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Development and health of 5 - 8-year-old singletons born after intracytoplasmic sperm injection.

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Chapter 3

Cognitive development of singletons
born after ICSI in comparison to IVF
and natural conception

3.

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Abstract

Objective: To investigate cognitive development of ICSI-singletons at 5-8 years of age.

Design: Follow-up study.

Setting: University medical centre, assessments between March 2004 and May 2005.

Patients: Singletons born between June 1996 and December 1999 following ICSI at the Leiden University Medical Center were compared with matched singletons born following IVF and natural conception (NC).

Intervention: Mode of conception.

Main outcome measure: IQ was measured with the Revised Amsterdam Child Intelligence Test (RAKIT, short form). The investigators were blinded to conception mode.

Results: ICSI-singletons (n=83) achieved lower IQ-scores than IVF-singletons (n=83) (adjusted mean difference IQ: 3.6, 95%CI [-0.8; 8.0]). After categorising IQ-outcomes into <85; 85-115; >115 no significant difference in the distribution of IQ was found (p=0.268). ICSI-singletons (n=86) achieved lower IQ-scores than NC-singletons (n=85); the adjusted mean difference varied between 5 and 7 points (5.6, 95%CI [0.9; 10.3]; 7.1, 95%CI [1.7 to 12.5]) depending on the covariates included in the model. Adjustment for prematurity did not change the results. Percentages in IQ-categories <85; 85-115; >115 were 12%; 64%; 24% for ICSI and 6%; 54%; 40% for NC (p=0.019).

Conclusion: In the relatively limited sample investigated, cognitive development among ICSI-singletons was lower than among IVF and NC-singletons. Infertility factors or unmeasured confounders may play a role.

Introduction

Artificial reproductive techniques (ART) such as in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) currently account for between 0.2-3.9% of childbirths in Europe.¹ Since the introduction of ICSI in 1992,² the health status and development of ICSI-children have been a matter of concern, as the technique is rather invasive.³⁻⁶ In ICSI, because the spermatozoon is selected by the laboratory technician and injected into the oocyte with a microinjection pipette, several natural selection barriers are bypassed. Fertilisation with spermatozoa of uncertain quality, and the possible damage caused by the in vitro manipulation of the oocyte warrant the study of possible long-term effects on ICSI-children.

In this study we compared the cognitive development of 5 - 8-year-old singletons that were born after an ICSI-procedure with two control groups: children born after standard in vitro fertilisation (IVF) and children born after natural conception (NC). ICSI and IVF-procedures are similar in maternal hormonal stimulation and in fertilisation taking place in vitro, but differ in sperm selection and oocyte penetration, which are not manipulated during IVF. By comparing ICSI-

children and IVF-children, we intended to investigate potential differences, given a similar background of an infertile couple, maternal hormonal stimulation and fertilisation in vitro. The second control group, consisting of children conceived naturally, was used to assess the cognitive outcome of ICSI-children compared to children born after natural conception in two ways: first we investigated the overall difference in cognitive development between ICSI and NC, as this represents the main clinical question of future ICSI-parents. Second, with a more biological approach, we investigated whether a net effect of ICSI existed on cognitive development as compared to NC, by controlling for known intermediate factors such as prematurity.⁷⁻⁹

All previous follow-up studies on the cognitive development of ICSI-children have concerned children up to the age of 5, except one.¹⁰ All studies but one¹¹ found no differences in cognitive development.^{10,12-18}

Our study assessed children beyond the age of 5. By strict selection, careful matching and adjustment for demographic variables, and by blinded assessment in a single centre, we aimed to enhance the validity of the comparisons between the different modes of conception.

Materials and methods

Institutional Review Board approval was obtained and at least one parent of each child signed for informed consent. The authors have no conflicts of interest to disclose. The assessments were carried out between March 2004 and May 2005.

Participants

Live birth ICSI-singletons born between June 1996 and December 1999 after fertility treatment in the Leiden University Medical Center laboratory were invited to participate. Exclusion criteria were: oocyte or sperm donation, cryopreservation of the embryo, and selective embryo reduction with medical indication. Similar criteria were used for the inclusion of IVF-children, who were selected to match person-to-person to the ICSI-participants on gender, socio-economic status, gestational age [preterm/term], maternal age at the time of pregnancy [± 3 years] and date of birth [closest]. Socio-economic status (low, medium, or high) was ascribed using the zip-code/socio-economic status indicator of Statistics Netherlands,¹⁹ which is based on home price and income. If no match was available within the maternal age range of ± 3 years, larger deviations were permitted.

