Mental and psychomotor development of 2-year-old children born after preimplantation genetic diagnosis/screening

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BACKGROUND: Embryo biopsy is a new invasive procedure applied in ART for diagnostic purposes in preimplantation genetic diagnosis (PGD) or to increase pregnancy rate in preimplantation genetic screening (PGS). The objective of this study is to assess mental and psychomotor developmental outcomes in 2-year-old children born after PGD/PGS, intracytoplasmic sperm injection (ICSI) and natural conception (NC). METHODS: Two-year-old PGD/PGS (n = 70), ICSI (n = 70) and naturally conceived (n = 70) singleton children were recruited. The participation rate in the NC group was 88.6% and 94.5% in both ART conception groups. The mental and psychomotor development of the children was assessed using the Dutch version of the Bayley Scales of Infant Development. The mothers were questioned about socio-demographic characteristics. RESULTS: Even after controlling for socio-demographic variables, no differences were found between the three conception groups for the mental and psychomotor developmental outcomes. Moreover, an equal number of PGD/PGS, ICSI and NC children obtained scores within the mildly delayed, the normal and the accelerated performance category of the BSID-II-NL. CONCLUSIONS: Children conceived after PGD/PGS show similar mental and psychomotor developmental outcomes at age 2 to children conceived after ICSI or naturally.

Keywords: PGD; PGS; mental development; psychomotor development; child follow-up

Introduction

Preimplantation genetic diagnosis (PGD) is a procedure, which was developed in the early 1990’s, in which embryos obtained through in vitro fertilization (IVF) are analyzed for a genetic disorder before the ‘unaffected’ embryos are implanted in the woman’s uterus. As such, PGD is a very early form of prenatal diagnosis (PND) (Braude et al., 2002). PGD is used for two broad indication groups (Sermon, 2006). The first group of couples are at risk of having children with a genetic disease or chromosomal aberrations. These couples have often experienced several terminations of pregnancies after a negative outcome of PND, have had concurrent infertility or have had recurrent spontaneous abortions (Sermon, 2006). For this group of patients, PGD offers an additional way to continue a pregnancy by confirming the absence of certain genetic diseases (Fasouliotis and Schenker, 1998). Especially for patients with religious or moral objections to abortion, the main advantage of PGD is that it avoids the implantation of defective embryos and hence a provoked termination of pregnancy. It therefore offers a way around the controversy surrounding selective (or ‘therapeutic’) abortion. The second group of patients consists of IVF patients, with a low genetic risk, whose embryos are screened for chromosome aneuploidies to increase their chance of a successful pregnancy (Sermon, 2006). PGD for aneuploidy screening (preimplantation genetic screening [PGS]) is applied to improve the effectiveness of IVF in low-prognosis patients, such as those with an advanced maternal age (Sermon, 2006). Nevertheless, as the diagnosis in PGD and PGS is based on the analysis of one or two cells and is therefore prone to error, many centres recommend and request follow-up PND in cases of pregnancy (Lissens et al., 1996). Simpson and Liebaers (1996) add that the safety of the embryo biopsy needs to be determined not only with prenatal follow-up but also with respect to pregnancy rate, neonatal assessment and incidence of congenital anomalies.

