ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Birth weight is associated with inner cell mass grade of blastocysts

Frederick Licciardi, M.D.,[a] Caroline McCaffrey, Ph.D.,[a] Cheongeun Oh, Ph.D.,[a] Cecilia Schmidt-Sarosi, M.D.,[b] and David H. McCulloh, Ph.D.[a]

[a] New York University Fertility Center, New York University Langone Medical Center; and [b] Offices for Fertility and Reproductive Medicine, New York, New York

Objective: To determine the relationship between blastocyst growth parameters and birth weight.
Design: Cohort study.
Setting: University-affiliated fertility center.
Patient(s): In vitro patients who delivered a singleton after a single-blastocyst transfer.
Intervention(s): None.
Main Outcome Measure(s): Birth weight adjusted for gestational age at delivery and gender, with adjusted birth weight examined for association with blastocyst scores and grades.
Result(s): After standard in vitro fertilization (IVF) and thawed embryo transfers, greater birth weight was associated with a higher inner cell mass grade. The grade of the trophectoderm and stage of the blastocyst did not relate to weight.
Conclusion(s): Embryonic growth as early as day 5 can predict the progress of fetal development as measured by birth weight. (Fertil Steril® 2014;■:■–■. ©2014 by American Society for Reproductive Medicine.)
Key Words: Birth weight, blastocyst grades, in vitro fertilization

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/licciardif-birth-weight-inner-cell-mass-blastocysts/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Birth weight (BW) has been shown to be influenced by many factors. Newborn gender, birth order, maternal weight, maternal weight gain, and body mass index are some of the more established predictors (1–3), but other determinants have been examined. Genetic links are highlighted by the correlations between maternal and offspring BW, and maternal and paternal heights and BW (4–7), along with a connection between maternal childhood height and BW (8). The role of nutrition on BW is clear, as the ingestion of energy-dense/nutrient-poor food (9), the consumption of milk (10, 11), and restricted vitamin absorption resulting from bariatric surgery (12) all have an effect. Environmental factors such as smoking (13–15) and exposure to air pollution reduce BW (16), as can maternal medical conditions such as chronic hypertension (17).

Anatomic assessment using advanced ultrasound technology in the first trimester has been used to forecast fetal growth, as variations in crown rump length, embryo volume, and volume of the gestational sac are all related to BW (18–20). In vitro embryonic morphologic parameters have likewise been shown to be predictive of fetal weight (21). In addition, levels of maternal reproductive hormones during an in vitro fertilization (IVF) cycle may affect implantation quality, which could ultimately affect BW (22). Our study was initiated to examine whether other early embryonic growth characteristics, as measured by blastocyst development on day 5, could relate to fetal growth as a whole, as measured by BW in relation to gestational age and gender.

MATERIALS AND METHODS

We performed a retrospective review of all autologous and donor egg recipient cycles, both fresh and frozen, in which a single blastocyst-stage embryo was transferred and resulted in a single live birth at New York University Fertility Center during the period of February 15, 2003, to December 4, 2011. Institutional review board approval was obtained (S13-00389).

Ovarian Stimulation

Controlled ovarian hyperstimulation protocols used included both gonadotropin-releasing hormone down-regulation and antagonist options. Gonadotropin doses varied and included follicle-stimulating hormone

Received May 3, 2014; revised October 26, 2014; accepted October 29, 2014.
F.L. has nothing to disclose. C.M. has nothing to disclose. C.O. has nothing to disclose. C.S.-S. has nothing to disclose. D.H.M. has nothing to disclose.
Reprint requests: Frederick Licciardi, M.D., 660 First Avenue, 5th Floor, New York, New York (E-mail: fredivf@yahoo.com).

Fertility and Sterility® Vol. ■, No. ■, ■ 2014 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2014.10.039

or combinations of follicle-stimulating hormone and human menopausal gonadotropin. When lead follicles had reached a mean diameter of 17–18 mm, human chorionic gonadotropin was administered intramuscularly or Ovidrel (500 units) was administered subcutaneously; ~35 hours later oocytes were collected by ultrasound-guided, transvaginal aspiration. Donor egg and frozen embryo recipients received oral micronized estradiol throughout the follicular and luteal phase. Patients received daily intramuscular progesterone supplementation (50–75 mg) beginning the day after retrieval and continuing until documentation of fetal cardiac activity.

