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Paternal sperm concentration and growth and cognitive development in children born with a gestational age more than 32 weeks after assisted reproductive therapy

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BACKGROUND: A possible impact of paternal sperm quality on the outcome in children born after assisted reproductive technologies, especially ICSI, has been discussed. The objective of this study was to assess whether sperm concentration has any influence on growth and cognitive development in children born with a gestational age more than 32 weeks after ICSI or IVF. METHODS: Singleton children born after ICSI (*n* = 492) or IVF (*n* = 265) from five European countries were examined at age 5 years. The ICSI group was divided into five subgroups according to paternal sperm origin and sperm concentration: (1) epididymal and testicular sperm group, (2) ejaculated sperm $<1 \times 10^6$/ml, (3) ejaculated sperm 1–4.99×10^6/ml, (4) ejaculated sperm 5–19.99×10^6/ml and (5) ejaculated sperm $\geq 20 \times 10^6$/ml. The IVF group was divided into two subgroups: (1) $<20 \times 10^6$/ml and (2) $\geq 20 \times 10^6$/ml. Growth parameters at birth and age 5 were evaluated. Cognitive development was assessed with the Wechsler Preschool and Primary Scale of Intelligence—Revised. RESULTS: No significant difference was found for gestational age, birth weight and birth weight standard deviation scores (SDS) between the ICSI and IVF sperm groups. No significant difference in height and weight at age 5 or SDS weight or height or BMIs at age 5 was found. There was no significant difference in total intelligence quotient (IQ)—performance or verbal IQ—between the groups. CONCLUSION: We found no indication that growth and cognitive development in ICSI and IVF children differed depending on paternal sperm concentration.

Key words: ART children/cognition/growth/sperm concentration

Introduction

Recently published meta-analyses (Rimm *et al*., 2004; Hansen *et al*., 2005) found a statistically significant 30–40% increased incidence of birth defects in children conceived after assisted reproductive technologies (ARTs) compared with naturally conceived children. Kallen *et al*. (2005) found similar results and showed that the increased risk could mainly be explained in terms of parental characteristics (maternal age, parity, years of known childlessness and maternal smoking) and a high rate of multiple births. The results were independent of the IVF technique used (IVF or ICSI), except for an excess of hypospadias after ICSI. A moderate excess of chromosomal abnormalities has been detected following ICSI (Aboulghar *et al*., 2001; Bonduelle *et al*., 2002; Ludwig and Katalinic, 2002). In a recent study, a significantly higher aneuploidy rate was found in sperm from patients with extremely severe male factor infertility (Gianaroli *et al*., 2005). The impact of sperm quality on the outcome after ART, especially ICSI, has been discussed. Bonduelle *et al*. (2002) evaluated the incidence of malformations according to sperm concentration and quality (above or below 20×10^6/ml) and found no differences for children conceived after ICSI. Men with very low sperm concentration ($<5 \times 10^6$/ml) have a higher incidence of genetic defects (gender chromosome aberrations, certain translocations and deletions and Y chromosome microdeletions) than men with normal sperm concentration (Aittomaki *et al*., 2004), but it is unknown whether the sperm concentration has an influence on the growth and cognitive development of children conceived after ICSI or IVF. Questions regarding the safety of ART per se, especially ICSI, have been raised (Lewis and Klonoff-Cohen, 2005). Recent case reports have suggested that the risk of imprinting defects with early developmental failure, such as

Angelman's syndrome and Beckwith–Wiedemann syndromes (BWS), is increased in children born after ART (Cox *et al*., 2002; DeBaun *et al*., 2003; Gicquel *et al*., 2003; Maher *et al*., 2003; Orstavik *et al*., 2003). However, in a recent Danish registry study comprising 6052 infants, no cases of imprinting disorders were found (Lidegaard *et al*., 2005). Neither specific ART method nor specific *in vitro* media were found to be associated with BWS in a retrospective case series of 19 children from the BWS registry born after ART (Chang *et al*., 2005).

