Neonatal outcome after preimplantation genetic diagnosis

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Objective: To examine whether embryo biopsy for preimplantation genetic diagnosis (PGD) influences neonatal outcomes.
Design: Prospective follow-up cohort.
Setting: Tertiary university-affiliated medical center.
Patient(s): 242 children born after PGD, 242 children born after intracytoplasmic sperm injection (ICSI) (158 singletons and 42 twins pairs in each group), and 733 children born after a spontaneous conception (SC) (493 singletons, 120 twins pairs), matched for maternal age, parity, and body mass index.
Intervention(s): None.
Main Outcome Measure(s): Gestational age, birth weight, prematurity (<37 and <34 weeks), low birth weight (<2,500 g, very low birth weight, <1,500 g), and intrauterine growth restriction (<10th percentile for gestational age).
Result(s): For singletons, the mean birth weight was higher after SC compared with ICSI but not compared with PGD. Mean gestational ages were lower after PGD and ICSI compared with SC. The low birth weight and intrauterine growth restriction rates were 4.4%, 12.0%, and 5.7% and 5.1%, 9.5%, and 5.5% for PGD, ICSI, and SC, respectively. Similar results were found when controlled for the number of embryos transferred and cryopreservation. The results for twins exhibited similar but less statistically significant trends. Polar body and blastomere biopsies provided similar outcomes.
Conclusion(s): Embryo biopsy itself did not cause intrauterine growth restriction or low birth weight compared with SC, despite lower gestational ages with PGD. The worsened outcomes in ICSI compared with PGD pregnancies may be due to the infertility itself. (Fertil Steril® 2014;102:1016–21. ©2014 by American Society for Reproductive Medicine.)
Key Words: Embryo biopsy, genetic diagnosis, intrauterine growth restriction, neonatal outcome, preimplantation, prematurity

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Both singleton and multiple pregnancies achieved with in vitro fertilization (IVF) are at higher risk than spontaneous conceptions (SC) for preterm delivery, low birth weight (LBW), perinatal mortality, and admission to neonatal intensive care (1–5). Children born after the more invasive procedure of intracytoplasmic sperm injection (ICSI) have significantly more major congenital malformations than children born after IVF or naturally conceived children (6). However, it remains unclear whether these increased risks can be attributed to the underlying infertility, characteristics of the infertile couple, or the use of assisted reproductive techniques per se.

Preimplantation genetic diagnosis (PGD) is used to select embryos that are unaffected by a genetic disorder, have a normal karyotype, show a human leukocyte antigen (HLA) match with a sibling, have a lessened cancer predisposition, or are the desired sex. Despite the relatively large number of studies on neonatal outcomes after IVF and ICSI, these data and conclusions cannot be extrapolated and used for PGD (7) because PGD is performed by analyzing one or two cells obtained through oocyte, zygote, or embryo biopsy, which adds further invasive manipulation (8).

A few reassuring studies have been published on the outcomes for children born after PGD: no higher rates of congenital defects have been observed at birth in children conceived by IVF-ICSI in association with PGD (9–11). The European Society of Human

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Reproduction and Embryology (ESHRE) PGD Consortium reported that pregnancies and babies born after PGD are similar to the pregnancies obtained and babies born after ICSI treatment (12). Desmyttere et al. (13) published a study of the neonatal outcomes of 995 children born after embryo biopsy for PGD in one Belgian center. They found no differences between the PGD and ICSI children regarding gestational age, birth weight, perinatal death, or major malformations. When compared with ICSI, fewer multiples born after PGD presented a low birth weight (LBW <2,500 g).

In our study, we compared the neonatal outcomes of all the neonates born after PGD performed in our unit with those of neonates born to mothers matched for age, body mass index (BMI), and parity during the same period after ICSI and after SC. In addition, we compared pregnancies after polar body biopsy to those after blastomere biopsy.

