Psychomotor development of children born after preimplantation genetic diagnosis and parental stress evaluation

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Background: **The increasing number of children conceived following preimplantation genetic diagnosis (PGD) necessitates the evaluation of their motor and cognitive development. The primary study objective was to evaluate the physical, developmental, and neurological outcome of children born after PGD in Greece. In addition, the secondary study objective was to compare the stress levels regarding parental roles between parents of PGD children and those of naturally conceived children.**

Methods: **A cross-sectional study design was applied. The study population consisted of 31 children (aged 2 months to 7.5 years) born after PGD analysis and their parents. The developmental evaluation of children included a detailed physical evaluation and cognitive assessment with the Bayley Scales of Infant Development. The parent stress index was applied to evaluate comparative parental stress levels between those parents of PGD children and those of naturally conceived healthy children.**

Results: **High rates of caesarean deliveries, increased incidence of prematurity, multiples and low-birth weight were observed among the 31 PGD children. Overall, 24 of the 31 PGD children had cognitive skills within normal range [general developmental quotient (GDQ): 86-115], while 6 children had lower levels of cognitive skills (GDQ<85). With regard to parental stress, PGD parents reported lower levels of parenting stress as compared to parents of naturally conceived children (P<0.01).**

Conclusions: **The enhanced frequency of poor cognitive and motor skills as well as low parental stress necessitates early detection and intervention for developmental delays among PGD children.**

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Key words: **general developmental quotient; parental stress level; preimplantation genetic diagnosis; psychomotor development**

Original article

Introduction

Preimplantation genetic diagnosis (PGD) constitutes one of the most recently developed means for the prenatal diagnosis of selected genetic conditions. PGD allows for the selection and transfer of embryos rendered from *in vitro* fertilization (IVF) and unaffected by the aforementioned genetic conditions.[1-4] The specific technique is undertaken with intracytoplasmic sperm injection (ICSI), followed by embryo biopsy, conducted most often during either the embryonic cleavage or blastocyst stages.[5]

Several studies have documented the health and developmental outcomes both during and beyond the perinatal period of children born following the use of assisted reproductive technology, including ICSI or PGD techniques.[6-17] Specifically, the use of IVF/ICSI procedures has been associated with adverse perinatal outcomes, including augmented rates of preterm delivery, low birth weight, perinatal mortality, neonatal complications, and disorders associated with genomic imprinting.[18-22] Even so, children conceived by assisted

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reproductive technology have not been observed to have elevated rates of unfavourable cognitive, motor, and behavioral outcomes as compared to their naturally conceived counterparts.[11,20,22,23]

In particular, approximately 2000 neonates have been born following the use of the PGD technique according to recent reports.[6,7] PGD children have not been observed to present with elevated rates of major malformations and/or deterred growth rates as compared with their ICSI counterparts.[14-16] In addition, compared with both ICSI and naturally conceived children, PGD children are reported to have similar cognitive and psychomotor developmental outcomes.[9] However, to date, the comparative evaluation of the developmental and psychosocial outcomes of PGD children has been conducted among cohorts arising from uniparous births and/or full-term delivery.[9,13-17] Moreover, while parents of both PGD and IVF children are reported to have lower parental stress levels as compared with parents of naturally conceived children,[13,24,25] the potential mediating effects upon children's cognitive and psychosocial outcome have not been elucidated.

The present study was undertaken to evaluate the physical, developmental, and neurological outcome of children born after PGD in Greece. In addition, the study also aimed to compare the stress levels regarding parental roles between parents of PGD children and those of naturally conceived children.

Methods

Study design and population

A cross-sectional study was conducted between May 1, 1997 and March 31, 2006 to assess the study objectives. The study protocol was approved by the Ethical Committee of the "Aghia Sophia" Children's Hospital Institutional Review Board (IRB5138). Informed written consent was obtained from all parents prior to the initiation of the study. The consent forms included the details of the study, in which measurements and clinical data would be used only for study purposes, and personal data of participants would not be published.

The source population consisted of children born following the PGD/ICSI techniques conducted at the Department of Medical Genetics, "Aghia Sophia" Children's Hospital of the National and Kapodistrian University of Athens School of Medicine in Greece. Our laboratory constitutes the single national center for PGD analysis in Greece. All parents referred to this center were verbally informed about the study objectives.