Pre-schools and primary schools with zip-codes that indicated social class distributions similar to the ICSI-cohort assisted in the sampling of naturally conceived singletons. We applied group matching on gender, socio-economic status, and date of birth. As the NC-children all had a cognitive development sufficient to attend regular education until the age of assessment, we excluded ICSI-children attending special education from the ICSI/NC comparison. A similar restriction was not required in the ICSI/IVF comparison, as IVF-children had been recruited without prior information on education.

Demographical information on ICSI and IVF non-participants was obtained from the Leiden University Medical Center database to evaluate selection bias.

Response

One hundred and ten ICSI-children met the inclusion criteria. Overall response was 97/110 (88%), 87 children joined in (90% of responders, 79% of all children invited) and 10 refused for various reasons. Participants and non-participants were comparable for gender, maternal age, and gestational age (data not shown). The rate of participation was higher in the upper socio-economic groups (91% among high socio-economic status, 71% among medium status, and 59% among the low status group).

In the IVF group 257 children met the inclusion criteria, and 126 were invited to participate. Overall response was 100/126 (79%); 92 participated (92% of responders, 73% of all invited IVF-children) and 8 refused. A deviation in maternal age of more than +/- three years was permitted in 11 cases. Reasons for refusal to participate were similar to those for ICSI-families. The 92 IVF participants differed from the 34 non-participants by gender (among participants 49% were male vs. 71% among non-participants), but the groups were comparable for maternal age, gestational age and birth weight. The participation rates according to socio-economic status approximated those of the ICSI-group (high socio-economic status: 81%, medium: 73%, low: 50%). In five cases, two IVF-matches were available for an ICSI-child. The best match was selected and n= 92 was restricted to n= 87. Of the original 110 ICSI-children, eight had been born prematurely. Six enrolled on the study, but in four cases no premature IVF-match could be found, reducing the n to 83.

Sixteen schools participated in the recruitment of NC-children and 85 of the 87 children that applied met the inclusion criteria (one twin boy and one child born after intrauterine insemination were excluded). Forty-three children refused for various reasons. A response rate could not be estimated for the NC-group, as we did not know the exact size of the target group. However, of those who responded, 67% participated. The response was higher among NC-children of higher socio-economic status: of the 16 schools that participated 9 were approached specifically to obtain the group of 7 low socio-economic status children. One ICSI-boy (1%) attended special education and was therefore excluded from the ICSI/NC comparison (n=86).

Assessment and outcome measures

When the study began, the Dutch norms for the WISC III had not yet been approved and we chose to use the Revised Amsterdam Child Intelligence Test (RAKIT),²⁰ the short version. This test is applicable for children aged 4-11 years. The six subtests measure the subscales: perceptual reasoning (Exclusion, Discs, Hidden Figures), verbal learning (Verbal Meaning, Learning Names), spatial orientation and speed (Discs), and verbal fluency (Idea Production).²⁰ The test correlates 0.93 with the IQ of the complete version,²⁰ which was not applied because of time limitation. The sum score of the subtest scores (mean 15, SD 5) is translated into a short version RAKIT-IQ (mean 100, SD 15), allowing for child

age. Nine trained investigators administered the tests. The observers were scheduled independently of child characteristics and were blinded to the mode of conception.

General characteristics and additional information on the study groups were obtained through questionnaires.

Statistical analysis

For statistical analyses we used the SPSS 11.0 for Windows package (SPSS Inc., Chicago, IL). The principal investigator performed the data-analysis. To reach a power of 0.80 with a standard deviation of 15 and a minimal detectable difference of 7.5 IQ-points²¹ (half a standard deviation) ≥ 63 children had to be included per group. We compared continuous data using the Student's t-test with a significance level of 0.05 and linear regression analysis was applied to adjust for potential confounders. As ICSI and IVF-children had been matched person to person, paired testing was appropriate: paired t-tests and linear mixed model analysis with couple number as a random factor. Through ordinal regression analysis we analysed and adjusted categorical data. We performed a one-way ANOVA to assess potential differences in scoring between the investigators.