Every year, the ESHRE Consortium reports a steady rise in the number of centres practicing PGD and PGS and in the number of cycles, pregnancies and babies born from this procedure (ESHRE PGD Consortium Committee, 2007). This growing popularity of PGD has highlighted the fact that there are no comprehensive data available on the use of PGD and the health outcomes of babies born after this treatment (Baruch et al., 2006). However, it is becoming apparent that
PGD/PGS babies are very comparable with intracytoplasmic sperm injection (ICSI) babies with respect to biometric characteristics (birth weight, length and head circumference), gestational age and the incidence of minor and major complications. A more unfortunate similarity between PGD/PGS and ICSI conception methods are the multiple pregnancies leading to morbidity and mortality in PGD/PGS and ICSI children (ESHRE PGD Consortium Committee, 2007). However, despite the fact that PGD and PGS procedures include an ICSI treatment in order to obtain embryos in vitro and the apparent comparability between PGD/PGS and ICSI babies, the developmental outcomes of ICSI children cannot be generalized for children born after PGD/PGS because of the more invasive nature of the latter ART. At the present time, research into specific developmental outcomes of PGD/PGS children is still non-existent. The development of ICSI children, however, has been investigated at different developmental stages by different centres around the world and has generated very reassuring results. Bonduelle et al. (1998, 2003), who studied the mental development of 2-year-old ICSI children with the Bayley Scales of Infant Development (BSID) (van der Meulen and Smrkovsky, 1983) found no indication that the ICSI children had a slower mental development than the general population. Later studies, in which 1–2-year-old ICSI children were assessed with the Griffith scales for mental development (Griffiths, 1996) or the BSID mental scale (MS) (Bayley, 1993) and compared with naturally conceived controls, confirmed that there are no differences between the two conception groups (Sutcliffe et al., 1999, 2001, 2003; Papaligoura, 2004). In addition to mental development, La Sala et al. (2004) and Agarwal et al. (2005) assessed the motor development of children born after ICSI and naturally conceived children and concluded that at age 2 both conception groups obtained mental and motor scores within the normal range. Studies focusing on 5–10-year-old ICSI children found that the cognitive, motor and socio-emotional development of the children (Place and Englert, 2003; Ponjaert-Kristoffersen et al., 2004, 2005; Leunens et al., 2006, 2008) as well as parental wellbeing, family functioning and parent–child relationships in families who conceived after ICSI–IVF or naturally are very similar (Barnes et al., 2006, 2008). Nevertheless, in most of these child follow-up studies socio-demographic variables (e.g. maternal age, educational level, social class and nationality) interacted in a small yet significant way with the outcomes as regards child development and parenting after ART. When infants are examined (<36 months) instead of young children, physiological factors (birthweight and gestational age) are more closely related to developmental outcomes than socio-demographic variables (Miceli et al., 2000). This has implications for future research, suggesting the need for more case-controlled studies that take into account both socio-demographic and physiological factors.

As for patients, practitioners and policy-makers, it is of great importance that the safety of the biopsy procedures be fully guaranteed. From this perspective, not only is it essential to ensure prenatal and neonatal follow-up, but formal child assessment is equally important. Research focusing on the ‘safety’ of this ART (as demonstrated by pregnancy rates, neonatal outcome, malformation rates, etc.) is growing along with the popularity of PGD/PGS. However, research into the specific developmental outcomes of PGD/PGS children is still non-existent. This is the first prospective case–control study focusing on a cohort of 2-year-old children born after PGD/PGS. The objective was to evaluate and compare the mental and psychomotor developmental outcomes of children born after PGD/PGS, ICSI and natural conception (NC). A control group of children born after ICSI was included to identify any differences in child outcomes due to the embryo biopsy or to the ICSI method. Given that this is the first follow-up study on PGD/PGS children’s development, the main research topics were kept rather explorative: (i) Does PGD/PGS have any impact on mental and psychomotor development? (ii) What is the role of demographic variables on mental and psychomotor developmental outcomes for the three conception groups? (iii) In line with previous studies on ICSI children, we expect that ICSI and NC children will be comparable with regard to mental and psychomotor development.

Materials and Methods

Study participants

PGD, PGS and ICSI children were recruited from the register of the Centre for Medical Genetics of the UZ Brussel. NC children were recruited from the university day-care centres and a paediatrician’s practice. Singleton children were recruited so that at the time of assessment between April 2005 and April 2007, they would be between 21 and 33 months old. Twins were excluded because of the possible confounders (e.g. prematurity and birthweight) that might have interfered with developmental outcome (Miceli et al., 2000). PGD or PGS children were eligible if they were singleton, Caucasian and living in Belgium and if their mother tongue was Dutch, French or English. ICSI and NC controls were selected to match PGD/PGS cases as closely as possible for gender, maternal educational level (high: higher education qualification or a degree; medium: fully passed school matriculation; low: partially passed school matriculation or no qualification at all), mother tongue and birth order (having an older sibling or otherwise) (Table I). Of the eligible PGD/PGS children (n = 74), 70 children or 94.5% participated in the study. In order to recruit 70 ICSI children and 70 NC controls matching the PGD/PGS children according to the above criteria, we had to contact 74 ICSI parents and 79 NC parents. The participation rate was 94.5% in the ICSI group and 88.6% in the NC group.