During the study period, 51 PGD children were born following 44 uniparous and multiparous pregnancies (218 PGD cycles). No exclusion criteria with respect to parity and length of gestation were applied. The initial response rate for study participation was 74.5% (38/51). Among the study population, complete assessment could not be undertaken for the following reasons: (a) 4 (10.5%) participants had reported invalid contact information, and (b) 3 (7.9%) had immigrated to third countries. The final study sample consisted of 31 children born to 24 couples treated with PGD/ICSI techniques, including 16 singletons, 13 children born from seven twin pregnancies, and 2 children born from a triplet pregnancy. Hence, the proportion of the eligible sample which agreed to participate in was 60.8%.

Clinical assessment

Participants' physical, developmental, and neurological results were evaluated at the Developmental Assessment Unit of the University Department of Pediatrics. Assessment included demographic characteristics, family medical history, children's medical history, successful achievement of developmental milestones, and presence of concomitant conditions. The clinical evaluation included measurements of length, weight, head circumference, as well as a thorough physical examination. When indicated, ultrasonographic examinations of the heart, kidneys, and abdomen were performed.

Developmental assessment

Developmental assessment was completed by an experienced developmental pediatrician and included the following components: (1) visual evaluation (fundoscopy and slit lamp); (2) audiological evaluation (autoacoustic emissions and auditory brainstem response); (3) assessment of cognitive and motor skills with the Bayley Scales of Infant Development for children aged less than 3 years, and either the Griffiths Scales for Mental Development or the Athina Test for children aged below 3 years.[26-28] Age correction for prematurity was undertaken for those children aged less than 2 years. Neurological assessment included the evaluation of tone, reflexes, symmetry, presence of muscular atrophy, and weakness in addition to the inspection of both seated posture and gait.

The results of both clinical and developmental assessments were returned to participants. In addition, detailed counseling regarding children's developmental status was provided. According to clinical findings, further developmental follow-up assessment and/or screening was recommended.

Parental stress assessment

Parental stress was evaluated using the Parent Stress

Index-Short Form (PSI-SF) standardized in the Greek language.[29] The PSI-SF comprises 36 items for the assessment of stress in the parent-child system associated with parenting. The PSI-SF consists of the following five subscales: a) Defensive Responding Score, for assessing the potential reporting bias regarding problems and/or stress related to the parent-child relationship; b) Parental Distress Score, for assessing distress associated with one's parental role; c) Parent-Child Dysfunctional Interaction Score, for assessing the adequacy of the parental bond; d) Difficult Child Score, for evaluating children's behavioral characteristics; and e) Total Stress Score, for evaluating overall parental stress levels. Scores greater than the 85th and lower than the 15th percentiles are indicative of high and low parental stress levels, respectively.

Overall, 32 parents (18 mothers and 14 fathers) of PGD children completed the PSI-SF test. A control group of 35 parents (19 mothers and 16 fathers) of naturally conceived healthy children were recruited from public kindergarten and elementary schools. Children were matched for age, gender, and socioeconomic status.

Statistical analyses

Students' *t* test for independent samples was conducted in order to compare PSI-SF scores between the aforementioned parent groups.

Results

The study population consisted of 31 PGD children born to 24 couples who proceeded with the PGD most frequently due to the elevated risk of severe monogenic disease (Table 1). Mean maternal age was 37 years (range: 32-47 years), while mean paternal age was 40 years (range: 33-48 years). Specifically, the most frequently reported reasons for using PGD technique were genetic risks for either β-thalassemia or sickle cell thalassemia and infertility.

Following embryo transfer, a total of 24 PGD pregnancies were confirmed with fetal sacs and heartbeat, including 16 (66.7%) singleton, 7 (29.2%) twin, and one (4.2%) triplet pregnancies. During gestation, 7 (29.2%) singleton and 3 (12.5%) twin pregnancies presented with complications, including hypertension, pre-eclampsia, diabetes, polyhydramnios, and premature membrane rupture. In addition to vitamin supplementation (including iron, folic acid, and vitamins) and hormonal support, six mothers received treatment for concurrent disorders, including diabetes, hypothyroidism, and hypertension.

Prenatal chromosomal diagnosis due to advanced maternal age was performed in 11 (45.8%) pregnancies with normal results, while prenatal diagnosis of monogenic diseases was performed in all cases. None of the embryos was diagnosed with monogenic diseases.

Table 1. Indications and characteristics of preimplantation genetic diagnosis (PGD) pregnancies

Variables	PGD pregnancy, *n* (%)
Indication (genetic risk) for PGD	
TH/SC and infertility	11 (45.8)
TH/SC and previous termination of pregnancy	7 (29.2)
TH/SC and objection to termination of pregnancy	4 (16.7)
TH/SC, previous termination of pregnancy and infertility	1 (4.2)
CF and infertility	1 (4.2)
Number of transferred embryos (mean)	
1	3 (12.5)
2	5 (20.8)
3	12 (50.0)
>3	4 (16.7)
Clinical pregnancy (positive heart beat)	
Singleton	16 (66.7)
Twins	7 (29.2)
Triplets	1 (4.2)

TH: β-thalassemia; SC: sickle cell thalassemia; CF: cystic fibrosis.

