Cognitive development of singletons born after intracytoplasmic sperm injection compared with in vitro fertilization and natural conception

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Objective: To investigate cognitive development of singletons conceived by intracytoplasmic sperm injection (ICSI) at 5–8 years of age.
Design: Follow-up study.
Setting: University medical center, assessments between March 2004 and May 2005.
Patient(s): Singletons born between June 1996 and December 1999 after ICSI at the Leiden University Medical Center were compared with matched singletons born after IVF and natural conception (NC).
Intervention(s): Mode of conception.
Main Outcome Measure(s): Intelligence quotient (IQ) was measured with the Revised Amsterdam Child Intelligence Test (short form). The investigators were blinded to conception mode.
Result(s): Singletons conceived by ICSI (n = 83) achieved lower IQ scores than IVF singletons (n = 83) (adjusted mean difference IQ: 3.6 [95% confidence interval (CI) −0.8, 8.0]). After categorizing IQ outcomes (<85, 85–115, >115), no significant difference in the distribution of IQ was found. Singletons conceived by ICSI (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, 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, and >115 were 12%, 64%, and 24% for ICSI and 6%, 54%, and 40% for NC, respectively.
Conclusion(s): 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. (Fertil Steril® 2008;90:289–96. ©2008 by American Society for Reproductive Medicine.)

Key Words: ICSI, IVF, child development, intelligence

Artificial reproductive techniques (ART) such as IVF and intracytoplasmic sperm injection (ICSI) currently account for between 0.2% and 3.9% of childbirths in Europe (1). Because ICSI is a rather invasive technique (2–5), the health status and development of ICSI children have been a matter of concern since its introduction in 1992 (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. Fertilization 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.

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In this study we compared the cognitive development of 5–8-year-old singletons who were born after an ICSI procedure with two control groups: children born after standard IVF and children born after natural conception (NC). The procedures for ICSI and IVF are similar in maternal hormonal stimulation and in fertilization 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 fertilization in vitro. The second control group, consisting of children conceived naturally, was used to assess the cognitive outcome of ICSI children compared with children born after natural conception in two ways. First, we investigated the overall difference in cognitive development between ICSI and NC children, because this represents the main clinical question of future ICSI parents. Second, with a more biologic approach, we investigated whether a net effect of ICSI existed on cognitive development as compared with NC, by controlling for known intermediate factors, such as prematurity (7–9).

With one exception (10), all previous follow-up studies on the cognitive development of ICSI children have concerned children up to the age of 5 years. All studies but one (11) found no differences in cognitive development (10, 12–18).

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

MATERIALS AND METHODS

Institutional review board approval was obtained. At least one parent of each child provided written 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 at 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 the ICSI participants person to person in terms of gender, socioeconomic status, gestational age (preterm/term), maternal age at the time of pregnancy (±3 years), and date of birth (closest). Socioeconomic status (low, medium, or high) was ascribed using the zip code/socioeconomic 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.

Preschools and primary schools with zip codes that indicated social class distributions similar to those of the ICSI cohort assisted in the sampling of NC singletons. We applied group matching on gender, socioeconomic status, and date of birth. Because 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 because IVF children had been recruited without prior information on education.

Demographic information on ICSI and IVF nonparticipants was obtained from the Leiden University Medical Center database to evaluate selection bias.

Response

A total of 110 ICSI children met the inclusion criteria. Overall response was 97 of 110 (88%); 87 children joined (90% of responders, 79% of all children invited), and 10 refused for various reasons. Participants and nonparticipants were comparable for gender, maternal age, and gestational age (data not shown). The rate of participation was higher in upper socioeconomic groups (91% among high socioeconomic 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 of 126 (79%); 92 participated (92% of responders, 73% of all invited IVF children), and 8 refused. A deviation in maternal age of more than ±3 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 nonparticipants by gender (among participants 49% were male vs. 71% among nonparticipants), but the groups were comparable for maternal age, gestational age, and birth weight. The participation rates according to socioeconomic status approximated those of the ICSI group (high socioeconomic 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, 8 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 who applied met the inclusion criteria (one twin boy and one child born after IUI were excluded). Forty-three children refused for various reasons. A response rate could not be estimated for the NC group because 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 socioeconomic status: of the 16 schools that participated, 9 were approached specifically to obtain the group of 7 low-socioeconomic-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 Wechsler Intelligence Scale for Children-III had not yet been approved, and we chose to use the short version of the Revised Amsterdam Child Intelligence Test (RAKIT) (20). 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 intelligence quotient (IQ) of the complete version (20), which was not applied because of time limitations. 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

