

Is IVF/ICSI with Fresh Embryo Transfer Associated with Higher Mean Singleton Birth Weight Compared to Spontaneous Conception?

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Abstract

Introduction: To investigate for differences in birth weight between singletons born after *in vitro* fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI) with fresh embryo transfer versus singletons born after spontaneous conception.

Materials and methods: Retrospective analysis of singleton live birth weight after IVF or ICSI with fresh embryo transfer and live birth weight of singletons born after spontaneous conception during a twelve years period in a German university hospital. Patients were treated at the fertility unit of the university hospital. Inclusion criteria were defined as singleton delivery, delivery after spontaneous conception and fresh embryo transfer after IVF/ICSI treatment. 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 and way of conception (spontaneous conception versus conception after IVF/ICSI with fresh embryo transfer).

Results: In total, 6,786 singleton live births met the inclusion criteria and were analysed: 276 live births (151 males/125 females) after IVF/ICSI with fresh transfer and 6,510 live births after spontaneous conception (3,125 male/3,385 female). Mean z-score was -0.11 (\pm 0.92) for IVF/ICSI and fresh embryo transfer and 0.009 (\pm 0.9) for spontaneous conception. Z-scores depicted no inter-group differences ($p=0.295$). Multivariate regression analysis indicated way of conception (conception after IVF/ICSI and fresh transfer and spontaneous conception) but not maternal age as significant predictor of fetal birth weight.

Conclusion: There is no association between IVF/ICSI with fresh embryo transfer and mean singleton birth weight compared to birth weight after spontaneous conception.

Keywords: ART; IVF; ICSI; Perinatal outcome; Spontaneous conception

Introduction

Modern assisted reproductive techniques have become an important tool in treating male or female infertility.

Recently, US and European registries report increasing numbers of new-borns delivered after IVF/ICSI with fresh embryo transfer or after cryopreservation [1-3]. Therefore, the evaluation of the safety of IVF/ICSI and cryopreservation in terms of child health remains important.

In literature, a variety of protocols for assisted reproductive techniques can be found.

Additionally, internationally a notable variety of ethical standards and laws exist impeding a rational comparison of procedures, standards and their outcomes.

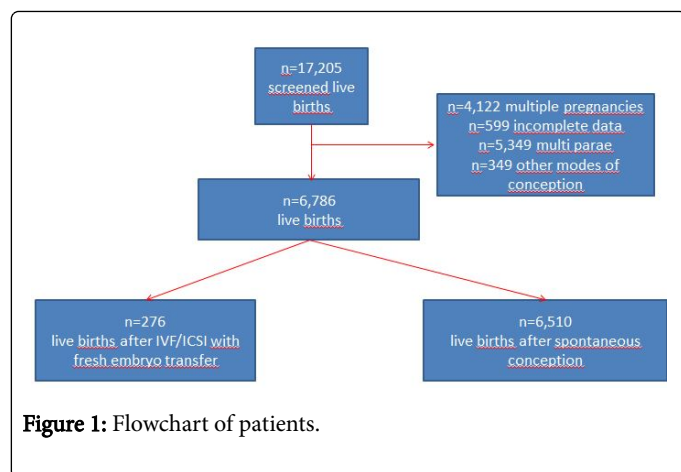
In a previous investigation, our research team revealed an association of fetal birth weight to previous vitrification of the embryo. This finding is in line with systematic reviews and cohort studies which indicated similar or even better neonatal outcomes for singletons born

after cryopreservation of the embryo compared to singletons born after IVF/ICSI with fresh embryo transfer [1-6].

Therefore, aim of the present study is to explore a possible association of singleton birth weight after IVF/ICSI with fresh embryo transfer compared to birth weight of singletons born after spontaneous conception.

Materials and Methods

This study is based on retrospective analysis of data of the fertility unit and delivery ward of the University hospital of Lübeck (software databases Recdate Advance[®]; View Point[®] 6.0, GE Healthcare). Data were retrieved 01/2014. Approval from the Institutional Review Board was obtained before data collection and the protocol of this study was prospectively registered (NCT 01088425). This study includes data on singleton deliveries after fresh embryo transfer in IVF or ICSI cycles and on singleton deliveries after spontaneous conception. Inclusion criteria were defined as: IVF or ICSI treatment with fresh embryo transfer and singleton delivery and singleton delivery after spontaneous conception at the University hospital of Luebeck (Figure 1).



Parental and fetal parameters were analyzed according to pregnancy age at of delivery and fetal sex. Birth weight of each case was standardized by calculating z-scores [1].

Power calculation

The a-priori sample size assessment was based on the assumption of a mean z-score of new-borns after IVF/ICSI with fresh embryo transfer of 0.2 standard deviations (SD) below reference population. Sample size of 143 observations achieves 80% power to detect a difference of 0.3 SD of new-borns of the fresh embryo transfer group assuming a SD of 0.9 for both groups and using alpha 0.05 and beta 0.2 (two-sided t-test).

Statistical analysis

Analysis included Chi-square test for categorical data and Fisher’s exact T-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) and way of conception (spontaneous conception versus conception after IVF/ICSI with fresh embryo transfer). The predictor variables were entered in a regression model using the backward stepwise elimination method. Concerning the inclusion of the variables into the regression model dichotomized dummy variables were built. 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.

Results

In total, 6,788 singleton live births met the inclusion criteria and were analyzed: 276 live births after IVF/ICSI with fresh embryo transfer (151 males/125 females) and 6,510 live births after spontaneous conception (3,125 males/3,385 females). Mean maternal age was 31 ± 3.1 years. Table 1 depicts an overview of baseline, treatment and outcome parameters in the two groups.