Table 2. Pre- and perinatal characteristics of preimplantation genetic diagnosis neonates (including 2 neonates who died perinatally)

Variables	Singletons *n*=16, *n* (%)	Twins *n*=14, *n* (%)	Triplets *n*=3, *n* (%)
Male gender	9 (56.2)	7 (50.0)	0 (0.0)
Pregnancy duration			
<32 wk	0 (0.0)	2 (14.3)	3 (100.0)
33-37 wk	4 (25.0)	8 (57.1)	0 (0.0)
>37 wk	12 (75.0)	4 (28.6)	0 (0.0)
Caesarean section	13 (81.3)	14 (100.0)	3 (100.0)
Prenatal chromosomal diagnosis	7 (43.8)	6 (42.8)	3 (100.0)
Prenatal diagnosis of heterozygosity for the disease	16 (100.0)	14 (100.0)	3 (100.0)
Birth weight, g (mean±SD)	2948 ± 280	2377 ± 180	1060 ± 110
Small for gestational age	4 (25.0)	6 (42.8)	3 (100.0)
Birth length, cm (mean±SD)	50.0 ± 2.3	46.0 ± 2.1	37.3 ± 1.5
Head circumference, cm (mean±SD)	34.2 ± 0.5	32.8 ± 0.4	25.3 ± 0.2
Apgar score			
>9	13 (81.2)	12 (85.7)	0 (0.0)
5-8	3 (18.8)	1 (7.1)	3 (100.0)
<5	0 (0.0)	1 (7.1)	0 (0.0)
Neonatal complications*	7 (43.8)	11 (78.6)	3 (100.0)
Respiratory distress syndrome	1 (6.2)	2 (14.3)	2 (66.7)
Apnea	1 (6.2)	2 (14.3)	0 (0.0)
Asphyxia	1 (6.2)	1 (7.1)	0 (0.0)
Intraventricular hemorrhage	1 (6.2)	1 (7.1)	0 (0.0)
Sepsis	0 (0.0)	1 (7.1)	2 (66.7)
Jaundice	6 (37.5)	5 (35.7)	3 (100.0)
Feeding difficulties	1 (6.2)	3 (21.4)	3 (100.0)
Delayed passage of meconium	1 (6.2)	0 (0.0)	0 (0.0)
Necrotizing enterocolitis	0 (0.0)	1 (7.1)	0 (0.0)
Torsion of inguinal hernia	0 (0.0)	1 (7.1)	0 (0.0)
Retinopathy of prematurity	0 (0.0)	0 (0.0)	2 (66.7)
Death	0 (0.0)	1 (7.1)	1 (33.3)

*: more than one complication reported.

Peri- and neonatal complications following PGD

Premature delivery (28 to 37 weeks) occurred in 10 (41.7%) pregnancies, including 4 (25.0%) of singleton pregnancies, 5 (71.4%) twin pregnancies, and 1 (100.0%) triplet pregnancies (Table 2). Of the 33 PGD born neonates (including 2 neonates who died perinatally), 17 (51.5%) were girls. The majority of PGD born children were small for gestational age (<10th percentile for gestational age), including one quarter of singleton, two fifths of twin, and all of triplet born neonates.

Eight (24.2%) PGD neonates had Apgar scores ≤8 and required admission to the intensive care unit. The occurrence of neonatal complications according to type of pregnancy among PGD neonates is presented in Table 2. Severe neonatal complications were more frequent among premature births and multiple pregnancies. Two (6.1%) perinatal deaths occurred among PGD neonates following sepsis, including one twin and one triplet births.

Clinical assessment of PGD infants and children

Among the 31 surviving PGD infants, the male/female ratio was 0.94 (Table 3). Growth parameters, including weight/height (normal weight/height: *n*=26; 83.9%), and head circumference (normal head circumference: *n*=25; 80.6%) were within normal range for the majority of PGD children, and only those who were either born prematurely (corrected age) or small for gestational age were observed to be below the 10th percentile for weight. With respect to congenital defects, 6.2% (*n*=1) of singleton neonates had congenital cardiopathy, 7.7% (*n*=1) of twins had pulmonary stenosis, inguinal hernia, and unilateral hydronephrosis. The presence of other concomitant disorders is presented in Table 3. The neurological assessments conducted among PGD children indicated that 19.4% (*n*=6) had abnormal neurological findings, including central (*n*=2; 6.4%) and peripheral (*n*=4; 12.9%) hypotonia.

