Cognitive and motor development of 8-year-old children born after ICSI compared to spontaneously conceived children

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BACKGROUND: As a continuation of two large-scale, multicentre studies on the development of 5-year-old ICSI children, we present results of the follow-up study undertaken on the cognitive and motor development of 8-year-old ICSI children. METHODS: Developmental outcomes of 151 8-year-old singletons born through ICSI after 32 weeks of gestation were compared with those of 153 singletons of the same age born after spontaneous conception (SC). Part of this population was seen in a cohort at the age 5 years. Outcome measures include Wechsler Intelligence Scale for Children-Revised (WISC-R) and Movement Assessment Battery for Children (ABC). RESULTS: Regarding intellectual functioning, ICSI children tend to obtain significantly higher total ($P < 0.01$), verbal ($P < 0.01$) and performance ($P < 0.05$) intelligence scores than SC children, nevertheless remaining in similar ranges. These effects are small (Cohen's $d < 0.50$). High maternal educational level stayed in the regression as a factor accounting for some of the variance in total IQ between the groups. In terms of motor development, no significant differences were found between ICSI and SC children regarding overall motor skills, manual, balance and ball skills. CONCLUSION: In this follow-up study, ICSI and SC children show a comparable cognitive and motor development until the age of 8 years.

Key words: child follow-up/cognitive/ICSI/motor development

Introduction

Since its introduction in the early 1990s, ICSI has become a widespread assisted reproduction technique (ART) for couples struggling with male infertility. However, the specificities of this technique have raised concerns about its medical outcomes for ICSI-born children. These concerns refer mainly to potential changes in genetic material, the possible transmission of foreign genetic material, the use of immature or senescent germ cells and associations between genetic disorders and some forms of male infertility (Bowen *et al*., 1998; te Velde *et al*., 1998; Tournaye, 2003). From a strictly medical perspective, an increased risk of adverse neonatal outcome has been documented (Helmerhorst *et al*., 2004; Jackson *et al*., 2004; Lie *et al*., 2005). Meta-analyses have shown a 30–40% increase in congenital malformations in children born after ICSI (Hansen *et al*., 2002; Rimm *et al*., 2004; Kallen *et al*., 2005). Nevertheless, medical follow-up studies have so far been reassuring overall, because they have failed to document detrimental outcomes for children born through the ICSI technique (Kurinczuk, 2003; Devroey and Van Steirteghem, 2004; Bonduelle *et al*., 2005). From a broader developmental perspective, it has been suggested that ICSI might also impede children's psychological development. Several studies have addressed these questions and have so far yielded mixed to reassuring findings regarding young ICSI children's motor and cognitive development.

Overview of previous studies

One of the first studies in this field, in which 1-year-old ICSI-born children were compared with spontaneously conceived (SC) and IVF children, revealed an increased risk of mildly to significantly delayed development (Bowen *et al*., 1998). However, a concurrent single-centre Belgian follow-up study found no signs of delayed development in 2-year-old ICSI children (Bonduelle *et al*., 1998).

Replication studies in a larger number of countries with ICSI children aged up to 5 years show no delayed development (Sutcliffe *et al*., 1999, 2001, 2003a,b; Neri *et al*., 2002; Bonduelle *et al*., 2003; Leslie *et al*., 2003; Place and Englert, 2003; Squires *et al*., 2003; Wennerholm *et al*., 2003; Papaligoura *et al*., 2004), although generalization of these findings should be treated with caution, given many methodological limitations, such as relatively small sample sizes, lack of formal child assessment and demographic matching of samples.

Large-scale, multicentre studies were undertaken to overcome such limitations by investigating the long-term effects of

ICSI across diverse medical systems. In this context, no significant differences were found on WPPSI-R (Wechsler, 1990) IQs between 5-year-old ICSI and SC children from Belgium, Sweden and USA (Ponjaert-Kristoffersen *et al.*, 2004). When analysing subtest scores, however, ICSI children appeared more likely to perform better on general factual/acquired knowledge (information) and less well for some visual–spatial abilities (mazes, block design and object assembly), which was attributed to a higher incidence of low birth weight and prematurity in the ICSI study group.

