two-sided t-test). After this calculation, the number of observations available in the data bases was judged sufficiently large for meaningful analyses.

Statistical analysis

Analysis included Mann–Whitney test for continuous data, Chi-square test for categorical data and Fisher's exact test. Multivariate linear regression analysis was used to investigate the association between the dependent variable *z*-score of fetal birth weight and the independent predictor variables maternal age (years), maternal weight (kg), maternal height (cm), maternal body mass index (BMI), respiratory distress prophylaxis administered (yes, no), type of embryo transfer (fresh embryo transfer; embryo transfer after vitrification), number of embryos transferred, indication for assisted reproductive treatment (male, female, both, idiopathic) and sperm quality (normal, abnormal according to WHO 2010 standards [12]. The predictor variables were entered in a regression model using the backward stepwise elimination method. A *p*-value of ≤0.05 was considered to indicate statistical significance. Statistical analysis was performed using SPSS statistical package version 17.0 for windows.

Table 1
Maternal, obstetrical and neonatal outcomes between "fresh" ETs and "vitrification" ETs.

Singleton gestation			
Parameter	Fresh live births $n = 276$	Vitrification live births $n = 188$	p
No. of vaginal deliveries (%)	149 (53.9)	103 (54.7)	0.924[X2]
No. of cesarean sections (%)	127 (46.0)	85 (45.2)	0.924[X2]
Mean gestational age, weeks	39 ± 1	39 ± 1.7	0.132[¥]
No. of preterm deliveries (<37 weeks) (%)	39 (14.1)	27 (14.3)	1.0[X2]
No. of very preterm deliveries (<34 weeks) (%)	4 (1.4)	3 (1.6)	1.0[X2]
No. of cases of gestational diabetes mellitus (%)	4 (1.4)	0	0.124[X2]
No. of cases of pregnancy induced severe hypertension (%)	1 (0.4)	0	1.0[X2]
Male/female	151/125	106/82	0.775
Mean APGAR score			
1 min	8 ± 0.7	9 ± 0.8	0.8[¥]
5 min	9 ± 0.5	10 ± 0.6	0.853[¥]
10 min	9 ± 0.3	10 ± 0.4	0.603[¥]
Mean birth weight, g (SD)	2956.8 ± 773	3123 ± 623	≤0.001[†]
Mean birth weight, *z*-score	−0.11 ± 0.92	0.72 ± 0.83	≤0.001[†]
Birth weight ≤1500 g (%)	1 (0.4)	1 (0.5)	1.0[X2]
Birth weight 1500–2500 g (%)	7 (2.5)	7 (3.7)	0.582[X2]
Birth weight ≥4000–4500 g (%)	13 (4.7)	10 (5.3)	0.535[X2]
Birth weight ≥4500 g (%)	1 (0.4)	1 (0.5)	1.0[X2]
SGA (<10. percentile) (%)	4 (1.4)	3 (1.6)	0.582[X2]
SGA (<3. percentile) (%)	0	0	
LGA (>90. percentile) (%)	13 (4.7)	10 (5.3)	0.535[X2]
LGA (>97. percentile) (%)	1 (0.4)	1 (0.5)	1.0[X2]
Neonatal intensive care unit admission (%)	10 (3.6)	10 (5.3)	0.486[X2]
No. of cases of neonatal resuscitation (%)	5 (1.8)	5 (2.7)	0.535[X2]
No. of major birth defects (%)	2 (0.7)	0	0.517[X2]
Neonatal deaths (%)	0	0	
Mean maternal age, years (SD)	33.6 (4.1)	32.5 (4.0)	0.080[†]
Mean maternal weight, kg (SD)	71.8 (14)	69.4 (13)	0.260[†]
Mean maternal height, cm (SD)	169 (6.5)	169 (6.4)	0.790[†]
Mean maternal Body-mass index, kg/m^2 (SD)	28 (7)	24 (6)	0.000[†]

[†] Fisher's exact test for independent samples.
X2: χ^2-test.
[¥] Mann–Whitney *U*-test.