Table 3. Physical examination and medical history of preimplantation genetic diagnosis in children

Variables	Singletons *n*=16, *n* (%)	Twins *n*=13, *n* (%)	Triplets *n*=2, *n* (%)
Male gender	9 (56.2)	6 (46.2)	0 (0.0)
Age at examination			
<6 mon	2 (12.5)	0 (0.0)	0 (0.0)
6-12 mon	5 (31.2)	6 (46.2)	0 (0.0)
1-3 y	5 (31.2)	7 (53.8)	2 (100.0)
4-7.5 y	4 (25.0)	0 (0.0)	0 (0.0)
Growth parameters (weight/height, %)			
Normal	13 (81.2)	12 (92.3)	1 (50.0)
>90th percentile	2 (12.5)	0 (0.0)	0 (0.0)
<10th percentile	1 (6.2)	1 (7.7)	1 (50.0)
Head circumference			
Normal	13 (81.2)	11 (84.6)	1 (50.0)
>90th percentile	0 (0.0)	1 (7.7)	0 (0.0)
<10th percentile	3 (18.8)	1 (7.7)	1 (50.0)
Concomitant disorders			
Hypothyroidism (congenital)	0 (0.0)	2 (15.4)	0 (0.0)
Gastroesophageal reflux	0 (0.0)	2 (15.4)	0 (0.0)
Milk allergy	1 (6.2)	0 (0.0)	0 (0.0)
Hypercholesterolemia	1 (6.2)	0 (0.0)	0 (0.0)
β-thalassemia/sickle cell thalassemia trait	9 (56.2)	7 (53.8)	1 (50.0)
Cystic fibrosis trait	0 (0.0)	1 (7.7)	0 (0.0)
Neurological examination			
Normal	13 (81.2)	11 (84.6)	1 (50.0)
Abnormal	3 (18.8)	2 (15.4)	1 (50.0)
Central hypotonia	2 (12.5)	0 (0.0)	0 (0.0)
Peripheral hypertonia	1 (6.2)	2 (15.4)	1 (50.0)

Cognitive development in PGD infants and children

Overall, more than three quarters of PGD children (*n*=24; 77.4%) had normal general developmental quotient (GDQ) scores (Table 4). However, 12.9% (*n*=4) and 6.4% (*n*=2) of PGD children had GDQ scores indicative of mild and severe developmental delay, respectively. Of the 6 PGD children with GDQ scores indicative of mild or severe developmental delay, 3 (50.0%) children had been delivered prematurely with severe perinatal complications (respiratory distress syndrome, RDS), necrotizing enterocolitis, torsion of inguinal hernia, intraventricular hemorrhage (IVH) and 2 (33.7%) were born small for gestational age with congenital hypothyroidism which had been managed with thyroxin administration since birth.

While a similar finding to that of the GDQ was observed with respect to the mental developmental quotient scores, 7 (22.6%) PGD children had motor

Table 4. Developmental assessment of preimplantation genetic diagnosis in children

Variables	Overall (*n*=31) *n* (%)	Singletons (*n*=16) *n* (%)	Twins (*n*=13) *n* (%)	Triplets (*n*=2) *n* (%)	Boys (*n*=15) *n* (%)	Girls (*n*=16) *n* (%)
General DQ score						
>115	1 (3.2)	1 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.2)
86-115	24 (77.4)	13 (81.2)	9 (69.2)	2 (100.0)	12 (80.0)	12 (75.0)
65-85	4 (12.9)	2 (12.5)	2 (15.4)	0 (0.0)	2 (13.3)	2 (12.5)
<65	2 (6.4)	0 (0.0)	2 (15.4)	0 (0.0)	1 (6.7)	1 (6.2)
Mental DQ score						
>115	1 (3.2)	1 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.2)
86-115	25 (80.6)	14 (87.5)	9 (69.2)	2 (100.0)	12 (80.0)	13 (81.2)
65-85	2 (6.4)	0 (0.0)	2 (15.4)	0 (0.0)	1 (6.7)	1 (6.2)
<65	3 (9.7)	1 (6.2)	2 (15.4)	0 (0.0)	2 (13.3)	1 (6.2)
Motor DQ score						
>115	1 (3.2)	1 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.2)
86-115	21 (6.8)	12 (75.0)	8 (61.5)	2 (100.0)	10 (66.7)	11 (68.8)
65-85	7 (22.6)	2 (12.5)	4 (30.8)	0 (0.0)	4 (26.7)	3 (18.8)
<65	2 (6.4)	1 (6.2)	1 (7.7)	0 (0.0)	1 (6.7)	1 (6.2)