A European collaborative follow-up study compared 5-year-old singleton ICSI-born children with IVF and SC controls (Ponjaert-Kristoffersen *et al.*, 2005), recruited in Belgium, Sweden, Denmark, Greece and UK and matched according to age, sex, birth order, maternal education, parental socioeconomic status and mother's age at birth. Although no significant differences for intelligence between groups were found, older maternal age at birth was significantly linked to lower full-scale IQ (FSIQ) and verbal IQ in ICSI/IVF children, as well as lower abilities to anticipate relationships among parts (object assembly) in IVF children. Although no significant differences for intelligence between groups were found, older maternal age at birth was significantly linked to lower full-scale IQ (FSIQ) and verbal IQ in ICSI/IVF children, as well as lower abilities on a subtest of the performance scale (object assembly) in IVF children. Higher maternal educational level was also linked to better abilities on the same performance subtest (object assembly) in ICSI/IVF children, whereas a low educational level in this group was linked to lower scores on spatial visualization an analysis (block design). Overall, these results suggest that factors other than conception mode, especially maternal age at birth and educational level, may prevail in explaining the long-term cognitive development of ICSI children.

Implications for the current study

Taken together, although findings on ICSI children's motor and cognitive development have so far been generally reassuring, several needs for further study come forward from the existing research literature. First, the ICSI population as a whole has been studied only up to an early age. Further research is therefore needed to evaluate whether ICSI children continue to show satisfactory development later in life. Additionally, some findings remain inconsistent given certain methodological limitations discussed above. Lastly, findings to date suggest that some demographic variables may be more important in explaining cognitive outcomes than children's conception mode *per se*. Further research should therefore clarify the relative impact of conception mode compared with other demographics.

Responding to these needs, this study is the first long-term, two-wave follow-up investigation at ages 8 and 10 years into ICSI children's psychological, family-relational and medical development (Leunens *et al.*, 2004a,b; 2005). This article discusses the first-wave study findings on the cognitive and motor development of ICSI children at age 8 years. Given that this is the first follow-up study on ICSI children's development at this age to our knowledge (Leunens *et al.*, in press), the research questions were mainly kept explorative: (i) Does ICSI have

any impact on children's intellectual development at 8 years? and (ii) Does ICSI have any impact on children's motor development at 8 years? Furthermore, we aimed to assess the relative role of demographic variables such as maternal education level and age at birth relative to conception mode. Overall, in line with previous studies on 5-year-old ICSI children, we expected that no effects resulting from the conception mode would be found on ICSI children's cognitive or motor development at 8 years.

Methods

Participants

Our study sample ($n = 304$) consisted of Dutch-speaking Belgian children recruited and assessed when they were 8 years old (up to 8 years 11 months). Singletons born after ICSI ($n = 151$) and controls born after SC ($n = 153$) were seen for individual assessment. The children's inclusion criteria were being born after 32 weeks of gestation, singleton and native language Dutch with at least one European parent. These inclusion criteria were chosen to maximize follow-up rates, to minimize confounding factors because of prematurity and exclude potential influences because of multiple births, linguistic barriers and sociocultural differences.

Children were not matched for gestational age, but no significant difference existed in mean gestational age between the study groups. Gender was quite evenly distributed, with 77 boys (50.99%) and 74 girls (49.01%) in the ICSI group and 78 boys (50.98%) and 75 girls (49.02%) in the SC group.

Procedure

The ICSI children were recruited from initial birth cohorts established at the Academic Hospital of the Vrije Universiteit Brussel. They had already been assessed in their second and/or fifth year (Bonduelle *et al.*, 1998; Ponjaert-Kristoffersen *et al.*, 2004, 2005). Approximately two-thirds ($n = 151/248$, 61%) of the eligible Dutch-speaking ICSI cohort aged 8 years between February 2001 and December 2003 ($n = 248$) was tested at 8 years. Of the remaining 39% of the cohort ($n = 97$), 16.5% ($n = 41/248$) of the families could not be reached (lost to follow-up) and 22.5% ($n = 56/248$) refused to participate in this study. Of all the families in the eligible cohort who were actually reached by telephone ($n = 207/248$), 73% responded positively ($n = 151/207$) and 27% refused participation ($n = 56/207$). A brief oral checklist was administered to those parents preferring not to participate, to obtain information on refusals and on major medical events concerning children in this group. This checklist included items relative to hospitalization, diseases, surgery, medication intake, additional therapies, learning difficulties along with reasons for refusal. Taken together, at least minimal information could thus be obtained on ~83.5% of the eligible children from our centre.