The ICSI-NC comparison was carried out to assess both the overall difference in cognitive development between ICSI and NC-children (clinical question), as well as the net difference (biological question). In answering the former question, the data were analysed without controlling for intermediate factors that are associated with both ART and cognitive outcome, such as prematurity.⁷⁻⁹ In answering the latter question, we indeed adjusted for these factors, assessing a potential net effect of ICSI on cognitive development.

Results

Characteristics

Table 1 compares the characteristics of the parents and children for the three groups. Maternal subfertility was more frequent among IVF-couples than among ICSI-couples, which was the inverse for paternal subfertility. ICSI-mothers had a lower frequency of pregnancy complications than IVF-mothers. Paternal educational level was lower in the ICSI-group (indexed according to the register of Statistics Netherlands)²³. Primary language spoken at home other than Dutch was 1% for ICSI-children and 4% for IVF-children. ICSI-fathers smoked more heavily than IVF-fathers. Furthermore the groups were comparable in drug use and excessive-drinking habits of the parents (data not shown).

When comparing the ICSI and NC-group, 74% of the ICSI-children were first-born versus 37% of the NC-children. The mean birth weight of ICSI-children was lower. ICSI-children showed a higher incidence of premature birth, low birth weight, small for gestational age characteristics, and caesarean sections than NC-controls. Parental mean ages were higher for ICSI-children. NC-controls were of higher socio-economic status and maternal educational level than ICSI-children.

Table 1. Characteristics of parents and children: ICSI versus IVF and ICSI versus NC

	ICSI n=83	IVF n=83	ICSI n=86	NC n=85
Gender: male, n(%)	41 (49)	41 (49)	43 (50)	47 (55)
Age at time of examination, mean	6.1 (5.3-7.7)	6.2 (5.3-8.3)§	6.1 (5.3-7.7)	6.3 (5.1-8.0)
Parity: first born, n(%)	63 (76)	61 (74)	64 (74)	31 (36)
Birth parameters				
gestational age, mean	40.0 (35-43)	39.7 (36-42)	39.9 (35-43)	39.8 (37-43)
birth weight, mean	3409 (1485-4750)	3349 (1725-4730)	3361 (1485-4750)	3555 (2300-4800)
prematurity (gest. age < 37 wks), n(%)	2 (2)	2 (2)	6 (7)	0 (0)
birth weight < 2500g, n(%)	5 (6)	4 (5)	7 (8)	1 (1)
small for gestational age †, n(%)	5 (6)	3 (4)	6 (7)	1 (1)
if Apgar score available, n(%)	59 (71)	58 (70)	59 (69)	62 (73)
Apgar 1 min < 5 or 5 min < 7, n(%)	2 (3)	2 (3)	2 (3)	1 (2)
Caesarean section, n(%)	12 (15)	10 (12)	12 (14)	6 (7)
Parental age at pregnancy, mean				
mother	32.8 (22-41)	33.4 (24-42)	33.0 (22-41)	30.6 (20-41)
father	36.9 (23-65)	37.2 (27-60)	37.0 (23-65)	32.6 (20-49)
Diagnosed infertility factor, n(%)				
mother	13 (16)	38 (46)	15 (17)	0 (0)
father	66 (80)	11 (13)	69 (80)	0 (0)
Pregnancy complications, n(%)	19 (23)	29 (35)	23 (27)	17 (20)
Medication during pregnancy, n(%)	10 (12)*	8 (10)	9 (11)*	14 (17)§
Smoking during pregnancy, n(%)				
mother	*		*	
no	72 (88)	72 (87)	76 (89)	75 (88)
yes, <10 per day	9 (11)	10 (12)	9 (11)	8 (9)
yes, >10 per day	1 (1)	1 (1)	0 (0)	2 (2)
father		‡		*
no	58 (70)	63 (78)	61 (71)	62 (74)
yes, <10 per day	8 (10)	11 (14)	9 (11)	15 (18)
yes, >10 per day	17 (21)	7 (9)	16 (19)	7 (8)
Ethnicity II, n(%)				
mother: non-Caucasian	7 (8)	9 (11)	9 (10)	8 (9)
father: non-Caucasian	8 (10)	8 (10)	10 (12)	11 (13)
Socio-economic status, n(%)				
low	8 (10)	8 (10)	10 (12)	7 (8)
medium	26 (31)	26 (31)	26 (30)	18 (21)
high	49 (59)	49 (59)	50 (58)	60 (71)