The applied biopsy technique (aspiration of blastomeres) on 8-cell embryos was the same in all the PGD and PGS conceptions. Embryos were decompacted prior to biopsy by short incubation (5–10 min) in Ca²⁺- and Mg²⁺-free medium (EB-10, Vitrolife). Laser technology was used to create an opening in the Zona Pellucida (Fertilase, MTM Medical Technologies, Montreux, Switzerland or Octax Laser Shot, Octax Microscience GmbH, Germany using Octax Eye Ware software). One or two nucleated blastomeres were then gently aspirated through the hole by means of an aspiration pipette (inner diameter 35–40 μm). After biopsy, the embryo was transferred to the sequential medium for blastocyst culture, leaving the blastomeres in the biopsy dish (A. De Vos, personal communication). One nucleated blastomere was removed in eight of the PGD/PGS cases and two blastomeres were removed in 57 of the PGD/PGS cases. For five cases, it was not possible to recover the number of blastomeres removed.
Table I. Infant characteristics.

<table>
<thead>
<tr>
<th></th>
<th>PGD/PGS n = 70</th>
<th>ICSI n = 70</th>
<th>NC n = 70</th>
<th>Test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>30/40</td>
<td>30/40</td>
<td>30/40</td>
<td>χ²(2) = 0.00</td>
<td>1</td>
</tr>
<tr>
<td>Eldest or only child/Youngest or middle child</td>
<td>49/21</td>
<td>49/21</td>
<td>46/24</td>
<td>χ²(2) = 0.40</td>
<td>0.820</td>
</tr>
<tr>
<td>Mother tongue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch/French/English</td>
<td>51/16/3</td>
<td>52/17/1</td>
<td>61/9/0</td>
<td>χ²(4) = 7.32</td>
<td>0.120</td>
</tr>
<tr>
<td>Age at assessment</td>
<td>2.22 ± 0.17</td>
<td>2.31 ± 0.16</td>
<td>2.29 ± 0.18</td>
<td>F = 5.71</td>
<td>0.004</td>
</tr>
<tr>
<td>Gestational age in weeks</td>
<td>38.59 ± 1.8</td>
<td>38.57 ± 2.24</td>
<td>39.13 ± 1.5</td>
<td>F = 1.99</td>
<td>0.139</td>
</tr>
<tr>
<td>Gestation&lt;37 weeks</td>
<td>8</td>
<td>9</td>
<td>3</td>
<td>χ²(2) = 3.45</td>
<td>0.180</td>
</tr>
</tbody>
</table>

Values are n unless otherwise stated.

Procedure

When the children were 2 years of age, they received an assessment of their mental and psychomotor development from a well-trained psychologist using the BSID-II-NL (Dutch version) (BSID-II-NL) (van der Meulen et al., 2002). This assessment was followed by a medical examination of the child by a paediatrician who also questioned the mothers about socio-demographic aspects, pregnancy, delivery and the neonatal outcomes of their child; these results will be reported elsewhere. The protocol was approved by the ethics committee of the UZ Brussel in accordance with national regulations. A midwife contacted all the PGD/PGS and ICSI parents by phone and invited them to participate in the study. The purpose of the study and the practical details were explained, and a date was set for the child’s assessment. Parents of naturally conceived children were invited by letter. The head of the day-care centres coordinated the participation by setting the test date and making the necessary logistical arrangements. All the mothers gave their informed consent. All the children were assessed by the same psychologist and by the same paediatrician. PGD, PGS and ICSI children were examined at the Centre for Medical Genetics and the NC controls at their day-care centre or in a paediatrician’s practice. The BSID-II-NL administration and the medical examinations were always completed in the presence of at least one parent, usually the mother or a primary caregiver. The BSID-II-NL assessment started with the MS and this was followed by the psychomotor scale. In some cases, the psychomotor scale was not administered if the children were too tired or restless. The psychologist was partially blinded with respect to the ART conception groups (PGD, PGS or ICSI). Because the NC control group was not administered if the children were too tired or restless. For nine PGD children, three ICSI children and four NC controls, the PDI could not be computed because again the children were too tired or restless.

Outcome measure

The BSID-II-NL is a standardized measure used to evaluate the mental and motor development of infants and young children between 1 and 42 months of age. It consists of two major scales (van der Meulen et al., 2002). The MS includes items that measure visual and auditory information processing, eye-hand co-ordination, imitation, language skills, memory and problem-solving. The motor scale assesses control of the gross and fine motor muscle groups (van der Meulen et al., 2002). A mental developmental index (MDI) and a psychomotor developmental index (PDI), with a mean value of 100 and a standard deviation of 15.0, are derived from the scores obtained on the mental and psychomotor scale. Scores of 115 or more indicate a significantly accelerated performance; scores between 114 and 85 reflect a normal performance. Scores between 84 and 70 reflect a mildly delayed performance and scores of 69 and less reflect a significantly delayed performance (van der Meulen et al., 2002). The BSID-II-NL was chosen because it was recently restandardized on a Dutch population (van der Meulen et al., 2002) and because it has been used extensively in ART child follow-up studies (Bowen et al., 1998; Bonduelle et al., 2003; Dittrichova et al., 2004; La Sala et al., 2004; Papaligoura et al., 2004; Agarwal et al., 2005).