SC children (controls) were selected to match children in the ICSI group (age and gender) with further group level matching for maternal education. The control children were recruited from surrounding schools, with an average response rate of 37.5%. The reasons for refusal in this group mainly pertained to a lack of interest or time to participate ('no time', 'don't see why' and 'not interested'). No fundamental study-related objections were recorded.

The full study procedure consisted of a comprehensive psychological assessment along with a pediatric neurological evaluation, as summarized in Table I. All children were individually assessed by one trained psychologist. Testing took place in a hospital consultation room (ICSI children) or in an isolated classroom at school (SC children), with ICSI children being assessed only on school-free periods, because most parents would not participate if their child would have

Table I. Assessment measures in study protocol

Name of test	Measuring
Children's assessment	
Psychological examination	
Wechsler Intelligence Scale for Children-Revised (Wechsler, 1974; Vander Steene *et al*., 1986)	Intelligence
Family Relations Test (Bene, 1985; Celestin-Westreich *et al*., 1999)	Child's perception of relationship with parents and siblings
Movement Assessment Battery for Children (Henderson and Sugden, 1998)	Motor development
Pediatric neurological examination	
Genital examination and Tanner scores	Status of prepubertal development
Congenital malformations (ICD-9-BPA)	
Physical examination and auxiological data	Heart auscultation, skin inspection, weight, height, head circumference, blood pressure
Neurological examination (Touwen's criteria)	Speech, tone, gait, balance, reflexes, strength against resistance, resistance against passive movements and coordination
Pure tone audiometry	Hearing
Snellen charts	Monocular visual acuity
Test of Lang	Binocular vision
Questionnaires administered to the parents	
Child Behavior Checklist for Children (Achenbach and Edelbrock, 1983; Verhulst *et al*., 1996)	Behavioural/emotional problems
Parenting Stress index (Abidin, 1990; de Brock *et al*., 1992)	
Dyadic Adjustment Scale (Spanier, 1976)	Quality of parental relationship
Greenberger Scales (Greenberger and Goldberg, 1989)	Commitment to parenting/to work
Parental Acceptance/Rejection Questionnaire (Rohner, 1999)	Nature of parent-child relationship
General Health Questionnaire (Goldberg and Hillier, 1979; Koeter and Ormel, 1991)	Parental emotional well-being

to miss class. After briefing on assessment purpose and duration of 1.5 h, the ICSI parents were handed over a stamped envelope with the questionnaires (see Table I) and asked to fill out at least the medical questionnaire on-site. Parents of the SC children received written assessment briefing after the school head's consent regarding participating in the study. Children's assessment consisted of respectively intelligence testing, the Family Relations Test and the Movement Assessment Battery for Children (ABC) test. SC children were given the stamped envelope with questionnaires to be filled out by their parents.

Although blind testing was not feasible, the use of standardized measures with fixed study protocol is considered sufficient to minimize potential observer bias. All participating families provided written informed consent.

Outcome measures

All outcome measures consisted of standardized tests with satisfactory psychometric properties regarding reliability and validity (Wechsler, 1974; Vander Steene *et al*., 1986; Henderson and Sugden, 1998) (Table I).

To address the present research questions, cognitive and motor developments were respectively measured with the Wechsler Intelligence Scale for Children-Revised (WISC-R) and Movement ABC.