Table 5. PSI Stress Questionnaire: comparison of parental stress between PGD parents and parents of naturally conceived children*

PSI subscales	Parental stress of PGD children (*n*=32)			Parental stress of controls (*n*=35)			*P* value
	Low, *n* (%)	Normal, *n* (%)	High, *n* (%)	Low, *n* (%)	Normal, *n* (%)	High, *n* (%)	
Total stress	10 (31.2)	20 (62.5)	2 (62.5)	6 (17.1)	21 (60.0)	8 (22.8)	0.01
Defensive responding	5 (15.6)	19 (59.4)	8 (25.0)	5 (14.3)	10 (28.6)	20 (57.1)	0.02
Parental distress	6 (18.8)	23 (71.9)	3 (9.4)	6 (17.1)	20 (57.1)	9 (25.7)	0.05
Parent-child dysfunctional interaction	7 (21.9)	24 (75.0)	1 (3.1)	3 (8.6)	29 (82.8)	3 (8.6)	0.15
Difficult child	6 (18.8)	22 (68.8)	4 (12.5)	7 (20.0)	24 (68.6)	4 (11.4)	0.19

*: Parental stress: low stress: <15th percentile; normal stress: 15th-85th percentile; high stress: >85th percentile. PSI: Parental Stress Index; PGD: preimplantation genetic diagnosis.

developmental quotient scores indicative of mild motor retardation (Table 4). However, it is noted that a significant discrepancy (>15 points) between motor and mental quotient scores was recorded for 12.9% (*n*=4) of children.

Parenting stress levels

The comparison of parental stress between PGD parents and parents of naturally conceived children is shown in Table 5. The occurrence of low parental stress among parents of PGD children was almost two-fold greater than that of the controls. The frequency of total stress significantly differed between parents of PGD children as compared to the controls. In addition, the occurrence of defensive responding significantly differed between the groups evaluated. Furthermore, PGD parents more often reported lower stress levels regarding their parental role as compared to the controls. No significant differences were observed regarding the parent-child dysfunctional interactions scores (*P*=0.15) and difficult child scores (*P*=0.19). The majority (>90%) of parents of PGD children with mental developmental delay had normal stress levels. In contrast, this percentage was limited to 70% among parents of PGD children with motor developmental delay.

Discussion

The present study investigated the physical, developmental, and neurological characteristics of children born after PGD. Also, parental stress levels regarding parental roles were compared between parents of PGD and naturally conceived children. The findings of the study indicated that PGD children had elevated rates of caesarean deliveries, prematurity, and low birthweight. Furthermore, the majority of PGD children had cognitive skills within normal range, while approximately one fifth had moderate or low cognitive skills. Finally, PGD parents reported lower levels of parenting stress. Thus, PGD children present with an enhanced occurrence of poor cognitive and motor skills in addition to low associated parental stress.

To date, conflicting evidence exists regarding the association between assisted reproductive technologies (ART), including IVF/ICSF and PGD, and occurrence of adverse pregnancy outcomes. Specifically, ART procedures are associated with elevated rates of prematurity, low birth weight, perinatal complications, and birth defects,[30-34] and may be attributed to parental characteristics, multiparous gestations, and specific ART techniques used.[35,36] Additionally, PGD requires embryo biopsy and further evidence is needed to elucidate whether such techniques adversely affect the outcome of children born after PGD.[14,37]

ART has been associated with multiple births and consequent high rates of prematurity, low birth weight, and infant mortality.[30,34,38] However, as most recent ART techniques utilize a limited number of embryos to be transferred per cycle, multiple births following ART have decreased.[39] Among the study population, the high mean number of embryos transferred may explicate the resulting proportion of multiparous PGD gestations. As reported previously, dire complications were observed among neither singleton nor multiple pregnancies evaluated.[6,7,37,40] Moreover, premature birth occurred in 5/7 multiple and 4/16 singleton pregnancies, respectively. Despite the limited sample size, our findings are comparable with previous reports regarding IVF/ICSI born children.[33,41-43]

Severe perinatal complications occurred most frequently among neonates born either prematurely or following multiple pregnancies.[33,37,44] In contrast, the incidence of congenital defects, including cardiac, gastrointestinal and urogenital malformations, approximated 6.4% in our cohort, and is markedly higher than that reported in either ICSI or naturally conceived neonates.[6,8,11,30,33,34,44]

The majority of PGD children had growth parameters within normal range. Hence, the findings in our study corroborate with other studies indicating that PGD is not associated with deterred growth development.[15,16] It is upheld that a "catch-up" effect may occur even among children at risk, including those with small gestational age.