Level of education, n(%)				
mother		*		
no education	0 (0)	1 (1)	0 (0)	0 (0)
low	25 (30)	25 (31)	27 (31)	11 (13)
medium	28 (34)	29 (35)	28 (33)	37 (44)
high	30 (36)	27 (33)	31 (36)	37 (44)
father	*		*	
no education	0 (0)	2 (2)	0	1 (1)
low	28 (34)	27 (33)	31 (36)	22 (26)
medium	26 (32)	16 (19)	25 (29)	26 (31)
high	28 (34)	38 (46)	29 (34)	36 (42)
child	*		*	
regular pre-/primary school	72 (88)	69 (83)	76 (89)	79 (93)
regular school, repeat class	7 (9)	8 (10)	7 (8)	4 (5)
regular school, remedial teaching	2 (2)	2 (2)	2 (2)	2 (2)
special education	1 (1)	4 (5)	0	0

* 1 missing value

† Sweden, Niklasson²²: birth weight for gestational age < -2SDS

‡ 2 missing values

§ 3 missing values

|| Turkey classified under non-Caucasian

bold: differences considered as of potential confounding effect

Primary language other than Dutch spoken at home was 1% among ICSI-children and 5% among the NC control group. ICSI-fathers tended to smoke more heavily than the NC-fathers who smoked. Furthermore the groups were comparable in drug use and excessive-drinking habits of the parents (data not shown).

Cognitive Development

The outcomes of cognitive developmental testing are listed in Table 2 and 3 and Figure 1. No difference was found by analysis of variance (ANOVA) among the mean IQ-scores for the nine investigators (p=0.843). Three IVF-children did not undergo the RAKIT because of (i) developmental delay of the child (n=2, an estimated total IQ-score of 84 was assigned) and (ii) many previous hospital visits due to a congenital malformation (n=1, regular education, no score assigned). The latter child was thus excluded from the analyses of cognitive development, but as congenital malformations were studied in parallel, the child was not replaced by another.

Table 2. Mean RAKIT-IQ and mean subtest scores

	ICSI n=83	IVF n=82	Crude difference [95% Confidence Interval]
Mean RAKIT-IQ	103	107	3.9 [-0.7; 8.4]
Mean subtest scores:	n=83	n=80	
Exclusion	15.4	16.8	1.3 [-0.2; 2.9]
Verbal Meaning	16.1	17.3	1.1 [-0.6; 2.8]
Discs	15.3	15.7	0.4 [-1.2; 2.0]
Learning Names	15.5	16.8	1.2 [-0.2; 2.7]
Hidden Figures	16.4	16.8	0.3 [-1.4; 2.1]
Idea Production	15.2	16.3	1.0 [-0.6; 2.6]

	ICSI n=86	NC n=85	Crude difference [95% Confidence Interval]
Mean RAKIT-IQ	103	110	6.8 [2.0; 11.6]
Mean subtest scores:			
Recognise Figures*	-	13.0	-
Exclusion	15.4	16.3	0.9 [-0.6; 2.3]
Verbal Meaning	16.1	17.9	1.8 [0.3; 3.4]
Discs	15.3	16.0	0.7 [-0.8; 2.1]
Learning Names*	15.5	17.5	1.9 [0.4; 3.5]
Hidden Figures*	16.3	18.4	2.1 [0.5; 3.6]
Idea Production	15.3	16.6	1.3 [-0.3; 2.8]

* if child age <5.2 years: Learning Names and Hidden Figures are replaced by Recognise Figures;
 NC: Recognise Figures n=1, Learning Names n=84 and Hidden Figures n=84.