Statistics

Univariate analyses of continuous variables were conducted using SPSS 15.0 for Windows to determine differences in mean scores between children conceived after PGD/PGS, ICSI and NC controls. If a group effect was identified post hoc, Tukey’s test was conducted to determine which conception groups differed significantly from each other. Categorical variables were analyzed using χ². Because this was the first study that investigated PGD/PGS children’s development, the analyses were not designed to test a preconceived model of factors influencing mental and psychomotor development, but instead to explore the role of demographic variables on these outcome measures for the conception groups. Hierarchical regression analyses were conducted in SPSS 15.0 to control for socio-demographic differences between the conception groups. In addition to the factor conception mode, the demographic factors that were not matched for were regressed as independent variables on the outcome measures mental and PDI. A significance level of 0.05 was accepted throughout.

Results

Demographics

Seventy children were assessed in each conception group. In the case of three children (one conceived after PGD, one after ICSI and one naturally), neither the MDI nor the PDI could be determined because the children were either too tired or restless. For nine PGD children, three ICSI children and four NC controls, the PDI could not be computed because again the children were too tired or restless. However, there was no statistically significant difference in the number of children per conception group for these characteristics (Tables I and II). Because more PGD (n = 13)/PGS (n = 27) girls (n = 40) than PGD (n = 15)/PGS (n = 15) boys (n = 30) were born between December 2002 and February 2005, more ICSI and NC girls compared with ICSI and NC boys were recruited to match the PGD/PGS children (χ²(3) = 2.19,
$$P = 0.53$$). Moreover, gestational age and the number of children born after less than 37 weeks of gestation were the same in the three conception groups (Table I). Although not clinically relevant, there was a difference in the average age of the children at the time of assessment between the conception groups with PGD/PGS children being slightly yet significantly younger than the ICSI and NC children (post hoc Tukey: PGD/PGS<ICSI $$P = 0.004$$ and PGD/PGS<NC $$P = 0.033$$) (Table I). Moreover, the NC mothers were significantly younger at the time of delivery than the mothers in the PGD/PGS and ICSI groups (post hoc Tukey: NC<PGD/PGS $$P = 0.000$$ and NC<ICSI $$P = 0.000$$). The NC fathers differed from the fathers in the other conception groups as they too were significantly younger at the time of the child assessment (post hoc Tukey: NC<PGD/PGS $$P = 0.000$$ and NC<ICSI $$P = 0.000$$). The fathers whose children were conceived after PGD/PGS or ICSI or naturally had the same educational level and were on average employed full time (±100%) (Table II). On average, the mothers who conceived after PGD/PGS worked more often part-time (working 63% of the time) than the ICSI mothers (working 77% of the time) and NC mothers (working 83% of the time) (post hoc Tukey: PGD/PGS<ICSI $$P = 0.059$$ and PGD/PGS<NC $$P = 0.002$$) (Table II). Most of the children in all three conception groups lived in a two-parent family consisting of both biological parents, although more NC children had parents who were divorced in comparison with the PGD/PGS children ($$\chi^2(1) = 7.99, P = 0.005$$) and ICSI children ($$\chi^2(1) = 4.16, P = 0.042$$) (Table II). The PGD/PGS children were more often at home with one parent than their ICSI ($$\chi^2(1) = 5.83, P = 0.016$$) and NC counterparts ($$\chi^2(1) = 8.32, P = 0.004$$), whereas the NC mothers used a day-care centre more often than the PGD/PGS mothers ($$\chi^2(1) = 9.26, P = 0.002$$) (Table II).