We have performed a comprehensive assessment of 5-year-old children born after ICSI and their families in a European collaborative study, the International Collaborative Study of ICSI: Child and Family Outcomes (ICSI-CFO). The primary objective of the study was to assess whether ICSI is associated with significant negative health, developmental and psychosocial adjustment outcomes at pre-school age. Children conceived after ICSI were compared with children conceived after IVF and with naturally conceived children. Results regarding medical, cognitive development and psychosocial adjustment have been published (Barnes *et al*., 2004; Bonduelle *et al*., 2005; Ponjaert-Kristoffersen *et al*., 2005).

In this article, we report on the influence of sperm concentration on growth and cognitive development in children born after ICSI or standard IVF.

Subjects and methods

This study was part of a larger study involving 1515 European children from five nations: Belgium, Denmark, Greece, Sweden and the UK. The study involved prospective evaluation of three groups of children who were recruited at age 5 years according to their mode of conception (540, ICSI; 437, IVF; 538, naturally conceived children). Children were eligible if they were singleton, Caucasian, born after at least 32 weeks' gestation, or first or second born and if their mother tongues were Dutch, Danish, Greek, Swedish or English.

In the UK and Belgium, the ICSI-conceived children were recruited mainly from established cohorts already assessed in their second year. Additional children were recruited from major fertility clinics. In Sweden, the ICSI children had been conceived after treatment at two fertility clinics and were recruited from their consecutive birth records. In Denmark, most of the ICSI children were recruited from one clinic, but additional children were recruited from three others. In Greece, the ICSI children were recruited from several clinics.

A comparison group of children conceived with standard IVF (i.e. IVF without ICSI) were also assessed. They were selected according to the criteria given above, and they were also matched for maternal education and parental socioeconomic status. The IVF comparison groups were recruited from participating fertility clinics in all countries in a similar manner to the ICSI-conceived children.

The participation rate varied between 25% and 96% for IVF and ICSI in the different countries (Bonduelle *et al*., 2005; Ponjaert-Kristoffersen *et al*., 2005).

A full history was taken from the parent(s) using a standard proforma protocol. Socioeconomic status was classified according to the British system (Classification of Occupations. London: HM Stationery Office, 1970 and revised 1995), and equivalencies between the five participant countries were established for parental educational levels.

The study was conducted over a 24-month period, commencing in November 2000.

Sperm parameters

Data on sperm concentration were collected from the medical records from the fertility clinics. The ICSI group was divided into five subgroups according to paternal sperm origin and sperm concentration: (1) epididymal and testicular sperm group, (2) ejaculated sperm $<1 \times 10^6$/ml, (3) ejaculated sperm 1–4.99 $\times 10^6$/ml, (4) ejaculated sperm 5–19.99 $\times 10^6$/ml and (v) ejaculated sperm $\geq 20 \times 10^6$/ml. The IVF group was divided into two subgroups: (1) $<20 \times 10^6$/ml and (2) $\geq 20 \times 10^6$/ml.

Cognitive development

Children's cognitive development was assessed with the Wechsler Preschool and Primary Scale of Intelligence—Revised (WPPSI-R; Wechsler, 1990). The WPPSI-R is an individually administered clinical instrument for assessing the intelligence of children aged from 3 years to 7 years and 3 months. The WPPSI-R provides standardized measures of a variety of abilities reflecting different aspects of intelligence. It consists of two main scales: verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ), each including six subtests. Scores on performance and verbal scale yield the full-scale IQ. All IQ scales have a mean of 100 and an SD of 15. A psychologist assessed all the children individually. For further details, see Ponjaert-Kristoffersen *et al*. (2005).

Growth

Using an identical protocol, trained paediatricians assessed the children.

Birth growth parameters were extracted from child health records and, in a minority, from parents.

Height and weight at age 5 were measured using standard auxiological equipment. In the UK and Belgium, two consecutive paediatricians (in each country) saw all the children, and in Denmark, Sweden and Greece, only one paediatrician assessed all the children in each country.