WISC-R

The WISC-R (Wechsler, 1974; Vander Steene *et al*., 1986) is a widely used, individually administered, standardized measure of intelligence for children aged 6–18 years. It yields a full-scale, verbal and performance intelligence quotient (mean 100, SD 15) along with six verbal (information, similarities, arithmetic, vocabulary, comprehension and digit span) and six performance subtest scores (picture completion, sequencing, block design, object assembly, substitution and mazes) (mean 10, SD 3). Because intelligence scores cannot be regarded as absolute figures, but are always embedded with a certain probability within confidence intervals, the confidence intervals computed by the test constructors of the Flemish/Dutch version of the WISC-R (Vander Steene *et al*., 1986) were used in this article. This

method allows assessing clinical importance of differences in IQ between the groups, which is impossible with other methodologies, like *z*-scores for example. These confidence intervals from the Vander Steene *et al*. (1986) test manual are computed based on estimated true IQ scores, defined as $IQ_t = (IQ_0 - 100) r_{tt} + 100$ (Nunnally, 1978, in Vander Steene *et al*., 1986), with r_{tt} being the reliability factor for Weighted Composite tests as defined by Mosier (1943, in Vander Steene *et al*., 1986). The Flemish/Dutch WISC-R test constructors derived the reliability factor for their sample of Flemish/Dutch children, which multiplied with the SD of the observed IQ score (Stanley, 1971, in Vander Steene *et al*., 1986) leads to the confidence intervals referred to in this article.

Movement ABC

The Movement ABC (Henderson and Sugden, 1998) test measures motor abilities for children aged 5–12 years on three scales: manual skill (e.g. placing pins in a peg board), ball skill (e.g. throwing a bean-bag over a 2-meter distance into a box) and balance (e.g. standing on each foot for 20 s). The Movement ABC test yields percentile scores with age norms. For Dutch-speaking children at age 8 years, the 15% percentile threshold is situated at a total test score of 8.5 with scores below 8.5 indicating above average motor skills with zero being the best obtainable score.

Statistical analysis

Between-factor analyses were carried out on interval or ratio data with two independent variables using ANOVA or *t*-tests in SPSS 13.0 for Windows. The independent measures used were the child's conception mode (ICSI or SC) and gender. The dependent measures were the WISC-R and Movement ABC test scores. Nominal data were analyzed using Pearson χ^2 tests. Significance levels of 0.05 were accepted throughout. 'Cohen's *d*'-values were computed to account for effect sizes. This value is defined as $d = $ (Experimental mean – Control mean)/Pooled SD (Cohen, 1988; Rosnow and Rosenthal, 1996).

Table II. Demographic description of the ICSI and spontaneous conception study populations

	ICSI (n = 151)		Spontaneous conception (n = 153)		Statistical analysis
	M/n/%	SD	M/n/%	SD	
Mean age at testing (years)	8.56	0.17	8.49	0.28	P = 0.013
Firstborn	115/76.2%		57/37.2%		P ≤ 0.001
Unknown	15/9.9%		29/18.9%		
Birth weight (g)	3314.8	531	3275	496	P = 0.587
Gestatational age (weeks)	39.4	1.2	39.3	1.5	P = 0.514
32–37	4/2.6%		12/7.8%		
≥37	147/97.4%		134/87.6%		
Unknown	0		7/4.6%		
Maternal age at birth (years)	31.9	4.0	29.9	5.2	P ≤ 0.001
Unknown	0		8/5.2%		
Maternal educational level					
High	97/64.2%		68/44.4%		P = 0.726
Medium	43/28.5%		30/19.6%		P = 0.856
Low	1/0.7%		4/2.6%		P = 0.082
Unknown	10/6.6%		51/33.3%		
Paternal education level					
High	90/59.6%		56/36.6%		P = 0.342
Medium	45/29.8%		38/24.8%		P = 0.248
Low	6/3.9%		3/1.9%		P = 0.644
Unknown	10/6.6%		56/36.6%		
Admission NICU	30/21%		9/9%		P = 0.012
≤7	20/13.2%		2/1.3%		
>7	6/3.9%		7/4.6%		
No of days unknown	4/2.6%		0		
Admission status unknown	8/5.3%		53/34.6%		