We used commercial software for statistical analyses (SPSS 11.0 for Windows; SPSS Inc., Chicago, IL). The principal investigator performed the data analysis. To reach a power of 0.80 with a SD of 15 and a minimal detectable difference of 7.5 IQ points (21) (half an SD), ≥63 children had to be included per group. We compared continuous data using Student's *t*-test with a significance level of 0.05, and linear regression analysis was applied to adjust for potential confounders. Because 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 analyzed and adjusted categorical data. We performed a one-way analysis of variance 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 (biologic question). In answering the former question, the data were analyzed 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; the inverse was true for paternal subfertility. The percentage of mothers with one or more pregnancy complications (hypertension, pre-eclampsia, gestational diabetes, ovarian hyperstimulation syndrome, extrauterine gravidity, prematurity, vanishing twin, or other) was lower among ICSI than among 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. The ICSI fathers smoked more heavily than the IVF fathers (data not shown). Furthermore, the groups were comparable in terms of drug use and excessive drinking habits of the parents (data not shown).

When comparing the ICSI and NC groups, ICSI parents were older at the time of pregnancy, and ICSI mothers had lower educational levels. Delivery by cesarean section was more frequent in the ICSI group. Seventy-four percent of the ICSI children were firstborn, compared with 37% of the NC children. The mean birth weight of ICSI children was lower. The ICSI children showed a higher incidence of premature birth, low birth weight, and small for gestational age characteristics than NC controls. The ICSI controls were of lower socioeconomic status than the NC children. Primary language other than Dutch spoken at home was 1% among ICSI children and 5% among the NC control group. The ICSI fathers tended to smoke more heavily than the NC fathers who smoked. Furthermore, the groups were comparable in terms of drug use and excessive drinking habits of the parents (data not shown).

Cognitive Development

The outcomes of cognitive developmental testing are listed in Tables 2 and 3 and Figure 1. No difference was found by analysis of variance among the mean IQ scores for the nine investigators (P=.843). Three IVF children did not undergo the RAKIT because of [1] developmental delay of the child (n = 2; an estimated total IQ score of 84 was assigned), and [2] 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 because congenital malformations were studied in parallel, the child was not replaced by another.

The mean RAKIT IQ for ICSI children was 3.9 points lower than for IVF children (103 vs. 107; 95% confidence interval [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 years, 6 to 7 years, 7 to 8 years, and >8 years). The difference among boys was greater than among girls (mean difference boys 5.4 [95% CI −2.6, 13.4]; mean difference girls 2.4 [95% CI −4.0, 8.8]). When the continuous RAKIT IQ was divided into three categories according to SD, 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=.268) (Fig. 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. The adjusted P value for the difference in distribution over the three IQ categories was .303.

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 favor of NC controls (ICSI 103, NC 110; mean difference 6.8 [95% CI 2.0, 11.6]) (Table 2). The 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 years, 6 to 7 years, 7 to 8 years, and >8 years) and for gender. In the three IQ categories based on the SD, the percentages were as follows: IQ <85: ICSI 12% vs.

TABLE 1

Characteristics of parents and children: ICSI vs. IVF and ICSI vs. NC.