bold p<0.05

The mean RAKIT-IQ for ICSI-children was 3.9 points lower than for IVF-children (103 vs. 107; 95%CI [-0.7; 8.4]) (Table 2). Mean subtest scores were all lower in the ICSI-group, with mean differences ranging from 0.3 to 1.3 points. The largest differences were found for the subtests Exclusion and Learning Names. The results were consistent in age categories <6; 6-7; 7-8; >8. The difference among boys was greater than among girls (mean difference boys 5.4, 95%CI [-2.6; 13.4]; girls 2.4, 95%CI [-4.0; 8.8]). When the continuous RAKIT-IQ was divided into three categories based on the standard deviation, the percentages in each group were as follows: IQ <85 ICSI 11% vs. IVF 9%; IQ 85-115 ICSI 65% vs. IVF 60%; IQ >115 ICSI 24% vs. IVF 32% (ordinal regression analysis p=0.268) (Figure 1).

Adjustment of the crude mean difference of 3.9 for the characteristics in which ICSI and IVF had differed (i.e. paternal education and pregnancy complications (Table 1)) resulted in a decrease of the difference to 3.6 95%CI [-0.8; 8.0] (Table 3). The minimal change was due to the opposite influence of pregnancy complications and paternal education. Correction for paternal smoking had no further effect. The adjusted p-value for the difference in distribution over the three IQ-categories was 0.303.

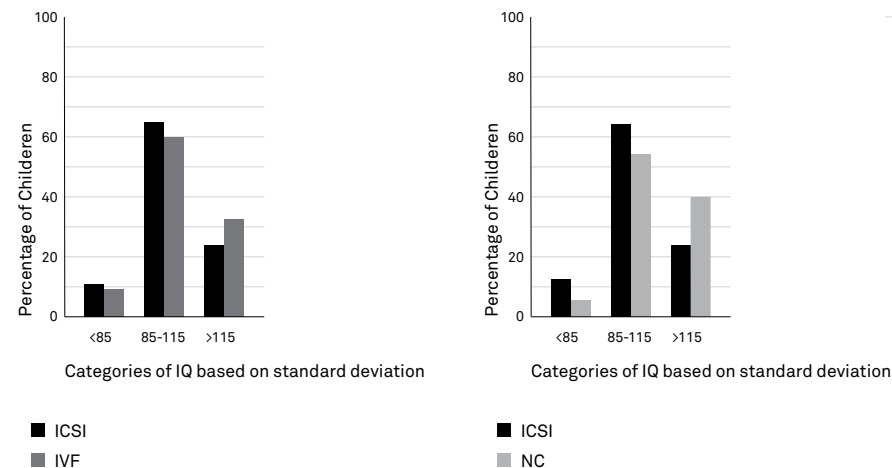


Figure 1. Percentage of children with IQ-scores <85, 85-115, and >115: ICSI versus IVF (p=0.268) and ICSI versus NC (p=0.019)

When comparing ICSI-children with NC-controls, both groups attending regular education, we found a difference in mean RAKIT-IQ of nearly 7 points in favour of NC-controls (ICSI 103, NC 110, mean difference 6.8, 95%CI [2.0; 11.6]) (Table 2). ICSI-children performed worse on all subtests with differences in mean scores ranging from 0.7 to 2.1. Significance was reached for the subtests Verbal Meaning, Learning Names and Hidden Figures. The results were consistent in age categories <6; 6-7; 7-8; >8 and for gender. In the three IQ-categories based on the standard deviation, the percentages were: IQ <85 ICSI 12% vs. NC 6%; IQ 85-115 ICSI 64% vs. NC 54%; IQ >115 ICSI 24% vs. NC 40% (ordinal regression analysis p=0.019) (Figure 1).

Regarding the clinical question, about the overall difference in cognitive development between ICSI and NC-children, the adjusted difference varied between 5 and 7 (Table 3), with the confidence intervals excluding zero. The two models included the main variables that are generally considered important in determining a child's IQ and in which the groups differed; with exception of variables that are assumed to be in the causal pathway from artificial conception procedure to intelligence outcome. The difference in paternal smoking habits did not account for the difference in IQ. The adjusted p-values for the difference in distribution over the three IQ-categories were 0.045 and 0.064. Regarding the biological question, about the net difference, we additionally adjusted for: caesarean section, premature birth, birth weight, low birth weight and small for gestational age (Table 3). Due to an effect of low birth weight, the adjusted mean difference decreased to 5.0, 95%CI [0.2; 9.8]. The p-value for the difference in distribution over the three IQ-categories was 0.067 after correction for maternal education, parity, socio-economic status, prematurity, and low birth weight.

