Risk of preterm birth after blastocyst embryo transfer: a large population study using contemporary registry data from Australia and New Zealand

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Objective: To investigate whether there is an increased risk of preterm birth with blastocyst transfer compared with cleavage-stage embryo transfer (ET) after assisted reproductive technology (ART).
Design: A retrospective, population-based study.
Setting: Not applicable.
Patient(s): A total of 50,788 infants conceived after ART treatment performed from 2009 to 2012.
Intervention(s): None.
Main Outcome Measure(s): The rates of preterm birth, low birth weight (LBW), and small for gestational age (SGA) for 43,952 singleton and 3,418 twin deliveries after transfers of blastocyst or cleavage-stage embryos.
Result(s): Among singletons, there was no significant difference in the odds of preterm birth between blastocyst and cleavage-stage ET (9.1% compared with 9.3%, respectively, adjusted odds ratio 1.00, 95% confidence interval 0.94–1.08). Among twins, the crude rates of preterm birth were similar after blastocyst and cleavage-stage ETs (61.5% and 64.4%, respectively). However, after adjusting for potential confounders, blastocyst transfer was associated with a lower odds of preterm birth among twins (adjusted odds ratio 0.80, 95% confidence interval 0.70–0.93). There was no difference in risks of LBW and SGA between blastocyst and cleavage-stage ETs for both singletons and twins after adjusting for potential confounders.
Conclusion(s): In contrast with the findings from a number of other studies, blastocyst culture in Australian and New Zealand is not associated with an increased risk of preterm, LBW, and SGA for singletons. Further studies are needed to assess longer-term outcomes of children born after ART treatment and possible biological or treatment factors related to adverse outcomes. (Fertil Steril® 2015;104:997–1003. ©2015 by American Society for Reproductive Medicine.)
Key Words: Assisted reproductive technology, singletons, twins, preterm, low birth weight, blastocyst

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The use of extended embryo culture to the blastocyst stage before ET in assisted reproductive technology (ART) is increasing worldwide. This trend has coincided with the trend to single embryo transfer (SET), in which the best embryo is selected for transfer (1–6). Recent evidence from a Cochrane Review on the effectiveness of blastocyst vs. cleavage-stage ET reported an increase in the live birth rate per couple after fresh blastocyst transfer

compared with fresh cleavage-stage ET (odds ratio [OR] 1.40, 95% confidence interval [CI] 1.13–1.74) (7). The increased live birth rate after fresh blastocyst transfer is largely explained by the selective transfer of embryos that have survived to 5 to 6 days in vitro, and a more favorable uterine environment that more closely mimics the timing of implantation in natural conception (8, 9). However, the Cochrane Review also found that the cumulative clinical pregnancy rate (derived from fresh and thaw cycles) was significantly higher for cleavage-stage ET cycles than for blastocyst transfer cycles, owing primarily to the lower embryo freezing rate in the latter group (7).

Although implantation, pregnancy, and live birth rates per embryo transferred are higher after blastocyst transfer compared with cleavage-stage ET, there are inconsistent findings in relation to adverse birth outcomes after blastocyst transfer. Three large studies from Canada, Sweden, and the United States using ART registry data reported that the preterm birth rate among ART singletons after blastocyst transfer was higher than those after cleavage-stage ET (10–12). The mechanism for the higher rate of preterm birth is hypothesized to relate to genetic or epigenetic effects on the trophectoderm cells due to extended culture, resulting in abnormal implantation and placentation (10). Other smaller studies have reported no increased risk of adverse perinatal outcomes after blastocyst transfer compared with cleavage-stage ET (13, 14). An Australian study using the Australian and New Zealand Assisted Reproduction Database (ANZARD) found lower rates of preterm birth (20.4% vs. 25.1%) and low birth weight (LBW) (15.7% vs. 20.2%) for babies conceived after blastocyst transfer compared with those conceived after cleavage-stage ET. However, this study did not adjust for potential confounding factors and used ART treatment from 2002–2006 (15). A recent meta-analysis that included data from four of the studies previously described (10–13) concluded that the risk of preterm birth in singletons was significantly higher after blastocyst culture (adjusted OR [AOR] 1.32, 95% CI 1.19–1.46) (16).