Height and weight were used to calculate BMIs (kg/m^2) at age 5. For further details, see Bonduelle *et al*. (2005).

To adjust for gender and differences in age at birth and at follow-up, we have used one reference for evaluating birth weight standard deviation scores (SDS) (Marsal *et al*., 1996) and another reference for evaluating height SDS and weight SDS at follow-up (Wikland *et al*., 2002). SDS is calculated as individual value minus mean value for reference population (given gender and age) divided by the SD for the reference population. Mean reference (in SDS) is therefore zero with SD = 1.

We report results of the children with paternal sperm data. There were 492 ICSI-conceived children and 265 IVF-conceived children with paternal sperm data that were included in this study. We excluded 48 ICSI children and 172 IVF children from the larger study owing to missing paternal sperm parameters—paternal sperm data were not registered in any of the 157 IVF children from UK. The children were examined at age 5 years.

Statistics

Descriptive statistics are given with mean and SD. Differences between groups within ICSI were analysed with chi-square test for dichotomous variables and with analysis of variance (ANOVA) test for ordered and continuous variables. Where a group effect was identified post hoc at a significance level of $P < 0.05$, Tukey's test was conducted.

Differences between the IVF subgroups were analysed with Fisher's exact test for dichotomous variables and with Student's *t*-test for ordered and continuous variables. A stepwise linear regression analysis was performed on the dependent variables total IQ and child height. Adjustment for centre effect was performed with a general linear

model, univariate analysis. All significance tests were two-tailed and were conducted at the 5% significance level.

With a sample size of 38 children in the smallest group, it was possible to detect a difference in height of 3.1 cm [assuming an SD of 4.7 cm (Wikland *et al*., 2002)] and a difference in total IQ of 10 [assuming an SD of 15 (Wechsler, 1990)], with an alpha error of 0.05 and a power of 80%.

The statistical package SPSS 12.0.1 for Windows was used.

Ethics

Ethical approval for participation in the study was obtained from ethics committees in each of the five participating countries.

Results

A total of 757 children were evaluated: 492 were conceived after ICSI and 265 after standard IVF. In the ICSI group, 38 were conceived using epididymal or testicular sperm preparation (ICSI group 1) and 454 were conceived with ejaculated sperm. These subgroups were further divided according to sperm concentration, giving 62, 84, 133 and 175 children in ICSI subgroups 2, 3, 4 and 5, respectively (Table I). In the IVF group, 31 children had paternal sperm concentration $<20 \times 10^6$/ml (IVF subgroup 1) and 234 had paternal sperm concentration $\geq 20 \times 10^6$/ml (IVF subgroup 2).

Parental sociodemographic and neonatal characteristics are presented in Table I. A significant difference in maternal age was found, with the highest maternal age in the ICSI group with paternal sperm concentration $\geq 20 \times 10^6$/ml (1–4.99 $\times 10^6$/ml versus $\geq 20 \times 10^6$/ml, $P = 0.006$, and 5–19.99 $\times 10^6$/ml versus $\geq 20 \times 10^6$/ml, $P = 0.011$, Tukey's post hoc test). No significant difference was found in maternal height, paternal age, maternal educational level or gender of infant.

Significant differences in sperm counts between centres were found. For example, in Sweden, the ICSI group with paternal sperm concentration $\geq 20 \times 10^6$/ml was larger than that in the other countries.

No significant difference was found for gestational age, birth weight or SDS birth weight between the ICSI and IVF sperm groups (Table I).

No significant difference in height and weight at 5 years or SDS weight or BMI at 5 years was found in the different sperm subgroups for ICSI or IVF (Table II).

A significantly lower SDS child height was found in the ICSI sperm group 1–4.99 $\times 10^6$/ml as compared with either sperm group $<1 \times 10^6$/ml or sperm group 5–19.99 $\times 10^6$/ml ($P = 0.023$ and $P = 0.028$, respectively, Tukey's post hoc test).