Stepwise linear regression analysis was conducted to control for demographic differences between the conception groups. Because of the pilot nature of this research on this population at this age, the analyses did not set out to test a preconceived model of factors influencing FSIQ, rather to explore the role of demographic variables on outcome measures for the conception groups. Therefore, the stepwise regression mode was preferred. (i) We started from the univariate variable 'maternal educational level'. In linear regression, 'standardized β' values indicate how strongly each predictor variable influences the criterion variable, in this case FSIQ. Beta is measured in units of SD. In a first step, the following rationale was applied to ascertain which factors should be included in a regression model of explaining variance in FSIQ between the conception mode groups. We started from the univariate differences between the conception mode groups, so conception mode was retained as a potential factor. (ii) Then, the demographic variables showed a univariate conception group difference as summarized in Table II, namely 'child's age', 'maternal age at birth', 'birth status firstborn' and 'admission to a neonatal intensive care unit (NICU)' were regressed separately as independent variables on the outcome variable FSIQ to see which of these satisfied criteria of association with both conception mode and outcome. (iii) Finally, maternal educational levels were 'admission to NICU', 'age of the child' and 'firstborn' and were not retained for further model-building. Only 'maternal age at birth' satisfied the association criteria. Finally, maternal educational levels were also retained because of the documented association with child intelligence outcome in previous ICSI research.

In a second step, only the variables coming forward from step 1 [conception mode, maternal age at birth and maternal educational level (high, medium and low)] were included in a stepwise regression model, with a probability of F to enter ≤0.10. This criterion was chosen to avoid the exclusion of meaningful variables with the conventional significance level of 0.05, while keeping a reasonable balance between type 1 error and power. After building the regression model, it was tested for stability on randomly drawn samples of 66% of all cases (see *Results*).

Results

Demographics

Despite ICSI and SC children's very similar average age at testing (Table II), statistical comparison of mean ages revealed a significant difference. Also, there were fewer firstborns in the SC group than in the ICSI group (Table II). Mean birth weight and gestational age were similar in both groups. Significantly more ICSI children had been admitted to a NICU, more specifically for 'short admissions' (7 days or less). Thus, ICSI and control children do not differ for 'long admissions' (over 7 days). The maternal ages at birth are significantly higher in the ICSI than in the SC group. Maternal educational levels, defined as high (postgraduate or a graduate degree), medium (entered university or completely passed school matriculation) and low (partially passed school matriculation or no qualifications at all), do not differ significantly between groups.

Cognitive development

ICSI children's FSIQs were significantly higher than those of SC children [ICSI 112, CI 95% (105–118), SD 14.8; SC 107, CI 95% (101–113), SD 13.6, P = 0.001, Cohen's d = 0.35]. It should also be noted that these IQ scores are still situated within the same SD, thus resulting in similar IQ ranges as shown in the confidence intervals indicated in the test manual, relevant to clinical practice, with Cohen's d showing that this is a small effect (d < 0.50). Gender does not affect IQ scores in either group. Additionally, there are no conception mode

effects for the small proportion of children showing marked developmental delay [defined as scoring one SD below the mean (<85)] on FSIQ (ICSI, four children; SC, three children; $P = 0.689$), VIQ (ICSI, three children; SC, two children; $P = 0.641$) and PIQ (ICSI, 12 children; SC, 12 children; $P = 0.973$).

Similarly, ICSI children obtain significantly higher verbal IQs than SC children. Again, however, effect size is small (Cohen's *d*) and mean scores remain in similar ranges (see confidence intervals). Boys obtain higher verbal IQ scores than girls. ICSI children also obtain slightly higher performance scale scores; yet again this effect is small and mean scores fall in similar confidence intervals. No gender effects are detected in either group. Table III summarizes verbal and performance IQ scores between the groups, as well as detailed subscale scores.

Several additional analyses were carried out to refine our insights in the variables that may explain the observed yet small differences in favour of ICSI children's IQs.

First, FSIQ scores were compared for ICSI and SC children born between 32 and 36 weeks of gestation, to check for possible prematurity effects. Premature ICSI children's FSIQ was still significantly higher compared with premature controls (ICSI 125.7, SD 9.8; SC 100.5, SD 15.3; $P = 0.008$). Mean FSIQ scores overall remain 'average' to 'high'.

Second, because of (i) the substantial number of missing data on maternal educational level in the SC group, (ii) the trend of higher educational levels in the ICSI group and (iii) documented effects of maternal educational level in previous ICSI research, we reran the analysis excluding all children whose maternal educational level was unknown. This analysis resulted in IQ outcomes comparable to the initial results (ICSI 112.1, SD 14.5; SC 107.9, SD 12.6; $P = 0.022$), leading to the assumption there is no manifest detrimental effect of missing maternal educational level data on the initial results. However, when comparing FSIQs of children with highly educated mothers, the significant difference in FSIQ between the groups disappeared (ICSI: 114.3; SC: 111.6; $P = 0.207$).