	ICSI (n = 83)	IVF (n = 83)	ICSI (n = 86)	NC (n = 85)
Maternal characteristics				
Age at pregnancy (y)	32.8 (22–41)	33.4 (24–42)	33.0 (22–41)[a]	30.6 (20–41)[a]
Diagnosed infertility factor	13 (16)[a]	38 (46)[a]	15 (17)[a]	0[a]
Ethnicity: non-Caucasian[b]	7 (8)	9 (11)	9 (10)	8 (9)
Level of education				
No education	0	1 (1)[c]	0[a]	0[a]
Low	25 (30)	25 (31)	27 (31)[a]	11 (13)[a]
Medium	28 (34)	29 (35)	28 (33)[a]	37 (44)[a]
High	30 (36)	27 (33)	31 (36)[a]	37 (44)[a]
Smoking during pregnancy				
No	72 (88)[c]	72 (87)	76 (89)[c]	75 (88)
Yes, <10 per day	9 (11)	10 (12)	9 (11)	8 (9)
Yes, >10 per day	1 (1)	1 (1)	0	2 (2)
Pregnancy complications	19 (23)[a]	29 (35)[a]	23 (27)	17 (20)
Cesarean section	12 (15)	10 (12)	12 (14)[a]	6 (7)[a]
Paternal characteristics				
Age at pregnancy (y)	36.9 (23–65)	37.2 (27–60)	37.0 (23–65)[a]	32.6 (20–49)[a]
Diagnosed infertility factor	66 (80)[a]	11 (13)[a]	69 (80)[a]	0[a]
Ethnicity: non-Caucasian[b]	8 (10)	8 (10)	10 (12)	11 (13)
Level of education				
No education	0[a,c]	2 (2)[a]	0[c]	1 (1)
Low	28 (34)[a]	27 (33)[a]	31 (36)	22 (26)
Medium	26 (32)[a]	16 (19)[a]	25 (29)	26 (31)
High	28 (34)[a]	38 (46)[a]	29 (34)	36 (42)
Child characteristics				
Gender: male	41 (49)	41 (49)	43 (50)	47 (55)
Age at time of examination	6.1 (5.3–7.7)	6.2 (5.3–8.3)[d]	6.1 (5.3–7.7)	6.3 (5.1–8.0)
Parity: first born	63 (76)	61 (74)	64 (74)[a]	31 (36)[a]
Birth parameters				
Gestational age	40.0 (35–43)	39.7 (36–42)	39.9 (35–43)	39.8 (37–43)
Birth weight (g)	3409 (1485–4750)	3349 (1725–4730)	3361 (1485–4750)[a]	3555 (2300–4800)[a]
Prematurity (gestational age <37 wk)	2 (2)	2 (2)	6 (7)[a]	0[a]
Birth weight <2500 g	5 (6)	4 (5)	7 (8)[a]	1 (1)[a]
Small for gestational age[e]	5 (6)	3 (4)	6 (7)[a]	1 (1)[a]
If Apgar score available	59 (71)	58 (70)	59 (69)	62 (73)
Apgar 1 min <5 or 5 min <7	2 (3)	2 (3)	2 (3)	1 (2)
Socioeconomic status				
Low	8 (10)	8 (10)	10 (12)[a]	7 (8)[a]
Medium	26 (31)	26 (31)	26 (30)[a]	18 (21)[a]
High	49 (59)	49 (59)	50 (58)[a]	60 (71)[a]
Education	72 (88)[c]	69 (83)	76 (89)[c]	79 (93)
Regular pre-/primary school				
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

Note: Values are number (percentage) or mean (range).

[a] Differences considered as of probable confounding effect.

[b] Turkish children classified under non-Caucasian.

[c] One missing value.

[d] Three missing values.

[e] Sweden, Niklasson et al. (22): birth weight for gestational age < −2 SD.

Knoester. IQ of ICSI children aged 5–8 years. Fertil Steril 2008.

TABLE 2

Mean RAKIT IQ and mean subtest score.

