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Growth and health outcome of 102 2-year-old children conceived after preimplantation genetic diagnosis or screening

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ABSTRACT

Objective: The major objective of this study was to determine whether the embryo biopsy procedure might cause growth restriction or affect health outcome of children.
Study design: Auxological data and physical findings were compared at birth and age 2 for 102 children (70 singletons and 32 twins) born after PGD/PGS and 102 matched children born after intracytoplasmic sperm injection (ICSI) **in a prospective study**.
Results: No statistically significant differences regarding weight, height and head circumference standard deviation scores (SDS) at birth and at age two years were observed. At two years of age the mean BMI SDS tended to be lower in PGD/PGS children ($p = 0.058$). PGD/PGS babies had been more often breastfed ($p = 0.013$), but mostly during a shorter time.
The prevalence of major as well as minor congenital anomalies, hospital admissions and surgical interventions was similar.
Conclusion: Children born after embryo biopsy applied in PGD/PGS present similar prenatal and postnatal growth and health outcome in the first two years of life compared to ICSI children. Up till now, PGD and PGS appear not to be associated with a higher risk for health problems.

1. Introduction

Assisted reproductive technology (ART) has evolved since the birth of Louise Brown, the first human born after in vitro fertilisation (IVF) in 1978. Intracytoplasmic sperm injection (ICSI) with injection of one spermatozoon through the oocyte membrane was introduced in 1991. ICSI which is a more sophisticated technique compared to IVF, bypasses the natural sperm selection. ICSI is used as ART to minimize the risk of contamination by DNA in PCR reactions and to reduce the risk of fertilisation failure in comparison to in vitro fertilisation (IVF). Preimplantation genetic diagnosis (PGD), first described in the early nineties as an early form of prenatal diagnosis, allows the embryonal determination of chromosomal imbalances, specific monogenic defects and gender of the embryo [12,17]. PGD is now increasingly used for couples with a genetic risk possibly combined with infertility, who want to avoid pregnancy interruption [21,22]. In the recruitment period of this study, preimplantation genetic screening (PGS) with enumeration of chromosomes or aneuploidy screening was applied to improve the effectiveness of assisted reproductive technology (ART) in patients with a low risk of transmitting a genetic disease, but with an increased incidence of embryonic numerical chromosome abnormalities, repeated abortions, multiple failed IVF cycles or advanced maternal age [18,19]. Today, however, it is a matter of controversy whether PGS improves the outcome of ART [13]. No higher rates of congenital defects were observed at birth in children born after PGD/PGS [8,20].

The safety of embryo biopsy is an issue that receives constant scrutinizing. The information on children follow-up data is helpful for patients and health care providers. With the increased utilization of PGD and the paucity of controlled outcome studies, it is important to have longer term follow-up data of children conceived with these methods. Therefore, a prospective study on physical and mental development was set up at our centre, where PGD/PGS is performed since 1996. A control group of children born after ICSI was included to determine whether potential differences in children's outcome were exclusively attributed to the embryo biopsy.

In this paper we report the auxological and clinical outcome after the second year of life in a matched case-control cohort study including 102 children in each group.

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2. Methods

2.1. Participants

The final sample consists of 102 (45 boys/57 girls) PGD/PGS and 102 matched ICSI children. All PGD/PGS and ICSI children are part of a cohort that is followed since birth [5]. Future parents were recruited for this prospective clinical follow-up study before starting PGD/PGS or ICSI and enrolled after a written informed consent was obtained. At the time of assessment (April 2005 and April 2007) the children were between 21 and 33 months old. Out of 115 eligible PGD/PGS children, 102 (88.7%) participated in this study and in order to include 102 ICSI children, 108 ICSI families had to be contacted resulting in a participation rate of 94.4% in the ICSI group.

In the PGD/PGS group, 40 children were born after PGD and 62 children after PGS. The applied biopsy technique through aspiration of blastomeres was the same in all PGD/PGS conceptions [9]. Eight singleton and 6 twin PGD/PGS children were born after biopsy of one blastomere, and 56 singleton and 24 twin PGD/PGS children underwent a two blastomere biopsy.

ICSI controls were selected to match PGD/PGS children as closely as possible according to birth date, gender, maternal educational level, maternal language and birth order (having an older sibling or not). These parameters were chosen to investigate the motor and mental development also [14–16].

2.2. Study procedure

All children of both groups were examined at the Centre for Medical Genetics of the Vrije Universiteit Brussel (Brussels) in accordance with a standardized protocol that included a medical history and physical examination by an experienced paediatrician and an assessment of the mental and motor development by a trained psychologist, who were both blinded to the type of ART treatment [7,15].

Information about the marital status, ethnic origin, height and weight and educational level of the parents, as well as information about the maternal age at the birth of the child, parity, maternal health during pregnancy, use of medication, alcohol and cigarettes during pregnancy and weight gain during pregnancy were obtained by a questionnaire.