The cognitive assessment conducted indicated that

19.4% of PGD children had GDQ scores indicative of mild or moderate cognitive delay. In contrast, previous reports indicated that the developmental outcomes of PGD children were not different from those of naturally conceived children.[9,17] However, our findings are also comparable to those conducted among IVF/ICSI children, indicating that multiplicity, prematurity, and low birth weight may confound GDQ scores.[17,45] As previously reported, the study findings reveal that singletons' cognitive skills are often within normal range,[9] while premature children or those born of multiple births have lower cognitive skills. Furthermore, twins have lower motor ability scores than singletons. To our knowledge, similar findings have not been reported to date.

With regard to parental stress, the study findings indicated that parents of PGD children, as compared to naturally conceived children, had lower parental stress levels. These findings corroborate with previous reports, indicating that prolonged fertility treatments are associated with lower overall parental stress.[24,25,46,47] The findings of the present study are in contrast to previous reports,[13] but may be attributed to the fact that previous studies were conducted solely among uniparous parents.

Furthermore, according to the PSI-SF test, parents of PGD children significantly differed from those of naturally conceived children with respect to both the parent distress and total stress subscales. Moreover, the parents of PGD children responded more defensively on the PSI-SF test, as indicated by the defensive responding scale. Previous reports have indicated that increased cycles of IVF treatment are associated with more defensive responses.[25] The parents of PGD children report more frequent warmth and/or affection, while concomitantly indicating less often aggression and/or hostility and rejection, as compared with the parents of naturally conceived children.[17] It is purported that reporting bias may justify these findings, since the parents who have struggled to conceive a child may be inclined to idealize parenthood, thus diminishing the perceived adverse effects of parenting problems.

The present study and similar reports[13] indicate that the parental stress levels of PGD parents are not significantly elevated. However, it is upheld that information about the potential manifestations of developmental disorders in children born after PGD, even if not attributed to congenital anomalies, may constitute a risk factor for increased parental stress. It is recommended that counseling should be provided by trained specialists to eligible couples prior to the implementation of PGD procedures.[48] During such sessions couples should be informed of the procedures and potential limitations of PGD. Specifically, counseling issues should include the potential risk of premature labor, intrauterine growth retardation, and perinatal mortality, as well as possible occurrence of congenital anomalies and adverse developmental outcome. Couples should also be informed of the importance of early and repeated developmental assessments of PGD children.[48] It is by these means that parental stress levels of PGD candidates may be mitigated.

The strengths of the study include that it entailed an objective medical evaluation of the physical, developmental, and neurological characteristics of children born after PGD. In addition, the cohort included both uniparous and multiparous pregnancies. However, the limitations of this study included the restricted number of PGD children evaluated. A response bias may have been introduced due to the moderate response rate recorded among PGD parents. Hence, the generalizability of the study findings to larger cohorts may be limited. Moreover, the developmental and cognitive outcomes of PGD children were not compared with those of either IVF or ICSI children. Finally, because of the study design applied, the etiological association could not be assessed between the development of PGD children and the progression of parental stress.

In conclusion, increased rates of prematurity, caesarian section and low birth weight were noted in PGD pregnancies. Regarding psychomotor development, it was normal in the majority of the evaluated PGD children while approximately one fifth of them presented with moderate or low cognitive skills. Parents of PGD children expressed lower stress compared to the control group of the parents of naturally conceived children. Hence, the study findings indicate that PGD children present with an enhanced occurrence of poor cognitive and motor skills, as well as low associated parental stress. The study findings suggest that due to the elevated risk of lower cognitive skills among PGD children, parental stress levels may be neither sufficient nor indicative of the necessity for pediatricians to evaluate the status of children's mental development. Therefore, early screening and detection of cognitive developmental delays among this high-risk population is necessary. Additional prospective cohort studies are needed to evaluate the implications of PGD techniques upon child development throughout adulthood.