When, in an additional analysis, assuming all mothers whose educational level was unknown were highly educated and comparing only FSIQs of children with these 'highly educated mothers' (real highly educated mothers plus mothers with missing info on educational level), the difference in FSIQ reappeared (ICSI: 114.2; SC: 108.7; $P = 0.004$). These additional analyses indicate (i) an effect of educational level on the FSIQ scores of children in both groups, with high maternal educational level thus being responsible for the slightly higher FSIQ scores in the ICSI group and (ii) that the mothers, whose educational level was unknown, were most probably not highly educated.

Third, to explore the influence of demographic differences between conception groups' FSIQ's, a stepwise regression analysis was carried out. Among those demographic descriptors showing a univariate group difference between the ICSI and SC groups, the following separately entered factors also showed an association with FSIQ: 'conception mode' (standardized $\beta = -0.181$, $t = -3.206$, $P = 0.001$) and 'maternal age at birth' (standardized $\beta = 0.127$, $t = 2.202$, $P = 0.028$). Additionally, 'high' (standardized $\beta = 0.295$, $t = 4.729$, $P = 0.000$), 'medium' (standardized $\beta = -0.250$, $t = -4.006$, $P = 0.000$) and 'low' (standardized $\beta = -0.163$, $t = -2.567$, $P = 0.011$) maternal educational level also showed to be associated with FSIQ. The factors 'admission to NICU', 'age of the child' and 'first-born' showed no significant association with FSIQ and were therefore excluded from the regression model. Given these results, the regression model (adjusted $R^2 = 0.099$; $P = 0.000$) retained the factors 'high maternal educational level' (standardized $\beta = 0.292$, $t = 4.782$, $P = 0.000$) and 'conception mode' (standardized $\beta = -0.140$, $t = -2.290$, $P = 0.023$), whereby higher FSIQ is linked to highly educated mothers and to ICSI as conception mode. Furthermore, when running this model on randomly drawn samples of 66% of the total population, the same two factors remain in many trials, confirming the stability of this regression model. Likewise, when composing a sample of all SC cases with full availability of demographic

Table III. Mean (M) of the verbal and performance IQs and subscales as measured by the Wechsler Intelligence Scale for Children-Revised

	ICSI			Spontaneous conception			Statistical analysis
	M	Confidence interval	SD	M	Confidence interval	SD	
Verbal IQ	113.3	106–119[c]	13.7	108.2	106–114[c]	12.3	$P = 0.001$[a], $P = 0.028$[b] Cohen's $d = 0.39$
Information	10.6		2.4	9.7		2.2	$P = 0.001$
Similarities	12.8		2.9	12.2		2.9	$P = 0.117$
Arithmetic	10.1		2.4	9.7		2.4	$P = 0.159$
Vocabulary	13		2.1	12.3		1.8	$P = 0.002$
Comprehension	13.3		2.9	12.4		2.8	$P = 0.006$
Digit span	11.8		3.3	11.1		3.0	$P = 0.054$
Performance IQ	107.9	99–114[c]	16.3	103.8	96–112[c]	15.2	$P = 0.024$[a]; Cohen's $d = 0.26$
Picture Completion	9.7		3.3	8.4		3.0	$P = 0.000$
Sequencing	10.7		3.0	9.8		3.4	$P = 0.009$
Block design	11.7		3.1	10.9		3.1	$P = 0.035$
Object assembly	11.8		3.4	10.9		3.2	$P = 0.024$[a]
Substitution	10.7		2.8	11.5		2.7	$P = 0.014$
Mazes	11.4		3.0	11.5		2.8	$P = 0.849$

[a]Significant conception mode effect.
[b]Significant gender effect.
[c]Vander Steene *et al.* (1986).