### Mental and psychomotor development

Univariate comparisons found no significant between-group differences regarding either the MDI or the PDI (Table III). Moreover, an equal number of PGD/PGS, ICSI and NC children were represented in each category of mental and psychomotor development (Table III). Scores for mental and psychomotor development were very similar for boys and girls when compared across conception groups (Table III). When boys and girls were compared within each conception group, a trend was observed in the ICSI group indicating that

<table>
<thead>
<tr>
<th>Table II. Socio-demographic characteristics.</th>
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<tr>
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<tr>
<td>Maternal age at child birth*</td>
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<td></td>
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<tr>
<td>Paternal age at child assessment*</td>
</tr>
<tr>
<td>Educational level</td>
</tr>
<tr>
<td>Mothers: high/Medium/Low</td>
</tr>
<tr>
<td>Fathers: high/Medium/Low</td>
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<tr>
<td>Family composition</td>
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<tr>
<td>Two-parent family</td>
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<td>Single parent family</td>
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<td>Divorced with parental sharing</td>
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<tr>
<td>Homosexual parents</td>
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<tr>
<td>Mean % of Maternal employment</td>
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<tr>
<td>Mean % of Paternal employment</td>
</tr>
<tr>
<td>Type of childcare</td>
</tr>
<tr>
<td>At home with one parent</td>
</tr>
<tr>
<td>With family</td>
</tr>
<tr>
<td>Day-care centre</td>
</tr>
<tr>
<td>Child Minder</td>
</tr>
<tr>
<td>School</td>
</tr>
</tbody>
</table>

Values are Mean ± SD. *Mean ± SD.

<table>
<thead>
<tr>
<th>Table III. MDI and PDI and number of children in each performance category.</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Bayley MDI</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Normal performance</td>
</tr>
<tr>
<td>Accelerated performance</td>
</tr>
<tr>
<td>Bayley PDI</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Normal performance</td>
</tr>
<tr>
<td>Accelerated performance</td>
</tr>
<tr>
<td>Mildly delayed performance</td>
</tr>
<tr>
<td>Normal performance</td>
</tr>
<tr>
<td>Accelerated performance</td>
</tr>
</tbody>
</table>

Values are Mean ± SD, n between brackets.
boys obtained lower scores on mental and psychomotor development than the ICSI girls (MDI $F = 3.36, P = 0.071$ and PDI $F = 3.64; P = 0.061$).

Two hierarchical regression analyses were conducted in order to remove all the variance in mental and psychomotor developmental outcomes that is associated with the socio-demographic variables for which no matching occurred. All the steps in the hierarchical regression analysis were performed for mental and psychomotor developmental outcomes separately. The socio-demographic variables included in the regressions were: age of the child at assessment, educational level of the fathers, age of the mothers at the birth of their child, age of the fathers at child assessment, employment percentage of mothers and fathers, gestational age, marital status, attendance at a day-care centre. We followed the analytic procedure for curvilinear regression analysis that was recommended by Pedhazur (1982).

<table>
<thead>
<tr>
<th>Blocks of variables in the regression of mental development</th>
<th>$R$</th>
<th>$R^2$</th>
<th>$\Delta R^2$</th>
<th>$F_{ch}$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1: quadratic trend</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 1: socio-demographic variables, Group, Group x Socio-demographic variables</td>
<td>0.715</td>
<td>0.512</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 2: socio-demographic variables, Group, Group x Socio-demographic variables, Socio-demographic variables</td>
<td>0.741</td>
<td>0.550</td>
<td>0.038</td>
<td>1.113</td>
<td>0.353</td>
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<tr>
<td><strong>Step 2: interaction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 1: socio-demographic variables, Group</td>
<td>0.671</td>
<td>0.450</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Block 2: socio-demographic variables, Group x Socio-demographic variables</td>
<td>0.715</td>
<td>0.512</td>
<td>0.061</td>
<td>1.196</td>
<td>0.269</td>
</tr>
<tr>
<td><strong>Step 3: overall effect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 1: socio-demographic variables</td>
<td>0.671</td>
<td>0.450</td>
<td>0.001</td>
<td>0.127</td>
<td>0.881</td>
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<tr>
<td>Block 2: socio-demographic variables x Group</td>
<td>0.671</td>
<td>0.450</td>
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<thead>
<tr>
<th>Blocks of variables in the regression of psychomotor development</th>
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<th>$\Delta R^2$</th>
<th>$F_{ch}$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1: quadratic trend</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Block 1: socio-demographic variables, Group, Group x Socio-demographic variables</td>
<td>0.823</td>
<td>0.677</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 2: socio-demographic variables, Group, Group x Socio-demographic variables, Socio-demographic variables</td>
<td>0.844</td>
<td>0.713</td>
<td>0.036</td>
<td>1.492</td>
<td>0.134</td>
</tr>
<tr>
<td><strong>Step 2: interaction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 1: socio-demographic variables, Group, Socio-demographic variables</td>
<td>0.799</td>
<td>0.639</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 2: socio-demographic variables, Group, Group x Socio-demographic variables</td>
<td>0.823</td>
<td>0.677</td>
<td>0.038</td>
<td>1.004</td>
<td>0.458</td>
</tr>
<tr>
<td><strong>Step 3: overall effect</strong></td>
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<td></td>
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<tr>
<td>Block 1: socio-demographic variables</td>
<td>0.797</td>
<td>0.635</td>
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<td></td>
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<tr>
<td>Block 2: socio-demographic variables, Group</td>
<td>0.799</td>
<td>0.639</td>
<td>0.004</td>
<td>0.949</td>
<td>0.389</td>
</tr>
</tbody>
</table>