Perinatal data, i.e. gestational age, birth weight, birth height, head circumference at birth, Apgar score, breastfeeding, reason and duration of admission to a neonatal care unit, were obtained from medical files from hospitals and well baby clinics ('Kind en Gezin' and 'Oeuvre Nationale des Enfants') with the consent of the parents.

Childhood medical history consisted of hospital admissions, surgical interventions and chronic illnesses. Chronic illness was defined as a disorder of at least 3 months in duration in 1 year, which required treatment or interfered with daily functioning. Reason, frequency and duration of hospital admission were noted. Intake of medication for more than 3 weeks, remedial treatment, complementary examinations were noted.

Biometrical data such as weight, height, head circumference, left mid-upperarm circumference, waist circumference were collected with standard equipment and according to a standardized procedure (www.vub.ac.be/groeicurven). Weight, height, head and arm circumference standard deviation scores (SDS) were calculated from the reference data of the recent Flemish growth survey in 2004 (www.vub.ac.be/groeicurven). Physical examination included a standardized assessment of major and minor physical anomalies, including skin defects like café-au-lait spots, hemangioma, and congenital naevi. Major malformations were classified according to criteria previously defined [3–5], while the remaining malformations were classified as minor anomalies according to a checklist for minor congenital defects [1].

2.3. Statistical analysis

Statistical analysis was conducted using SPSS 15.0 for Windows. Results are expressed as mean ± standard deviation. Categorical variables were analysed using χ^2. Between-group differences on continuous variables were analysed using the Student *t*-test . A significance level of 0.05 was accepted throughout. A power analysis showed that 102 children in each group allow to detect a difference in height of 0.65 SDS between both groups at the age of two years for an alpha level of 0.05 and 90% power. The same number of children allows to detect a 1.41 times higher malformation rate in the PGD/PGS group, assuming a baseline prevalence of 2.6% in the control group for an alpha level of 0.05 and 80% power. The study power analysis and sample size calculations were validated with nQuery Advisor version 5.0 (Statistical Solutions Ltd. Ireland).

2.4. Ethics

The study was approved by the ethical committees of the University Hospital Brussels, and written informed consent was obtained from the parents.

3. Results

3.1. Neonatal auxological data

Gestational age, birth weight, height and head circumference and the calculated standard deviation scores (SDS) were comparable for both conception groups (Table 1). Birth weights less than 2500 g and 1500 g were observed in respectively 34 children and 1 child in the PGD/PGS group and in respectively 26 and 2 children in the ICSI group ($p = 0.2$ for a birth weight < 2500 g and $p = 0.6$ for a birth weight < 1500 g). Anthropometrical data at birth were comparable for neonates born after biopsy of one blastomere to those after biopsy of two blastomeres (data not shown).

Maternal determinants of foetal growth such as age, parity, pre-pregnancy BMI and stature, medical complications and maternal weight gain during pregnancy were comparable (Table 2). Mean gestational age ($p = 0.749$) and the number of children born before 37 weeks (23 ICSI children and 28 PGD/PGS children) were comparable ($p = 0.419$) and no more PGD/PGS offspring was born after caesarian section compared to ICSI babies ($p = 0.089$).

3.2. Auxological data at physical examination

PGD/PGS children were slightly but significantly younger than ICSI children at the time of assessment ($p = 0.024$) (Table 3). Therefore, growth parameters were compared using SD-scores. Standard deviation scores for weight, height, head circumference, waist and arm circumference standard deviation scores were comparable in both conception groups. Those for the BMI however tended to be lower in PGD/PGS children ($p = 0.058$). PGD/PGS babies had been more often breastfed ($p = 0.013$), but mostly during a shorter time.

Table 1
Neonatal auxological parameters (mean ± SD, *n* between brackets) in PGD/PGS and ICSI children.

	PGD/PGS	ICSI	Test	*P*
Gestational age (weeks)	37.7 ± 2.2 (102)	37.8 ± 2.6 (102)	$t = 0.321$	0.749
Birth weight (g)	2875 ± 658 (102)	2935 ± 685(102)	$t = 0.637$	0.525
Birth length (cm)	48.0 ± 3.3 (97)	48.2 ± 3.4 (99)	$t = 0.570$	0.569
Birth head circumference (cm)	33.6 ± 1.7 (91)	33.6 ± 1.9 (87)	$t = -0.24$	0.981
Birth weight SDS	−0.64 ± 1.07 (102)	−0.53 ± 1.10 (102)	$t = 0.736$	0.463
Birth height SDS	−0.46 ± 1.07 (97)	−0.34 ± 1.20 (99)	$t = 0.710$	0.479
Birth head circumference SDS	0.15 ± 0.93 (91)	−0.15 ± 0.97 (87)	$t = 0.027$	0.979