Table IV. Mean (M) total motor score, manual skill score, ball skill score and balance score as measured by the Movement ABC

	ICSI		Spontaneous conception		Statistical analysis
	M	SD	M	SD	
Total motor score	1.43	1.89	1.24	1.76	$P = 0.377$
Manual skill score	0.57	1.2	0.50	1.02	$P = 0.584$, $P = 0.001$[a]
Ball skill score	0.67	1.22	0.62	1.22	$P = 0.743$
Balance score	0.19	0.58	0.13	0.36	$P = 0.232$

[a]Significant gender effect.

information, and a random sample of an equivalent number of ICSI cases (also with full demographics), the same two factors remain in the regression.

In sum, these results show that ICSI children obtain significantly, yet only slightly, higher IQ's compared with SC controls, probably because of higher maternal educational levels in the ICSI group. However, the difference is not clinically important, high maternal educational level is positively related to IQ overall, and the model explains only 10% of the variability in FSIQ scores. Future analyses should investigate additional family-related characteristics to shed light on the possible role of other factors.

Motor development

As summarized in Table IV, no significant differences were found between ICSI and SC children's motor skills as measured by the Movement ABC. However, girls did perform significantly better on manual skills in both groups ($P \leq 0.001$).

Discussion

This study aimed to explore the cognitive and motor development of 8-year-old ICSI children compared with spontaneously conceived age-matched controls. Overall, the results regarding ICSI children's cognitive and motor development appear to be reassuring for parents and clinicians. Because this is the first follow-up study of ICSI children at the age of 8 years, these findings cannot be compared with outcomes of similar studies. The present results are however in line with previous large-scale studies indicating ICSI children's reassuring cognitive and motor development at younger ages (e.g. age 5 years, Ponjaert-Kristoffersen *et al.*, 2005).

Thus, 8-year-old ICSI children do not display any significant developmental delays as compared with SC children, be it regarding cognitive or motor functioning. The statistical power of the analysis to detect a difference of 5 IQ points at a 0.05 significance level, given the sample sizes, was found to be at 0.826. ICSI children's intelligence scores are slightly higher in this study, although these effects are small and the difference is not clinically important. Besides WISC-R test characteristics (mean 100, SD 15), which clearly indicate that ICSI and SC children's mean FSIQ scores fall within the same SD of the test, it is accepted in clinical practice that intelligence scores should not be regarded as absolute figures but rather embedded between confidence intervals. Therefore, we compared confid-

ence intervals for ICSI and SC children's mean FSIQ scores provided by the Dutch/Flemish test constructors, which indicate that ICSI and control children's IQs still remain in similar ranges when situated within the intelligence levels applied in practice. It is worth remembering in this context that the statistically significant univariate group differences in favour of ICSI children's IQs cannot be directly transposed to the interpretation of individual cases. Hereafter, we further discuss the implications of these quite straightforward findings in the light of the study limitations and the possible role of influencing demographic variables.

One study limitation that limits generalizing these findings refers to the response rate. Indeed, although 61% of the eligible ICSI cohort was formally assessed, approximately one-third of the initial birth cohort could not be seen in this study, which requires questioning potential participation bias. This difficulty is evidently inherent to the nature of long-term follow-up studies and underlines the complexity of longitudinal research. Given that the main consideration in this context would be that because of dropout rates we might miss out on information regarding ICSI children who do present difficulties (in contrast to the participating ICSI children), several indicators however can be considered as reassuring to this regard. Thus, it can be assumed that the ICSI families who were 'lost to follow-up' would be randomly distributed in the birth cohort, therefore not necessarily presenting more problems. Apart from these, 73% of the ICSI families who had actually been reached could also be assessed. Moreover, although the possibility of a participation bias cannot entirely be ruled out, we did gather information on around 83% of the eligible cohort (including the refusing families) by means of a telephone checklist concerning major medical events, learning difficulties and additional therapies. This allowed us to ascertain that no major problems were identified in the dropout ICSI group (Belva *et al.*, in press), suggesting that our findings are not biased by participant versus dropout ICSI populations. Likewise, a participation bias cannot be ruled out for the control group given the low response rate of 37%, which tends to be typical when participation is voluntary [e.g. recruitment not based on established (medical) structures such as a national birth registry existing in other countries, no financial rewards]. As a result, the recruited control group may have been biased towards children with either few or many problems. However, our findings on ICSI and SC children's cognitive and motor development are based on the use of statistically normed instruments, thus resulting from comparison with normative data for Dutch-speaking Belgian children (cf *Methods* and *Outcome measures*). Comparison of the mean and SD IQ's in our sample with the Belgian norms indicate that these are situated in the (above) average range.