Z-score

The mean z-score was -0.11 (± 0.92) for IVF/ICSI with fresh embryo transfer and 0.009 ± (0.9) for spontaneous conception. Z-scores showed no significant inter-group differences (p≤0.295) (Table 1).

Singleton live birth			
Parameter	live births fresh ET (n=276)	live births SC (n=6,510)	p
No. of vaginal deliveries (%)	149 (53.9)	3,619 (55.6)	0.000 X2
No. of caesarean sections (%)	127 (46.0)	2,563 (39.4)	0.000 X2
Mean gestational age, weeks	39 ± 1	38 ± 3	0.020 ¥
No. of preterm deliveries (<37 weeks) (%)	39 (14.1)	646 (9.9)	0.000 X2
No. of very preterm deliveries (<34 weeks) (%)	4 (1.4)	782 (12)	0.000 X2
Male/Female	151/125	3.125/3.385	
Mean APGAR Score			
1 min (SD)	8 (± 0.7)	9 (± 0.8)	
5 min (SD)	9 (± 0.5)	10 (± 0.6)	
10 min (SD)	9 (± 0.3)	10 (± 0.4)	
Mean birth weight, g (SD)	2,956.8 (± 773)	3,128 (± 755)	0.295†
Mean birth weight, z-Score (SD)	-0.11 (± 0.92)	0.009 (± 0.9)	0.295†
Birth weight ≤ 1,500 g (%)	1 (0.4)	287 (4.4)	
Birth weight 1,500–2,500 g (%)	7 (2.5)	802 (12.3)	

Birth weight ≥ 4,000-4,500 g (%)	13 (4.7)	459 (7)	
Birth weight ≥ 4,500 g (%)	1 (0.4)	86 (1.3)	
Neonatal intensive care unit admission (%)	10 (3.6)	506 (7.7)	
No. of cases of neonatal resuscitation (%)	5 (1.8)	186 (2.7)	
No. of major birth defects (%)	2 (0.7)	51 (0.007)	
Mean maternal age, years (SD)	33.6 (± 4.1)	28.7 (± 5.4)	0.000†
Mean maternal weight, kg (SD)	71.8 (± 14)	81.4 (± 4.6)	0.260†
Mean maternal height, cm (SD)	169 (± 6.5)	167 (± 6.4)	0.738†
Mean maternal Body-mass index (SD)	28 (± 7)	29 (± 6)	0.231†

Table 1: Maternal, obstetrical and neonatal outcomes between IVF/ICSI with “fresh” ETs and SC live births (†: Fisher exact T- test for independent samples; ‡: X2-Test; ET=Embryo Transfer; SC=Spontaneous Conception; SD=Standard Deviation).

Multivariate regression analysis

Multivariate regression analysis indicated only way of conception (conception after IVF/ICSI with fresh embryo transfer and spontaneous conception) but not maternal age as significant predictor of fetal birth weight (Table 2). Residuals from the regression equation are shown. The model has an R²=0.003.

	Estimate	P-value
Maternal age	-0.005	0.02
Way of conception (SC/Fresh/transfer)	-0.259	0

Table2: Multivariate regression analysis of the dependant variable z-score of fetal birth weight. The estimates indicate the relationship between the dependant variable (z-score) and the predictor variables. This is done by quantifying the amount of increase in z-score that would be predicted by a one unit increase in the predictor variable. The created model has an R²=0.003.

Discussion

This study does not prove the thesis of an association of IVF or ICSI with fresh embryo transfer to higher mean singleton birth weights compared to mean birth weights after spontaneous conception. Nevertheless, the regression model indicates an association of fetal birth weight to the way of conception. These results are in line with previous findings presented by several systematic reviews and cohort studies which indicate a similar or even better neonatal outcome for singletons born after IVF/ICSI procedure with cryopreservation compared to singletons born after IVF/ICSI with fresh embryo transfer [4-9].

Furthermore, the regression model demonstrated maternal age is not associated to fetal birth weight. This finding was expected since it was found already by several studies [2,3].

Previous studies indicate singletons born after being cryopreserved as embryo suffer from an increased risk of being large for gestational age or from macrosomia (birth weight ≥ 4500 g) compared to newborns after spontaneous conception or IVF/ICSI with fresh embryo transfer [2-5,9].

The present study shows singletons born after IVF/ICSI with fresh embryo transfer have a tendency towards lower birth weights compared to singletons born after spontaneous conception. The results of the regression analysis underline this assumption (p ≤ 0.001) which is confirmed by previous studies as well [2].

Furthermore, this study shows that patients who delivered after spontaneous conception were younger (mean age 28.7 years) than women delivering after IVF/ICSI with fresh embryo transfer (33.4 years). As expected, the C-section rate was increased with 46% in the IVF/ICSI with fresh embryo transfer group (vs. 39% spontaneous conception group) [2].

In conclusion, this study does not support the thesis of an association of IVF/ICSI with fresh embryo transfer to higher mean singleton birth weight versus birth weight after spontaneous conception. Nevertheless, this study suggests an association of fetal birth weight to the way of conception [10-16].

Limitations of this Study

This study has several limitations. Analysis is retrospective and there is a discrepancy between sample sizes of both groups. Additionally, registry data were sparse on the information about smoking and gestational diabetes of ART patients which bring the risk of confounding.

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