A stepwise linear regression analysis was performed for the dependent variable child height at 5 years for the ICSI and for the IVF group. Of possible predictors in the regression analysis (mother's height, paternal sperm count, gestational age at delivery, age of child at examination and gender of child), only mother's height, age of child at examination and gender of child showed a significant association with child height for the ICSI group ($P < 0.001$ for all three variables, adjusted $R^2 = 0.396$). For the IVF group, mother's height and child's age at examination showed a significant association with child height ($P < 0.001$ for both variables, adjusted $R^2 = 0.243$). When predicting child height, the variables selected in the stepwise regression analysis still proved to be significant even after adjustment for centre (for both the ICSI and IVF groups).

No significant difference in total IQ, VIQ or PIQ was found between the ICSI or IVF sperm subgroups (Table III).

A stepwise linear regression analysis was performed on the dependent variable total IQ for the ICSI and for the IVF group. Of possible predictors in the regression analysis (mother's age, father's age, mother's education, father's education, paternal sperm count, gestational age at delivery, age of child at examination and gender of child), only mother's age, mother's education and gestational age showed a significant association with total IQ in the ICSI group ($P < 0.001$ for all three variables, adjusted $R^2 = 0.060$). For the IVF group, mother's age, mother's education, gender and age of child at examination showed a significant association ($P < 0.001$ for all variables, adjusted $R^2 = 0.209$) with total IQ. When predicting IQ, mother's age was no longer considered to be significant after adjustment for centre (for both the ICSI and IVF groups).

Discussion

The main findings in this study, that growth and cognitive development in IVF and ICSI children born with a gestational age more than 32 weeks did not differ in relation to paternal sperm concentration, are reassuring. In this study, we grouped the children according to paternal sperm concentration following the World Health Organization's definition of low sperm concentration and recent studies indicating an increased rate of chromosomal aberrations and microdeletions in men with low sperm concentration (Aittomaki *et al*., 2004, 2005).

Further studies of children followed-up after ART are needed. Particular concerns have been raised about the outcome when using sperm of lower quality in connection with ICSI. A higher rate of malformations has been reported in ART children, in observational cohort studies (Anthony *et al*., 2002; Hansen *et al*., 2002; Bonduelle *et al*., 2004; Bonduelle *et al*., 2005), in registry studies (Ericson and Kallen, 2001; Hansen *et al*., 2002; Ludwig and Katalinic, 2002; Kallen *et al*., 2005) and in meta-analyses (Rimm *et al*., 2004; Hansen *et al*., 2005). However, the risk of major malformations does not seem to be related to the sperm count (Ludwig and Katalinic, 2003).

The general results from the European project on children's development after ART (Bonduelle *et al*., 2005; Ponjaert-Kristoffersen *et al*., 2005), and from which the population in this study is derived, did not show any significant differences in mean height and mean IQ between ICSI, IVF and children born after natural conception. Furthermore, no differences were found among the groups in number of children scoring below 1 SD from the mean IQ. The current study adds further information to that data indicating that no association was found between sperm count and IQ. The significantly lower SDS height in the sperm group 1–4.99 $\times 10^6$/ml might be a random effect, and there is no indication that the lower SDS height is attributable to low sperm count. Also, to compare mean values for children's height and IQ between groups with different sperm cut-off levels, we performed a linear regression analysis on the dependent variables height and IQ. The sperm count was not significantly associated with outcome in any

Table I. Parental sociodemographic variables and neonatal characteristics in relation to sperm concentration levels