The aim of this present study was to investigate whether singletons and twins are at increased risk of preterm birth, LBW, and small for gestational age (SGA) after the transfer of blastocyst compared with cleavage-stage embryos using the most recently available ANZARD treatment data from 2009–2012 and controlling for known confounding factors.

MATERIALS AND METHODS

Population

The study included 47,370 live deliveries (singleton and twin infants) after transfers of blastocyst or cleavage-stage embryos during 2009–2012 in Australia and New Zealand. Data were extracted from ANZARD, which is a population-based registry of all ART cycles undertaken in Australia and New Zealand including information on the resulting pregnancy and birth outcomes.

During the study period, 50,788 babies (43,952 singletons and 6,836 twins) were born after blastocyst or cleavage-stage ETs. Of these, 822 singletons and 186 twins did not have complete information on sex and birth weight and were therefore excluded from analysis. The final analysis included 43,130 singleton and 6,650 twin live birth infants.

Study and Outcome Factors

The primary outcome measure was preterm birth, defined as a gestational age of <37 weeks. Secondary outcomes include LBW (<2,500 g at birth) and SGA (<10th percentile on intrauterine growth chart). Australian national birth weight percentile charts for singletons and twins were used to assign SGA status (17, 18). Birth weight percentiles were not available on 94 twins and were therefore excluded from the SGA analysis. The main study parameter of interest was stage of ET, which was categorized as cleavage-stage embryos transfer (day 2/3 embryos) or blastocyst transfer (day 5/6 embryos). Other explanatory factors included maternal age, cause of subfertility, parity, type of insemination (IVF or intracytoplasmic sperm injection [ICSI]), number of embryos transferred, type of transferred embryo (fresh or frozen/thawed embryo), and treatment year. Maternal age was classified into 3-year groups: <35 years, 35–39 years, and ≥40 years. The cause of subfertility was classified as male factor, female factor infertility, combined male–female factor infertility, unexplained infertility, and not stated. Parity was categorized as nulliparous, parous, and not stated. Number of embryos transferred was categorized as SET or double embryo transfer (DET).

Statistical Analysis

The demographic data (maternal age, cause of infertility, and parity) and treatment factors (IVF/ICSI, type of transferred embryo, number of embryos transferred, and treatment year) were compared by cleavage-stage embryo and blastocyst transfers using the χ^2 test. The rates of preterm birth, LBW, and SGA were calculated and compared according to the stage of ET. Univariate and multivariate logistic regressions stratified for singletons and twins were used to assess the risk of preterm birth. Generalized estimating equations were used to assess the risks of LBW and SGA adjusting for twin infants. Subanalysis by SET and DET was performed to assess the interaction between the number of embryos transferred and the stage of embryo development. Odds ratios and AORs (adjusting for woman's age, parity, type of infertility, IVF/ICSI, number of embryos transferred, fresh/thawed embryo, and treatment year) were computed. Infants conceived after ETs involving three or more embryos were excluded from the analysis. Data were analyzed with SPSS software (version 22.0).

Ethics

Ethical approval was obtained from the Human Research Ethics Advisory Panel of University of New South Wales (UNSW Approval No. 9-14-058).

RESULTS

Of the 47,370 live deliveries, 43,952 (92.8%) were singleton deliveries, and 3,418 (7.2%) were twin deliveries. Most demographic and treatment-related factors were unevenly distributed between the deliveries after cleavage-stage and blastocyst transfers (Table 1). The overall proportion of live deliveries resulting from blastocyst transfer increased from 58% in 2009 to 71% in 2012. Among singleton deliveries, 34.9% (15,337) were after transfer of cleavage-stage embryos and