Table 3. Linear regression analysis on the effect of conception mode on IQ-score

ICSI and IVF	Mean difference*	95%CI
Conception crude	3.9	[-0.7; 8.4]
<i>Adjustment for:</i>		
paternal education, pregnancy complications	3.6	[-0.8; 8.0]
ICSI and NC	Mean difference †	95%CI
Conception crude	6.8	[2.0; 11.6]
<i>Clinical question, adjustment for:</i>		
maternal education, parity, SES ‡	5.6	[0.9; 10.3]
maternal education, parity, SES, maternal age, paternal age	7.1	[1.7; 12.5]
<i>Biological question, adjustment for:</i>		
maternal education, parity, SES, caesarian section	5.6	[0.9; 10.3]
maternal education, parity, SES, prematurity	5.4	[0.5; 10.2]
maternal education, parity, SES, birth weight	5.7	[0.9; 10.4]
maternal education, parity, SES, low birth weight	5.0	[0.2; 9.8]
maternal education, parity, SES, small for gestational age	5.5	[0.7; 10.2]
maternal education, parity, SES, prematurity, low birth weight	5.1	[0.3; 9.9]

* in favour of IVF

† in favour of NC

‡ SES = socio-economic status

The number of children attending special education was 1 out of 83 (1.2%) among ICSI-children and 4 of 83 (4.8%) among IVF-children; of the latter four, two had been born preterm. In the total group of ICSI-children, including prematurely born children, 1 of 87 (1.1%) followed special education. In the Dutch population 1.0% of children aged 5-7 years attended special schools in 2004/2005.²⁴

Discussion

This study of the cognitive development of 5 - 8-year-old ICSI-children has found a lower adjusted mean IQ (not statistically significant) among ICSI-children in comparison with IVF-children and a lower adjusted mean IQ (statistically significant) among ICSI-children relative to naturally conceived controls. As compared to NC-children, ICSI-children had statistically significant lower scores on three subtests (verbal learning and perceptual reasoning scales) and the IQ-distribution in total shifted to lower IQ-scores. The percentage of ICSI-children attending special education was similar to the reference population.²⁴

The difference in IQ between ICSI and IVF-children was 3.6 points and was greater in boys than in girls. Based on this study, the IQ of children conceived through ICSI may be expected to be between 5 and 7 points lower than of those conceived naturally, among parents with similar characteristics up to the time of conception. The net difference in IQ between ICSI and NC-children, i.e. the difference after additional adjustment for prematurity, (low) birth weight, small for gestational age status, and caesarean section, was 5 points.

ICSI and IVF-children were invited independently of school performance and could be analysed without limitations. Because all NC-controls were recruited from regular pre- and primary schools, the ICSI-NC comparison was restricted to children attending regular education.

Assigning an estimated score of 84 to the IVF-girls with developmental delay might be an overestimation of their skills. Assigning a score of 70 would have resulted in an adjusted mean IQ-difference between ICSI and IVF of 3.2 [-1.2; 7.7].

The use of multiple observers did not influence our results as they were blinded and haphazardly distributed over the children. Besides, the analysis of variance showed no differences in IQ-scores between the investigators.

The clinical significance of the differences in IQ between ICSI-children and both IVF and NC-controls is debatable. On the one hand, the mean IQ of ICSI-children was within the normal range and the mean differences of 3-7 points were less than half a standard deviation (population mean of 100, standard deviation 15; Dutch children attending regular education, 1987)²⁰. On the other hand, a shift of the total ICSI-population to lower IQs may result in children crossing borders at the lower edge of the normal range. Indeed, ICSI-children more often scored <85 than NC-children.