	ICSI							IVF			
	All (n = 492)	Epididymal/testicular sperm (n = 38)	<1 × 10^6/ml (n = 62)	1–4.99 × 10^6/ml (n = 84)	5–19.99 × 10^6/ml (n = 133)	≥20 × 10^6/ml (n = 175)	P	All (n = 265)	<20 × 10^6/ml (n = 31)	≥20 × 10^6/ml (n = 234)	P
Maternal age (years)	33.4 ± 3.8 (n = 491)	33.1 ± 3.5 (n = 38)	33.2 ± 3.8 (n = 61)	32.7 ± 3.6 (n = 84)	33.0 ± 4.0 (n = 133)	34.3 ± 3.7 (n = 175)	0.008*,[a]	33.2 ± 3.7 (n = 265)	32.6 ± 3.6 (n = 31)	33.3 ± 3.8 (n = 234)	0.314[b]
Maternal height (cm)	165.5 ± 6.6 (n = 450)	164.7 ± 5.2 (n = 35)	166.5 ± 7.0 (n = 53)	164.4 ± 6.3 (n = 78)	166.3 ± 7.0 (n = 122)	165.3 ± 6.7 (n = 162)	0.230[a]	167.5 ± 6.3 (n = 239)	166.9 ± 6.5 (n = 27)	167.6 ± 6.3 (n = 212)	0.563[b]
Paternal age (years)	34.6 ± 4.8 (n = 489)	33.7 ± 4.8 (n = 38)	34.1 ± 5.2 (n = 60)	34.2 ± 4.5 (n = 84)	35.0 ± 5.3 (n = 132)	34.9 ± 4.5 (n = 175)	0.415[a]	35.1 ± 5.0 (n = 264)	34.1 ± 5.7 (n = 30)	35.2 ± 5.0 (n = 234)	0.273[b]
Gestational age (days)	275 ± 12 (n = 492)	275 ± 12 (n = 38)	275 ± 13 (n = 62)	273 ± 13 (n = 84)	275 ± 12 (n = 133)	275 ± 12 (n = 175)	0.784[a]	274 ± 13 (n = 265)	275 ± 12 (n = 31)	274 ± 13 (n = 234)	0.925[b]
Preterm birth <37 weeks (%)	9.3	7.9	8.1	11.9	9.0	9.1	0.926[a]	12.5	12.9	12.4	1.000[b]
Birth weight (g)	3298 ± 574 (n = 491)	3390 ± 540 (n = 38)	3249 ± 564 (n = 62)	3291 ± 597 (n = 84)	3365 ± 619 (n = 133)	3248 ± 535 (n = 174)	0.333[a]	3319 ± 586 (n = 265)	3365 ± 556 (n = 31)	3313 ± 591 (n = 234)	0.647[b]
SDS birth weight	0.31 ± 1.11 (n = 491)	–0.13 ± 1.05 (n = 38)	–0.42 ± 1.09 (n = 62)	–0.25 ± 1.22 (n = 84)	–0.15 ± 1.19 (n = 133)	–0.46 ± 0.99 (n = 174)	0.094[a]	–0.25 ± 1.03 (n = 264)	–0.15 ± 0.96 (n = 31)	–0.26 ± 1.04 (n = 233)	0.579[b]
Gender (% boys)	53.7	57.9	40.3	59.5	51.9	56.0	0.170[c]	54.2	51.6	54.5	0.849[c]
Centre	n = 492	%	%	%	%	%	0.002[c]	n = 265	%	%	0.001[c]
Belgium	173	6.9	9.8	17.3	29.5	36.4		117	20.5	79.5	
Denmark	68	2.9	13.2	20.6	33.8	29.4		67	3.0	97.0	
Greece	25	4.0	16.0	24.0	40.0	16.0		14	7.1	92.9	
Sweden	64	14.1	3.1	7.8	20.3	54.7		67	6.0	94.0	
UK	162	8.6	18.5	17.9	22.2	35.6		0	0	0	
Maternal education level (university entry examination or higher) (%)	51.4	60.5	53.2	44.0	52.6	51.4	0.517[c]	55.9	71.0	53.9	0.084[c]

Values are expressed as mean ± SD. SDS, standard deviation scores.
[a]Analysis of variance (ANOVA) with Tukey's post hoc test.
[b]Student's t-test
[c]Chi-square test/Fisher's exact test.
*P = 0.014 1–4.99 × 10^6/ml versus ≥ 20 × 10^6/ml and P = 0.033 5–19.99 × 10^6/ml versus ≥ 20 × 10^6/ml, Tukey's post hoc test.