MATERIALS AND METHODS

Patients

The study population comprised all PGD pregnancies from Shaare Zedek Medical Center (SZMC) for which live births occurred between January 2005 and December 2012 (245 children, 158 singletons, 42 pairs of twins, and 1 set of triplets). They were compared with two groups: [1] 242 children (158 singletons, 42 pairs of twins) born after consecutive ICSI treatment during the same time period to mothers matched for age, preconception BMI, and parity (ICSI group); and [2] randomly selected 733 children (493 singletons, 120 sets of twins) born after SC during the same time period to mothers matched for age and parity (control group, for whom data on BMI before conception was not available). The SC babies were randomly assigned by use of an integral computer randomization from among the more than 12,000 babies born annually in the SZMC. Pregnancies from donated gametes, surgically retrieved sperm, and live-born infants delivered from pregnancies with associated selective fetal reduction were not included. The mechanical zona-pellucida breaching (partial zona dissection), polar body and blastomere biopsies, ICSI, and embryo cultures were performed as previously described elswhere (14, 15). Demographic and clinical data are presented in Table 1. The study was approved by the SZMC institutional review board in accordance with national regulations.

Data Collection

The data was collected from the computerized hospital databases and when needed, from the patient's files (IVF, delivery room, and neonatal and maternity units). This included parental demographic information; maternal pregestation BMI; the type of biopsy performed for PGD (polar bodies vs. blastomere), the number of embryos transferred and whether they were frozen-thawed or fresh; gynecologic and obstetric history before and during the index pregnancy; gestational age, mode of delivery (vaginal or cesarean delivery), and birth weight; and complications during hospital stay and outcome at discharge. As a part of the routine follow-up evaluation of children born after PGD, at 2 to 4 months the parents were contacted regarding any congenital malformations that were not diagnosed at birth.

We defined LBW as <2,500 g and very low birth weight (VLBW) as <1,500 g. Preterm was defined as birth before 37 completed weeks of gestation and very preterm as before 34 weeks. Intrauterine growth restriction (IUGR) was defined as birth weight below the 10th percentile for gestational age, and large for gestational age (LGA) was defined as weight above 90th percentile (16).

Statistical Analysis

Data are presented as mean ± standard deviation (SD) unless indicated otherwise. Statistical analysis for comparing the PGD with the ICSI or the SC groups included Student's *t*-test (continuous variables) and Fisher's exact test (categorical variables). One-way analysis of variance (ANOVA), Fisher's exact and chi-square tests were used to compare the three groups. $P<.05$ was considered statistically significant.

RESULTS

There was no statistically significant difference in demographics or clinical data among the groups in terms of mean age, BMI, or parity for both singletons and twins (see Table 1). The incidence of pregnancy complications such as hypertension and diabetes was similar in the three groups: hypertension, 1%, 1%, and 3%; diabetes 2%, 6%, and 4% in the PGD, ICSI, and SC groups, respectively.

Singletons

The mean birth weight was statistically significantly different among the three groups ($P=.005$; Table 2). The SC children

TABLE 1

Demographic and clinical data (mean ± standard deviation).

	Singletons			Twins		
	PGD	ICSI	SC	PGD	ICSI	SC
Number of neonates	158	158	493	84	84	240
Maternal age (y)	30.5 ± 4.1	30.5 ± 4.7	30.3 ± 4.6	28.7 ± 3.7	30.5 ± 4.4	30.1 ± 4.3
BMI (kg/m^2)[a]	23.6 ± 4.4	23.9 ± 4.3	—	23.8 ± 4.6	23.9 ± 4.6	—
Nulliparous (%)	51 (32)	51 (32)	173 (35)	18 (43[b])	18 (43[b])	57 (47[b])

Note: BMI = body mass index; ICSI = intracytoplasmic sperm injection; PGD = preimplantation genetic diagnosis; SC = spontaneous conception.
[a] Before treatment.
[b] Two women in each group had four or five previous deliveries.

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