Strengths and weaknesses of the study

The strength of this study lies in the assessment within a single centre/laboratory, the careful selection criteria, the matched and controlled design, and the blinded assessment of each individual child. We have compared ICSI-children with both IVF-children and children born after natural conception. Additionally, we have assessed the children at a later age, which increases the predictive value of the test outcomes.²⁵

Our sample size is not large, but this is less important in a study with positive (difference found) than with negative results (no difference found). Larger sample sizes permit controlling for multiple confounders. By strict matching we have decreased the number of confounders to control for and as a consequence the precision of our results is fairly high despite the smaller sample size.

With response rates of 79% and 73% we assume that the samples are representative of the population of ICSI and IVF-children at this centre. Selection bias could have occurred if parents decided to enrol their child based on the child's (low or high) developmental status and if this selection differed between the ICSI and IVF-group. However, with the common background of infertility we have assumed that ICSI and IVF-parents had comparable motives to participate and that selection bias will not have influenced our results. The higher rate of participation among

upper socio-economic status families will not have influenced our outcomes as we matched for socio-economic status and the rates were comparable between ICSI and IVF. The higher rate of male gender in IVF non-participants (n=34) was unexpected and could not be explained.

A limitation of our study was that 4 of the 6 preterm ICSI-children were excluded as we had difficulty finding a matching preterm IVF-child. Our conclusions therefore mainly apply to full-term ICSI and IVF-children.

The representativeness of the natural conception control group might be a point of discussion. This group may have been subject to selection as we cannot examine potential differences between responders and non-responders. The low socio-economic status group might have been at highest risk for selection bias, as of the 16 schools that participated, 9 were schools with low socio-economic status, while eventually only seven control children with low socio-economic status applied. In the ICSI-group, 59% of low socio-economic status children participated. Excluding the children of low socio-economic status from the ICSI versus NC analysis indeed resulted in a decrease of the adjusted difference from 5.6 to 4.5 [-0.4; 9.4]. An argument against selection bias might be found in the fact that the direction of the difference in IQ was similar to the difference when ICSI and IVF-children were compared.

When comparing ICSI and IVF-children, the effect of the procedure can never be detached from the type of underlying infertility, since ICSI will be the treatment of choice in couples with male infertility, while in couples with female infertility IVF will generally be offered first. A comparable drawback in the comparison of ICSI and NC was that known important differences between the ICSI and NC-group were adjusted for, but we could not assure that we allowed for all appropriate factors (residual confounding). Obtaining parental IQ-scores would have been a valuable extension.

Related studies

With one exception,¹¹ previous studies comparing the cognitive development of ICSI and IVF-children found no differences.^{12-14,16} Bowen et al.¹¹ showed that ICSI-children had a lower mean developmental score than IVF-children, a difference that was larger among boys than girls – as discussed by Te Velde et al.²⁶ Our findings are in line with those of Bowen et al., but their study has been criticised for using an unstandardised testing system, insufficient adjustment for demographic differences between groups, and inclusion of cryo and multiple pregnancies.^{5,13,26,27} However, the majority of studies had one or more of these or other limitations (e.g. low response rates, young age of the study group, unblinded observers).^{12-14,16} In the present study we accounted for these important points of critique.

No indication of delayed cognitive development in ICSI versus NC-children has been found^{10,14-18} apart from the report of Bowen et al.¹¹ Leunens et al.,¹⁰ reported higher IQ-levels in 151, 8-year-old ICSI-singletons as compared to 153 NC-controls, although this effect might have been due to a difference in maternal educational level. In their study, the higher prevalence of prematurity in the NC-group combined with the lower IQ-scores of premature NC-children as compared to term NC-children

may have also lowered the mean IQ-scores of the NC-group. The study by Ponjaert-Kristoffersen et al.¹⁶ was potentially the most reassuring, finding no differences in cognitive development between ICSI and NC-children, including 511 ICSI and 488 NC-children at age 4.5-5.5 years and allowing for appropriate matching and correction. Why our findings in children aged 5-8 years differ substantially is unclear, although of course we examined a different population of children.

In conclusion, in the relatively limited sample investigated, the cognitive development (IQ) of 5 - 8-year-old ICSI-singletons was slightly lower than of matched IVF and NC-children. We tried to safeguard the validity of our results by using blinded observers and by careful matching of singleton children between the ICSI and the IVF-group. Although selection bias and unmeasured confounders may still play a role in the origin of these differences, an effect of ICSI per se cannot be excluded.

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