Table II. Growth parameters in relation to paternal sperm concentration levels in children at 5 years of age born after assisted reproductive therapy

	ICSI							IVF			
	All (n = 492)	Epididymal/testicular sperm (n = 38)	<1 × 10^6/ml (n = 62)	1–4.99 × 10^6/ml (n = 84)	5–19.99 × 10^6/ml (n = 133)	≥20 × 10^6/ml (n = 175)	P^a	All (n = 265)	<20 × 10^6/ml (n = 31)	≥20 × 10^6/ml (n = 234)	P^b
Evaluated age (years)	5.0 ± 0.33 (n = 492)	5.0 ± 0.28 (n = 38)	5.1 ± 0.36 (n = 62)	5.0 ± 0.34 (n = 84)	5.0 ± 0.36 (n = 133)	5.1 ± 0.30 (n = 175)	0.265	5.1 ± 0.33 (n = 264)	5.1 ± 0.31 (n = 31)	5.0 ± 0.33 (n = 233)	0.473
Child height (cm)	111.3 ± 5.5 (n = 492)	110.9 ± 5.6 (n = 38)	112.6 ± 5.1 (n = 62)	109.9 ± 5.3 (n = 84)	111.5 ± 5.7 (n = 133)	111.3 ± 5.6 (n = 175)	0.053	111.9 ± 5.2 (n = 264)	112.1 ± 4.7 (n = 31)	111.9 ± 5.3 (n = 233)	0.837
Child weight (kg)	19.6 ± 3.2 (n = 486)	19.9 ± 4.0 (n = 38)	20.4 ± 4.1 (n = 61)	18.8 ± 2.8 (n = 84)	19.8 ± 3.1 (n = 129)	19.5 ± 2.9 (n = 174)	0.052	19.6 ± 2.9 (n = 264)	19.6 ± 2.8 (n = 31)	19.6 ± 2.9 (n = 233)	0.972
SDS child height	0.32 ± 1.13 (n = 492)	0.28 ± 1.34 (n = 38)	0.57 ± 0.95 (n = 62)	0.01 ± 1.02 (n = 84)	0.46 ± 1.16 (n = 133)	0.29 ± 1.13 (n = 175)	0.018*	0.47 ± 1.14 (n = 263)	0.45 ± 1.10 (n = 31)	0.47 ± 1.15 (n = 232)	0.938
SDS Child weight	0.34 ± 1.23 (n = 486)	0.42 ± 1.59 (n = 38)	0.56 ± 1.41 (n = 61)	0.03 ± 1.07 (n = 84)	0.45 ± 1.21 (n = 129)	0.30 ± 1.13 (n = 174)	0.069	0.33 ± 1.16 (n = 263)	0.31 ± 1.12 (n = 31)	0.33 ± 1.17 (n = 232)	0.950
Child BMI (SD)	15.8 ± 1.83 (n = 486)	16.0 ± 2.14 (n = 38)	16.0 ± 2.86 (n = 61)	15.5 ± 1.46 (n = 84)	15.8 ± 1.67 (n = 129)	15.7 ± 1.56 (n = 174)	0.459	15.6 ± 1.44 (n = 264)	15.5 ± 1.36 (n = 31)	15.6 ± 1.46 (n = 233)	0.892

Values are expressed as mean ± SD. SDS, standard deviation scores.
[a]Analysis of variance (ANOVA).
[b]Student's *t*-test.
*P = 0.023 1–4.99 × 10^6/ml versus <1 × 10^6/ml and P = 0.028 1–4.99 × 10^6/ml versus 5–19.99 × 10^6/ml, Tukey's post hoc test.

