OBSTETRICS

Neonatal and maternal outcome after blastocyst transfer: a population-based registry study

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BACKGROUND: Previous studies have shown a higher risk of birth defects and preterm birth (PTB) in singletons born after blastocyst transfer as compared to singletons born after cleavage-stage transfer. Few studies have investigated the maternal outcomes.

OBJECTIVE: We sought to analyze the neonatal and maternal outcome after blastocyst transfer (day 5-6) compared to transfer of cleavage-stage embryos (day 2-3) and spontaneous conception.

STUDY DESIGN: This was a population-based retrospective registry study including all singleton deliveries after blastocyst transfer in Sweden from 2002 through 2013. The in vitro fertilization register was cross-linked with the Swedish Medical Birth Register, the Register of Birth Defects, and the National Patient Register. Deliveries after blastocyst transfer were compared with deliveries after cleavage-stage transfer and deliveries after spontaneous conception. Outcome measures included birth defects, PTB, low birthweight, small for gestational age, large for gestational age, perinatal mortality, placenta previa, placental abruption, and preeclampsia. Crude and adjusted odds ratios (AOR) with 95% confidence interval (CI) were calculated. Adjustment was made for year of birth of child, maternal age, parity, smoking, body mass index, years of involuntary childlessness, and child's sex and, for cleavage stage, also for number of oocytes retrieved, number of embryos transferred, and fresh/frozen embryo transfer.

RESULTS: There were 4819 singletons born after blastocyst transfer, 25,747 after cleavage-stage transfer, and 1,196,394 after spontaneous conception. Singletons born after blastocyst transfer had no increased risk of birth defects compared to singletons born after cleavage-stage transfer (AOR, 0.94; 95% CI, 0.79—1.13) or spontaneous conception (AOR, 1.09; 95% CI, 0.92—1.28). Perinatal mortality was higher in the blastocyst vs the cleavage-stage group (AOR, 1.61; 95% CI, 1.14—2.29). When comparing singletons born after blastocyst transfer to singletons born after spontaneous conception, a higher risk of PTB (<37 weeks) was seen (AOR, 1.17; 95% CI, 1.05—1.31). Singletons born after blastocyst transfer had a lower rate of low birthweight (AOR, 0.83; 95% CI, 0.71—0.97) as compared to cleavage-stage transfer. The rate of being small for gestational age was lower in singletons born after blastocyst transfer as compared to both cleavage-stage and spontaneous conception (AOR, 0.71; 95% CI, 0.56—0.88 and AOR, 0.70; 95% CI, 0.57—0.87, respectively). The risk of placenta previa and placental abruption was higher in pregnancies after blastocyst transfer as compared to pregnancies after cleavage-stage (AOR, 2.08; 95% CI, 1.70—2.55 and AOR, 1.62; 95% CI, 1.15—2.29, respectively) and spontaneous conception (AOR, 6.38; 95% CI, 5.31—7.66 and AOR, 2.31; 95% CI, 1.70—3.13, respectively).

CONCLUSION: No increased risk of birth defects was found in singletons born after blastocyst transfer. Perinatal mortality and risk of placental complications were higher in the blastocyst group as compared to the cleavage-stage group, observations that need further investigations.

Key words: assisted reproductive technology, birth defects, congenital anomalies, malformations, placenta previa, preterm birth

Introduction

Worldwide, the use of assisted reproductive therapy (ART) is expanding, and the number of children born through ART has passed 6 million. In Sweden, around 4000 children are born through ART each year and they comprise today 3.6% of the total national birth cohort in Sweden.[1]

In vitro fertilization (IVF) is associated with an increased risk of preterm birth (PTB) and low birthweight (LBW) as compared to spontaneous conception, which mainly can be explained by the higher incidence of multiple pregnancies.[2-4] However, an increased risk of PTB, LBW, and birth defects has also been demonstrated in singleton pregnancies after IVF.[4-9]

In spontaneous conception the implantation occurs 5-7 days after fertilization. In conventional IVF, the cleavage-stage embryos (day-2 to -3 embryos) are replaced in the uterus. Modern technology has made it possible to wait until the blastocyst stage (day 5-6 embryos) and then replace the embryo in the uterus. Blastocyst transfer has been shown to increase delivery rates in fresh cycles, although not cumulatively.[10]

Conflicting results have been reported concerning neonatal and maternal outcomes after blastocyst vs cleavage-stage transfers. A systematic review and meta-analysis showed an increased risk of PTB (<37 gestational weeks) (4 studies) and birth defects (2 studies) when using blastocyst transfer.[11] Other recent studies from Australia and Japan showed no significant differences in PTB or LBW between singletons from blastocyst and cleavage-stage transfers.[12,13] A previous Swedish study including 1311 singletons and multiples born after fresh and frozen blastocyst transfers, covering the years 2002 through 2006 and partially overlapping the present study, showed a significantly increased risk of birth defects as compared to children born after cleavage-stage transfer.[14] However, in a Canadian study covering the years 2001 through 2009 including 3206 singletons after fresh blastocyst transfer there was no increased risk of birth defects after blastocyst transfer.[15]

Few studies have reported on maternal outcomes after blastocyst vs

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cleavage-stage transfers. A Swedish registry study, covering the years 2002 through 2006 and partially overlapping the present study, showed increased risk of placenta previa in singleton pregnancies from fresh blastocyst vs fresh day-2 to day-3 transfers.[16] However, other studies have shown no significant differences in placental complications.[13,17,18]

The aim of this study was to examine neonatal and maternal outcomes in singleton deliveries after blastocyst transfer in Sweden from 2002 through 2013, and compare these deliveries with all singleton deliveries after cleavage-stage transfer and after spontaneous conception during the same period of time.