Group: PGD/PGS, ICSI and NC conception groups; Socio-demographic variables: age at assessment, educational level of fathers, age of the mothers at the birth of their child, age of the fathers at child assessment, employment percentage of mothers and fathers, gestational age, marital status, attendance at a day-care centre. We followed the analytic procedure for curvilinear regression analysis that was recommended by Pedhazur (1982).

Discussion
The aim of this study was to explore the mental and psychomotor development of 2-year-old singleton PGD and PGS children compared with ICSI and NC controls. As this was the first
study of the development of PGD and PGS children, the research questions were kept rather explorative and the findings cannot be compared with the outcomes of similar studies. In reply to our main research question, we can conclude that conception after embryo biopsy in the case of PGD and PGS has no impact on the mental and psychomotor development of 2-year-old children when compared with ICSI and NC children. Moreover, equal numbers of children from the three conception groups were observed in each of the performance categories of mental and psychomotor development and none of the children participating in this study showed a significantly delayed performance. Even after controlling for sociodemographic variables, the mode of conception had no impact on mental or psychomotor development. In line with previous studies of ICSI children, our expectation regarding comparability between ICSI and NC children on mental and psychomotor development was confirmed.

The strengths of this study are manifold. Participation rates were very high, even in the NC control group, which means that participation bias was reduced to a minimum. One single administrator assessed all the children and very similar control groups were recruited. More specifically, possible socio-demographic confounders (maternal educational level, birth rank, gender and mother tongue) were eliminated by case–control matching, whereas others were controlled for in the statistical analyses.

Given that twins were excluded from this study because of the possible interference of prematurity and low birthweight with developmental outcome, which are known to be more common in twins and triplets, the generalizability of our findings is limited. Moreover, the children were assessed with the BSID-II-NL, which had undergone recent restandardization in 2002. Information on its psychometric qualities is therefore still scarce. Developmental tests like the BSID-II-NL assess the current developmental functioning of young children (up to 42 months of age) and are constructed with the premise that an ability may or may not have been acquired. Tests of developmental abilities do not assume that the measure of ability at one point in time will predict ability at a subsequent point in time (Bayley, 1993). With this measurement, predictability for later intellectual functioning remains inconclusive. Continuing assessment at later ages is therefore very important. In this study, PGD and PGS children were considered as one and the same conception group, as the embryo biopsy in the two treatment groups was performed by aspiration of blastomeres. Although in our study in the majority of the PGD/PGS treatments, two blastomeres were removed from the embryo, the number of blastomeres removed might also have an impact on the later development of the children. Moreover, the indication to perform PGD or PGS differs, with PGD being more indicative in the event of genetic problems and PGS in the event of advanced maternal age and/or fertility problems. The PGD and PGS populations therefore have different medical histories and family backgrounds which might indirectly influence the mental and psychomotor outcomes.

In conclusion, the results of this study suggest that PGD and PGS singleton children have normal mental and psychomotor abilities at age 2 when compared with ICSI and NC controls. Since this was a single-centre study, confirmatory investigations from other centres with larger cohorts at later ages are needed. Further research could benefit from considering PGD and PGS as different conception groups and take into account the number of blastomeres removed in the PGD/PGS treatment. Further research might also include PGD and PGS twins and preferably compare them with naturally conceived twins. In order to provide reassurance for other areas of child development, emotional, behavioural and parental aspects after PGD/PGS conception should also be evaluated.

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