The generalization of our findings may also be limited given that only children born after 32 weeks of gestation were included. It should be noted however that this inclusion criterion still contains children who were born as premature infants between 32 and 37 weeks of gestation, whose IQs were average to high in both groups regardless of possible major birth defects and low birth weights, which were not *per se* excluded from this study.

Regarding the impact of demographic factors in our analyses, high maternal educational levels contributed to the small amount of the variance in the FSIQ. These findings are consistent with the knowledge that children's intelligence scores, especially verbal ones, tend to be sensitive to stimulation, including a positive influence of higher maternal educational level in particular (Neiss and Rowe, 2000). Our regression analysis confirms this tendency, showing that both ICSI and SC children with highly educated mothers obtain higher FSIQ's, persistently so when analysing only the subsample of children with full demographic information (no missing data). However, one could suspect higher levels of education in the ICSI group given the amount of missing data on this variable in the control group. This assumption was confirmed by the additional analyses performed on subgroups of the sample; children with highly educated mothers in both groups have comparable IQs. When comparing children with full demographic data, the significant FSIQ difference reappeared. When finally assuming all children with missing data on maternal educational level had highly educated mothers, and comparing this 'new' sample of children with highly educated mothers in both groups, the significant FSIQ difference also reappeared. These analyses imply that indeed maternal educational level is responsible for the slightly higher intelligence scores in the ICSI group, through the missing data on this variable in the control group and the fact these mothers whose educational level was unknown probably were not highly educated. Additionally, because in our sample ICSI children's mothers were significantly older when they gave birth, it could be hypothesized that ICSI children's mothers being older when they give birth and overall highly educated tend to stimulate their children more.

From a more practical perspective, the small difference in IQ scores in favour of the ICSI children may also have been facilitated by the fact that these were accompanied by their parents at the hospital. Parental presence may have heightened immediate testing motivation for ICSI children, compared with children in the SC group who were tested in their schools without such potentially encouraging parental presence. Although the difference in testing situation was a practical necessity and the assessment measures were chosen for their relative robustness against immediate environmental influences, these cannot be entirely excluded for the ICSI group (Wechsler, 1974; Vander Steene *et al.*, 1986; Henderson and Sugden, 1998).

Finally, a broader contextual influence pertinent to the generation of ICSI children being investigated at present may contribute to the observed slight intellectual 'advantage' at age of 8 years. The children in this study are indeed part of the first generation of families in the world to use the ICSI technique. Given that ICSI was initially unknown to the public at large, we can suppose that the families constituting this initial cohort are 'privileged' to some extent, for instance as regards access to specialized (medical) information sources. This 'select first generation effect' may positively influence the outcomes of ICSI children currently studied. To cite Barnes *et al.* (2004), 'Families who conceived from fertility treatment are undoubtedly the successful ones, (...) a selected group whose intrinsic qualities have contributed to the success of their treatment'. Given the documented effects of contextual and family factors

on children's development, continuing follow-up research on subsequent ICSI cohorts from more socioeconomically and cultural-ethnically diverse populations are needed (Neiss and Rowe, 2000; Barnes *et al.*, 2004; Celestin-Westreich and Celestin, in press).

In conclusion, the results of the present study are reassuring regarding singleton ICSI children's cognitive and motor abilities up to middle elementary school age. Our findings so far suggest that these ICSI children do not suffer any significant developmental delay as compared with naturally conceived children, displaying at least average cognitive abilities. Further research should evaluate emotional, behavioural and family-relational components to investigate to what extent these conclusions apply to other areas of ICSI children's development. Also, the possible role of other personal, family and contextual variables in the development of children born after ICSI should be explored. As mentioned earlier, the follow-up of later cohorts will benefit from including socioculturally more diverse populations. Furthermore, given the pilot nature of research on ICSI youth, continuing follow-up is needed to make sure that they continue to do well, as is the case in currently ongoing reassessment of these children at ages 10 years and above.

Acknowledgements

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