Materials and Methods

Study design

This study was a population-based retrospective registry study carried out in Sweden. We collected data from all IVF clinics, both public and private, in Sweden on IVF treatments performed from 2002 through 2013. The IVF clinics reported data on deliveries to the Swedish National Board of Health and Welfare for years 2002 through 2006, and for years 2007 through 2013, to the National Registry of Assisted Reproduction.[1] All reported IVF singleton and twin deliveries with autologous oocytes were included in the study and divided into fresh blastocyst, frozen blastocyst, fresh cleavage-stage, and frozen cleavage-stage transfers. Using the unique personal identification number given to all citizens in Sweden we cross-linked data on deliveries after IVF with the Swedish Medical Birth Register (MBR), the Register of Birth Defects (formerly Register of Congenital Malformations), and the National Patient Register (formerly the Hospital Discharge Register) and collected information about maternal characteristics, pregnancy, delivery, and the neonatal period.

Data on deliveries included all live births and stillbirths. Before July 1, 2008, stillbirths $\geq$28 completed gestational weeks were included and from July 1, 2008, stillbirths $\geq$22 completed gestational weeks were included.

Data from the IVF registers included information about treatment, ie, blastocyst or cleavage-stage transfer, fresh or frozen-thawed embryo transfers, number of oocytes retrieved, number of embryos transferred, date of embryo transfer, singleton or twin gestation, and date of delivery. Data from MBR included maternal characteristics (ie, age, parity, body mass index [BMI], smoking habits, years of involuntary infertility) and data on delivery and neonatal outcomes. The MBR has been found to have high validity and covers almost all deliveries in Sweden since 1973.[19,20]

Typically, blastocyst transfers were performed on days 5-6 and cleavage-stage transfers on days 2-3. Cryopreservation methods included both vitrification and slow freezing for blastocysts and slow freezing for cleavage-stage embryos.

Singleton deliveries after blastocyst transfers were compared with deliveries after cleavage-stage transfers and with deliveries after spontaneous conception (n = 1,196,394).

Outcomes

For singletons, the main neonatal outcome was birth defects. Other neonatal outcome measures were PTB (<37 weeks, <32 weeks [very PTB], <28 weeks), LBW (<2500 g), very LBW (<1500 g), small for gestational age (SGA) (<−2SD), large for gestational age (LGA) (>+2SD, >+3SD), macrosomia (>4500 g), low Apgar score (<7 at 5 minutes), perinatal mortality (defined as stillbirths and early neonatal deaths within 7 days after birth), child's sex, and rate of cesarean delivery. The Swedish gender- and gestational age–specific growth standard was used as a reference for SGA and LGA.[21] We also analyzed any composite neonatal adverse outcome (defined as any of PTB, LBW, SGA, or perinatal mortality) and severe composite adverse neonatal outcome (defined as any of very PTB, very LBW, or perinatal mortality).

Birth defects were defined according to *10th revision of the International Statistical Classification of Diseases and Related Health Problems* (*ICD-10*) codes beginning with Q. Minor birth defects such as preauricular appendix, tongue tie, patent ductus arteriosus in preterm infants, single umbilical artery, undescended testicle, hip luxation/subluxation, clicking hip, and nevus were excluded. Subanalyses were made within 6 different groups of birth defects: cardiac defects, neural tube defects, orofacial clefts, gastrointestinal defects, hypospadias, and limb reduction defects. Information on birth defects were collected from 3 sources: the MBR (*International Classification of Diseases* codes given at the pediatric examination of the newborn), the Register of Birth Defects, and the National Patient Register. The Register of Birth Defects and the National Patient Register supplied information on birth defects during the infant's first year of life.[22]

Gestational age was determined from the second-trimester ultrasonography for the majority of spontaneous conception pregnancies, or from the first day of the last menstrual period if information from ultrasonography was not available. For IVF pregnancies gestational age was calculated from the day of embryo transfer, ie, day 5 or 6 for blastocyst and day 2 or 3 for cleavage-stage embryos. If the information was not available, gestational age was calculated from ultrasonography.

The maternal outcomes in singleton pregnancies included placenta previa (*ICD-10* code O44), placental abruption (*ICD-10* code O45), preeclampsia/eclampsia (*ICD-10* codes O14 or O15), preterm prelabor rupture of the membranes (*ICD-10* code O42), gestational diabetes (*ICD-10* code O244), and postpartum hemorrhage (*ICD-10* code O72; >1000 mL).

Outcomes for multiples included only birth defects.

Ethics

Permission for this study was given from the Regional Ethical Committee at the University of Gothenburg (Dnr 304/06, T876-14).

Statistical analysis

Descriptive data are given as numbers and percentages. Statistical analysis was performed on neonatal and maternal outcomes for singleton pregnancies after