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References

1 Handyside AH, Kontogianni EH, Hardy K, Winston RM. Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification. Nature 1990;344:768-770.
2 Kanavakis E, Traeger-Synodinos J. Preimplantation genetic diagnosis in clinical practice. J Med Genet 2002;39:6-11.
3 Kuliev A, Verlinsky Y. Place of preimplantation diagnosis in genetic practice. Am J Med Genet A 2005;134A:105-110.
4 Sermon K, Van Steirteghem A, Liebaers I. Preimplantation genetic diagnosis. Lancet 2004;363:1633-1641.
5 Kokkali G, Vrettou C, Traeger-Synodinos J, Jones GM, Cram DS, Stavrou D, et al. Birth of a healthy infant following trophectoderm biopsy from blastocysts for PGD of beta-thalassaemia major. Hum Reprod 2005;20:1855-1859.
6 Harper JC, Boelaert K, Geraedts J, Harton G, Kearns WG, Moutou C, et al. ESHRE PGD Consortium data collection V: cycles from January to December 2002 with pregnancy follow-up to October 2003. Hum Reprod 2006;21:3-21.
7 Sermon K, Moutou C, Harper J, Geraedts J, Scriven P, Wilton L, et al. ESHRE PGD Consortium data collection IV: May-December 2001. Hum Reprod 2005;20:19-34.
8 Sermon KD, Michiels A, Harton G, Moutou C, Repping S, Scriven PN, et al. ESHRE PGD Consortium data collection VI: cycles from January to December 2003 with pregnancy follow-up to October 2004. Hum Reprod 2007;22:323-336.
9 Nekkebroeck J, Bonduelle M, Desmyttere S, Van den Broeck W, Ponjaert-Kristoffersen I. Mental and psychomotor development of 2-year-old children born after preimplantation genetic diagnosis/screening. Hum Reprod 2008;23:1560-1566.
10 Strom CM, Levin R, Strom S, Masciangelo C, Kuliev A, Verlinsky Y. Neonatal outcome of preimplantation genetic diagnosis by polar body removal: the first 109 infants. Pediatrics 2000;106:650-653.
11 Bonduelle M, Ponjaert I, Steirteghem AV, Derde MP, Devroey P, Liebaers I. Developmental outcome at 2 years of age for children born after ICSI compared with children born after IVF. Hum Reprod 2003;18:342-350.
12 Ponjaert-Kristoffersen I, Bonduelle M, Barnes J, Nekkebroeck J, Loft A, Wennerholm UB, et al. International collaborative study of intracytoplasmic sperm injection-conceived, *in vitro* fertilization-conceived, and naturally conceived 5-year-old child outcomes: cognitive and motor assessments. Pediatrics 2005;115:e283-e289.
13 Nekkebroeck J, Bonduelle M, Desmyttere S, Van den Broeck W, Ponjaert-Kristoffersen I. Socio-emotional and language development of 2-year-old children born after PGD/PGS, and parental well-being. Hum Reprod 2008;23:1849-1857.
14 Liebaers I, Desmyttere S, Verpoest W, De Rycke M, Staessen C, Sermon K, et al. Report on a consecutive series of 581 children born after blastomere biopsy for preimplantation genetic diagnosis. Hum Reprod 2010;25:275-282.
15 Desmyttere S, De Schepper J, Nekkebroeck J, De Vos A, De Rycke M, Staessen C, et al. Two-year auxological and medical outcome of singletons born after embryo biopsy applied in preimplantation genetic diagnosis or preimplantation genetic screening. Hum Reprod 2009;24:470-476.
16 Desmyttere S, Bonduelle M, Nekkebroeck J, Roelants M, Liebaers I, De Schepper J. Growth and health outcome of 102 2-year-old children conceived after preimplantation genetic diagnosis or screening. Early Hum Dev 2009;85:755-759.
17 Banerjee I, Shevlin M, Taranissi M, Thornhill A, Abdalla H, Ozturk O, et al. Health of children conceived after preimplantation genetic diagnosis: a preliminary outcome study. Reprod Biomed Online 2008;16:376-381.
18 Bonduelle M, Wennerholm UB, Loft A, Tarlatzis BC, Peters C, Henriet S, et al. A multi-centre cohort study of the physical health of 5-year-old children conceived after intracytoplasmic sperm injection, *in vitro* fertilization and natural conception. Hum Reprod 2005;20:413-419.
19 Cox GF, Bürger J, Lip V, Mau UA, Sperling K, Wu BL, et al. Intracytoplasmic sperm injection may increase the risk of imprinting defects. Am J Hum Genet 2002;71:162-164.
20 Devroey P, Van Steirteghem A. A review of ten years experience of ICSI. Hum Reprod Update 2004;10:19-28.
21 Halliday J, Oke K, Breheny S, Algar E, J Amor D. Beckwith-Wiedemann syndrome and IVF: a case-control study. Am J Hum Genet 2004;75:526-528.
22 Squires J, Kaplan P. Developmental outcomes of children born after assisted reproductive technologies. Infants Young Child 2007;20:2-10.
23 Ponjaert-Kristoffersen I, Tjus T, Nekkebroeck J, Squires J, Verté D, Heimann M, et al. Psychological follow-up study of 5-year-old ICSI children. Hum Reprod 2004;19:2791-2797.
24 Golombok S, Cook R, Bish A, Murray C. Families created by the new reproductive technologies: quality of parenting and social and emotional development of the children. Child Dev 1995;66:285-298.
25 McMahon CA, Gibson F, Leslie G, Cohen J, Tennant C. Parents of 5-year-old *in vitro* fertilization children: psychological adjustment, parenting stress, and the influence of subsequent *in vitro* fertilization treatment. J Fam Psychol 2003;17:361-369.
26 Bayley N. Bayley Scales of Infant Development Manual. San Antonio: Psychological Corporation, Harbour & Brace Corporation, 1993.
27 Griffiths R. A comprehensive system of measurement for the first eight years of life. In: The abilities of young children, child development. Oxford: The Test Agency, 1984: 101-172.
28 Paraskevopoulos I, Kalatzi-Azizi A, Giannitsas N. Athina Test for the diagnosis of learning difficulties. Athens: Ellinika Grammata, 1999.
29 Abidin R. Parenting Stress Index Test manual. Charlottesville: Paediatric Psychology Press, 1990.
30 Hansen M, Kurinczuk JJ, Bower C, Webb S. The risk of major birth defects after intracytoplasmic sperm injection and *in vitro* fertilization. N Engl J Med 2002;346:725-730.
31 Ludwig M, Diedrich K. Follow-up of children born after assisted reproductive technologies. Reprod Biomed Online 2002;5:317-322.
32 Mayor S. Babies born after preimplantation genetic diagnosis need follow-up. BMJ 2006;332:254.
33 Pinborg A, Loft A, Rasmussen S, Schmidt L, Langhoff-Roos J, Greisen G, et al. Neonatal outcome in a Danish national cohort of 3438 IVF/ICSI and 10,362 non-IVF/ICSI twins born between 1995 and 2000. Hum Reprod 2004;19:435-441.
34 Schieve LA, Meikle SF, Ferre C, Peterson HB, Jeng G, Wilcox LS. Low and very low birth weight in infants conceived with use of assisted reproductive technology. N Engl J Med 2002;346:731-737.