Embryo Culture

Over the period of this retrospective analysis, our culture systems have remained very consistent as described herein. Basically, oocytes were isolated from follicular fluid, rinsed in HEPES buffered media (Irvine Scientific) and were immediately placed in 75-μL droplets of pre-equilibrated human tubal fluid (Irvine Scientific) supplemented with 6% Plasmanate (Bayer). Drops had been overlaid with mineral oil (Cooper Surgical) and incubated at 37°C, 6%CO_2/air. Oocytes were inseminated or treated via intracytoplasmic sperm injection (ICSI) at 4 to 6 hours after retrieval. Indications for ICSI were severe male factor infertility or a prior history of failed or low fertilization. The resulting zygotes were then transferred to pre-equilibrated 30-μL droplets of Quinn's cleavage media (Cooper Surgical) supplemented with 10% Plasmanate for culture to day 3. On day 3 after retrieval, the embryos were assessed for blastomere number, symmetry, degree of fragmentation, and overall quality and were graded on a scale of 1 to 4 (where 1 was best, and 4 was very poor quality). After the embryo assessment, the embryos were then transferred to 30-μL droplets of Quinn's blastocyst media (Cooper Surgical) supplemented with 10% Plasmanate where they remained through day 5. Embryos were transferred using Quinn's blastocyst media and a Wallace catheter under ultrasound guidance.

Blastocyst Scores and Grading

Blastocysts were graded using the criteria of Gardner and Lane (23). In summary, the blastocyst score is related to the degree of expansion of the blastocele. The inner cell mass (ICM) grade indicates the number of cells included in the ICM, and the trophectoderm (TE) grade indicates the number of cells included in one focal plane of the trophectoderm. In both cases, the number of cells included is greater in the blastocysts that have more favorable grades. The number of cells included follows the inequality A > B > C, such that A grades are associated with more cells than B grades, which are associated with more cells than C grades.

Cryopreservation of Surplus Blastocysts

Surplus blastocysts that had reached a stage 3 or greater with at least one B letter grade for either the ICM or TE were considered for cryopreservation using either a slow-freezing methodology in vials or more recently (mid-2009) vitrification using cryolocks.

Statistical Analysis

Weight measurement was shown to demonstrate a normal distribution from a Shapiro-Wilk test for normality, and no further transformation was required. Descriptive information via the mean (± standard deviation) and proportion was first compared across different groups. To evaluate the association of weight with independent variables, we performed a linear regression on weight in a univariate manner, which is equivalent to calculating the correlation coefficient for continuous variables and an unpaired t test for dichotomous variables such as gender. Multiple linear regression was used to adjust BW for the effects of gestational age and gender. Results of the multiple linear regression were reported as regression coefficients with standard deviations. Birth weights after adjustment were reported as mean with standard deviation. Two-sided $P < .05$ was considered statistically significant. Statistical analysis was performed using R software (www.R-project.org).

RESULTS

A total of 224 deliveries resulting from single blastocyst transfers were analyzed. Figure 1 shows the relationship between BW, gender, and gestational age. As expected, males were heavier than females, and their regression lines were close to parallel. Visual inspection reveals that the distribution of BW about the regression lines was close to normal.

Table 1 provides the descriptive data for the study population, in which 135 women used autologous oocytes with a fresh embryo transfer, 32 used a fresh oocyte donation transfer, and 57 had an autologous thaw cycle. All groups were similar for mean BW and mean gestational age. The donor egg recipients (DE) delivered more males than females. Blastocysts achieving a stage of 5 or 6 (total n = 6) were placed in the stage 4 category.

Table 2 examines the association between blastocyst development and BW. Associations exist between birth weight and either gestation age or gender. BW was not associated with the type of IVF cycle, the blastocyst stage or the trophectoderm score. There was a significant difference in BW when comparing blastocysts with ICM grades of A versus B or grades of A versus B or C (A was associated with a greater BW); whereas there was no significant difference in weight when comparing blastocysts with ICM grades of A versus C, possibly in association with the small number of blastocysts graded C.

Univariate linear regression revealed significant associations between BW and gestational age (GA) and between BW and gender (Table 2, column labeled univariate linear regression on BS). No association was seen between BW and either the Source (cycle types), the blastocyst stages or the TE grades.

Because BW was associated with gestational age and with gender, multiple linear regression was used to adjust birth weight for its association with these two parameters (Table 2, column labeled after adjustment for age and gender). After adjusting BW for both gestational age and gender, BW was associated with ICM score, such that babies from blastocysts with an ICM score of A had an adjusted weight 152 g greater than that of babies from blastocysts scored as a B. The association was also significant with babies born from