	ICSI (n = 83)	IVF (n = 82)	Crude difference (95% CI)	ICSI (n = 86)	NC (n = 85)[a]	Crude difference (95% CI)
Mean RAKIT IQ	103	107	3.9 (−0.7, 8.4)	103	110	6.8 (2.0, 11.6)[b]
Mean subtest scores	(n = 83)	(n = 80)				
Recognize Figures[c]				—	13.0	—
Exclusion	15.4	16.8	1.3 (−0.2, 2.9)	15.4	16.3	0.9 (−0.6, 2.3)
Verbal Meaning	16.1	17.3	1.1 (−0.6, 2.8)	16.1	17.9	1.8 (0.3, 3.4)[b]
Discs	15.3	15.7	0.4 (−1.2, 2.0)	15.3	16.0	0.7 (−0.8, 2.1)
Learning Names[c]	15.5	16.8	1.2 (−0.2, 2.7)	15.5	17.5	1.9 (0.4, 3.5)[b]
Hidden Figures[c]	16.4	16.8	0.3 (−1.4, 2.1)	16.3	18.4	2.1 (0.5, 3.6)[b]
Idea Production	15.2	16.3	1.0 (−0.6, 2.6)	15.3	16.6	1.3 (−0.3, 2.8)

[a] Recognize Figures, n = 1; Learning Names, n = 84; Hidden Figures, n = 84.
[b] $P<.05$.
[c] If child aged <5.2 y old, Learning Names and Hidden Figures are replaced by Recognize Figures.

Knoester. IQ of ICSI children aged 5–8 years. Fertil Steril 2008.

NC 6%; IQ 85–115: ICSI 64% vs. NC 54%; IQ >115: ICSI 24% vs. NC 40% (ordinal regression analysis, $P=.019$) (Fig. 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 adjusted P values for the difference in distribution over the three IQ categories were .045 and .064. Regarding the biologic question, about the net difference, we additionally adjusted for cesarean section, premature birth, birth weight, low birth weight, and small for gestational age (Table 3). Because of an effect of low birth weight, the adjusted mean difference decreased to 5.0 (95% CI 0.2, 9.8). The

TABLE 3

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

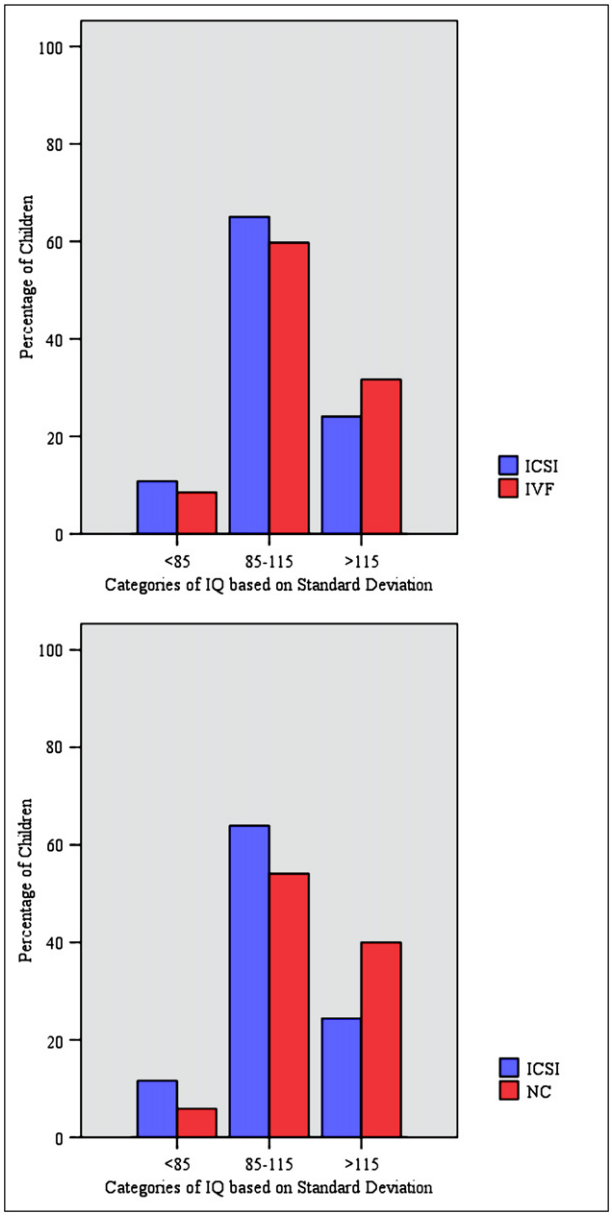
	Mean difference[a]	95% CI
ICSI and IVF		
Conception crude	3.9	(−0.7, 8.4)
Adjustment for: paternal education, pregnancy complications	3.6	(−0.8, 8.0)
ICSI and NC		
Conception crude	6.8	(2.0, 11.6)
Clinical question, adjustment for:		
Maternal education, parity, SES	5.6	(0.9, 10.3)
Maternal education, parity, SES, maternal age, paternal age	7.1	(1.7, 12.5)
Biological question, adjustment for:		
Maternal education, parity, SES, cesarean 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)