35 Lambert RD. Safety issues in assisted reproductive technology: aetiology of health problems in singleton ART babies. Hum Reprod 2003;18:1987-1991.
36 Soini S, Ibarreta D, Anastasiadou V, Aymé S, Braga S, Cornel M, et al. The interface between assisted reproductive technologies and genetics: technical, social, ethical and legal issues. Eur J Hum Genet 2006;14:588-645.
37 Sermon KD. Preimplantation genetic diagnosis. Verh K Acad Geneeskd Belg 2006;68:5-32.
38 Van Steirteghem A, Bonduelle M, Devroey P, Liebaers I. Follow-up of children born after ICSI. Hum Reprod Update 2002;8:111-116.
39 Thornhill AR, deDie-Smulders CE, Geraedts JP, Harper JC, Harton GL, Lavery SA, et al. ESHRE PGD Consortium 'Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)'. Hum Reprod 2005;20:35-48.
40 ESHRE PGD Consortium Steering Committee. ESHRE Preimplantation Genetic Diagnosis Consortium: data collection III (May 2001). Hum Reprod 2002;17:233-246.
41 Hampton T. Panel reviews health effects data for assisted reproductive technologies. JAMA 2004;292:2961-2962.
42 Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following *in vitro* fertilization: a meta-analysis. Obstet Gynecol 2004;103:551-563.
43 National Center for Health Statistics, 2001. www.cdc.gov/nchs/data/nvsr/nvsr51/nvsr51_02 (accessed July 18, 2003).
44 Bonduelle M, Liebaers I, Deketelaere V, Derde MP, Camus M, Devroey P, et al. Neonatal data on a cohort of 2889 infants born after ICSI (1991-1999) and of 2995 infants born after IVF (1983-1999). Hum Reprod 2002;17:671-694.
45 Papaligoura Z, Panopoulou-Maratou O, Solman M, Arvaniti K, Sarafidou J. Cognitive development of 12 month old Greek infants conceived after ICSI and the effects of the method on their parents. Hum Reprod 2004;19:1488-1493.
46 Allen KD, Maguire KD, Williams GE, Sanger WG. The effects of infertility on parent--child relationships and adjustment. Child Health Care 1996;25:93-105.
47 Golombok S, Brewaeys A, Cook R, Giavazzi MT, Guerra D, Mantovani A, et al. The European study of assisted reproduction families: family functioning and child development. Hum Reprod 1996;11:2324-2331.
48 Thornhill AR, deDie-Smulders CE, Geraedts JP, Harper JC, Harton GL, Lavery SA, et al. ESHRE PGD Consortium 'Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)'. Hum Reprod 2005;20:35-48.

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