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

Kay Neumann1, Christoph Cirkel1 and Daniel Alexander Beyer2

1Department of Obstetrics and Gynaecology, University Hospital of Schleswig-Holstein, Germany
2Department of Obstetrics and Gynaecology, Westpfalz-Klinikum GmbH, Germany

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 (± 0.92) for IVF/ICSI and fresh embryo transfer and 0.009 (± 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 newborns 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 Recdata 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 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 newborns 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 newborns 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).

| 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       | 39 (14.1)                   | 646 (9.9)               | 0.000 X2 |
| (<37 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)              |     |
studies which indicate a similar or even better neonatal outcome for
Nevertheless, the regression model indicates an association of fetal
transfer [2-5,9]. This was found already by several studies [2,3].

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.

References
1. Ferraretti AP, Goossens V, de-Mouzon J, Bhattacharya S, Castilla JA, et al. (2008) Ion and Embryology (ESHRE). Assisted reproductive technology in Europe results generated from European registers by ESHRE. Hum Reprod 27: 2571-2584.
2. Sunderam S, Kissin DM, Flowers L, Anderson JE, Folger SG, et al. (2012) Centers for Disease Control and Prevention (CDC). Assisted reproductive technology surveillance—United States, 2009. MMWR Surveill Summ 61:1-23.
3. Rosque M, Lattes K, Serra S, Solà I, Geber S, et al. (2012) Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: A systematic review and meta-analysis. Fertil Steril 99: 156-162.
4. Pelkonen S, Koivunen R, Gissler M, Nuojua-Huttunen S, Suikkari AM, et al. (2010) Perinatal outcome of children born after frozen and fresh

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).

| 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) |
| Mean maternal weight, kg (SD) | 71.8 (± 14) | 81.4 (± 4.6) |
| Mean maternal height, cm (SD) | 169 (± 6.5) | 167 (± 6.4) |
| Mean maternal Body-mass index (SD) | 28 (± 7) | 29 (± 6) |

Table 2: Multivariate regression analysis of the dependant variable 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.

|                      | Estimate | P-value |
|----------------------|----------|---------|
| Maternal age         | -0.005   | 0.02    |
| Way of conception    | -0.259   | 0       |

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.

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.

References
1. Ferraretti AP, Goossens V, de-Mouzon J, Bhattacharya S, Castilla JA, et al. (2008) Ion and Embryology (ESHRE). Assisted reproductive technology in Europe results generated from European registers by ESHRE. Hum Reprod 27: 2571-2584.
2. Sunderam S, Kissin DM, Flowers L, Anderson JE, Folger SG, et al. (2012) Centers for Disease Control and Prevention (CDC). Assisted reproductive technology surveillance—United States, 2009. MMWR Surveill Summ 61:1-23.
3. Rosque M, Lattes K, Serra S, Solà I, Geber S, et al. (2012) Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: A systematic review and meta-analysis. Fertil Steril 99: 156-162.
4. Pelkonen S, Koivunen R, Gissler M, Nuojua-Huttunen S, Suikkari AM, et al. (2010) Perinatal outcome of children born after frozen and fresh
embryo transfer: The Finnish cohort study 1995-2006. Hum Reprod 25: 914-923.

5. Pinborg A, Loft A, Aaris Henningsen AK, Rasmussen S, Andersen AN (2010) Infant outcome of 957 singletons born after frozen embryo replacement: The Danish National Cohort Study 1995-2006. Fertil Steril 94: 1320-1327.

6. Wennerholm UB, Söderström-Anttila V, Bergh C, Aittomäki K, Hazekamp J, et al. (2009) Children born after cryopreservation of embryos or oocytes: A systematic review of outcome data. Hum Reprod 24: 2158-2172.

7. Pinborg A, Wennerholm UB, Romundstad LB, Loft A, Aittomäki K, et al. (2013) Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. Hum Reprod Update 19: 87-104.

8. Maheshwari A, Pandey S, Shetty A, Hamilton M, Bhattacharya S (2012) Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen thawed versus fresh embryos generated through in vitro fertilization treatment: A systematic review and meta-analysis. Fertil Steril 98: 368-377.

9. Wennerholm UB, Henningsen AK, Romundstad LB, Bergh C, Pinborg A, et al. (2013) Perinatal outcomes of children born after frozen-thawed embryo transfer: A Nordic cohort study from the CoNARTaS group. Hum Reprod 28: 2545-2553.

10. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW (2003) A nearly continuous measure of birth weight for gestational age using a United States national reference. BMC Pediatr 3: 6.

11. Martin RM, Smith GD, Frankel S, Gunnell D (2004) Parents’ growth in childhood and the birth weight of their offspring. Epidemiology 15: 308-316.

12. Xue F, Willett WC, Rosner BA, Forman MR, Michels KB (2008) Parental characteristics as predictors of birth weight. Hum Reprod 23: 168-177.

13. Sazonova A, Källen K, Thurin-Kjellberg A, Wennerholm UB, Bergh C (2012) Obstetric outcome in singletons after in vitro fertilization with cryopreserved/thawed embryos. Hum Reprod 27: 1343-1350.

14. Beyer DA, Griesinger G (2016) Vitrified-warmed embryo transfer is associated with mean higher singleton birth weight compared to fresh embryo transfer. Eur J Obstet Gynecol Reprod Biol 203: 104-107.

15. Pinborg A, Henningsen AA, Loft A, Malchau SS, Forman J, et al. (2014) Large baby syndrome in singletons born after frozen embryo transfer (FET). Is it due to maternal factors or the cryotechnique? Hum Reprod 29: 618-627.

16. Neumann K, Cirkel C, Rody A, Beyer DA (2017) Do ART patients face higher C-section rates during their stage of delivery? A German monocenter experience. Arch Gynecol Obstet 295: 481-485.