Table III. Cognitive development in relation to paternal sperm concentration levels in children at 5 years of age born after assisted reproductive therapy

	ICSI							IVF			
	All (n = 492)	Epididymal/testicular sperm (n = 38)	<1 × 10^6/ml (n = 62)	1–4.99 × 10^6/ml (n = 84)	5–19.99 × 10^6/ml (n = 133)	≥20 × 10^6/ml (n = 175)	P^a	All (n = 265)	<20 × 10^6/ml (n = 31)	≥20 × 10^6/ml (n = 234)	P^b
Verbal IQ	108.5 ± 14.0 (n = 465)	109.6 ± 17.6 (n = 38)	107.3 ± 14.3 (n = 60)	105.9 ± 13.3 (n = 78)	109.5 ± 13.2 (n = 122)	109.2 ± 13.7 (n = 167)	0.357	111.3 ± 13.7 (n = 254)	111.4 ± 16.4 (n = 30)	111.3 ± 13.4 (n = 224)	0.984
Performance IQ	106.0 ± 15.2 (n = 466)	106.8 ± 15.5 (n = 38)	105.2 ± 17.1 (n = 60)	105.2 ± 16.0 (n = 78)	106.2 ± 14.8 (n = 122)	106.2 ± 14.5 (n = 168)	0.965	105.2 ± 16.0 (n = 254)	106.6 ± 17.9 (n = 30)	105.0 ± 15.7 (n = 224)	0.614
Total IQ	108.4 ± 14.5 (n = 465)	109.5 ± 17.0 (n = 38)	107.2 ± 16.0 (n = 60)	106.4 ± 14.2 (n = 78)	109.2 ± 13.9 (n = 122)	109.0 ± 13.9 (n = 167)	0.592	109.6 ± 14.5 (n = 254)	110.5 ± 18.3 (n = 30)	109.5 ± 14.0 (n = 224)	0.704

Values are expressed as mean ± SD.
[a]Analysis of variance (ANOVA).
[b]Student's *t*-test.

regression analysis. We can state with reasonable certainty that ICSI and IVF children have similar heights and IQs at the age 5 year, independently of paternal sperm count.

Growth is regarded as a robust variable, reflecting both genetic background and general health. It may therefore be a suitable variable to analyse when assessing new techniques such as IVF and ICSI. It is also easy to measure and has little subjective influence. It is known from numerous publications (Bergh *et al*., 1999; Helmerhorst *et al*., 2004; Jackson *et al*., 2004; Schieve *et al*., 2004) that ART singletons are smaller at birth than spontaneously conceived singletons and that the rate of preterm babies is higher, even after adjustment for confounders (Bergh *et al*., 1999). At the age of 5 years, catch up seems to have taken place and groups of IVF and ICSI children did not differ in height or weight as compared with naturally conceived children (Bonduelle *et al*., 2005).

Few studies have been published on cognitive development on ART children beyond the age of 1–2 years. In a Swedish study (Stjernqvist, 2001) involving 72 IVF children and 72 controls at age 7–14 years, more IVF children had IQs below 2 SD, although the mean IQ did not differ between groups. Bonduelle *et al*. (2003) found similar developmental outcome at 2 years of age for ICSI and IVF children and found that the development of ICSI children from fathers with low sperm counts did not differ the development of from children conceived from fathers with normal sperm parameters. An Australian study (Bowen *et al*., 1998) found developmental delay in ICSI children at the age of 1 year. However, at 5 years no differences were found (Leslie *et al*., 2003). In a recent study from Ponjaert-Kristoffersen *et al*. (2004), 300 ICSI children and 300 controls from Belgium, Sweden and the USA were investigated. No differences in mean IQ at the age of 5 years between groups were noted.

The main limitation of this study is the rather high rate of nonparticipation for ICSI and IVF children in some of the countries, which may introduce a selection bias. However, results were comparable between countries with a high participation rate and countries with a low participation rate.

In conclusion, this study reports no negative effects of lower sperm concentration on growth and cognitive development in IVF and ICSI children at the age of 5 years and is thus reassuring.

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