Note: SES = socioeconomic status.
[a] In favor of IVF in the ICSI–IVF comparison; in favor of NC in the ICSI–NC comparison.

Knoester. IQ of ICSI children aged 5–8 years. Fertil Steril 2008.

FIGURE 1

Percentage of children with IQ-scores <85, 85–115, and >115: ICSI vs. IVF (P=.268) and ICSI vs. NC (P=.019).



Knoester. IQ of ICSI children aged 5–8 years. Fertil Steril 2008.

P value for the difference in distribution over the three IQ categories was .067 after correction for maternal education, parity, socioeconomic status, prematurity, and low birth weight.

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 4, 2 had been born preterm. In the total group of ICSI children, including prematurely born children, 1 of 87 (1.1%) attended 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 compared with IVF children and a lower adjusted mean IQ (statistically significant) among ICSI children relative to NC controls. Compared with 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 that in the reference population (24).

The difference in IQ between ICSI and IVF children was 3.6 points and was greater among boys than girls. On the basis of this study, the IQ of children conceived through ICSI may be expected to be between 5 and 7 points lower than that 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 cesarean section) was 5 points.

The ICSI and IVF children were invited independently of school performance and could be analyzed 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 (95% CI −1.2, 7.7).

The use of multiple observers did not influence our results because they were blinded and haphazardly distributed over the children. Besides, the analysis of variance showed no differences in IQ scores between 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 SD (population mean of 100, SD 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 center/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 center. Selection bias could have occurred if parents decided to enroll their child on the basis of the child's (low or high) developmental status and if this selection differed between the ICSI and IVF groups. 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 socioeconomic status families will not have influenced our outcomes because we matched for socioeconomic status and the rates were comparable between ICSI and IVF. The higher rate of male gender in IVF nonparticipants (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 because 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 NC control group might be a point of discussion. This group may have been subject to selection because we cannot examine potential differences between responders and nonresponders. The low socioeconomic status group might have been at highest risk for selection bias, because of the 16 schools that participated, 9 were schools with low socioeconomic status, although eventually only 7 control children with low socioeconomic status applied. In the ICSI group, 59% of low socioeconomic status children participated. Excluding the children of low socioeconomic status from the ICSI vs. NC analysis indeed resulted in a decrease of the adjusted difference, from 5.6 to 4.5 (95% CI −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, because ICSI will be the treatment of choice in couples with male infertility, whereas in couples with female infertility IVF will generally be offered first. Another drawback in both the ICSI–IVF and the ICSI–NC comparison was that we adjusted for known important differences between the groups, but we could not ensure that we allowed for all appropriate factors. For example, we used socioeconomic status and parental education as a proxy for parental cognitive ability, which is an important predictor of the child's cognitive development (14, 26). In future research, parental IQ scores should be obtained if possible.

Related Studies

With one exception (11), previous studies comparing ICSI and IVF children found no difference in cognitive development (12–14, 16). Our results are in line with those of Bowen et al. (11), who found a difference in cognitive development between ICSI and IVF children; this was larger among boys than girls, as discussed by te Velde et al. (27). The Bowen et al. study has been criticized for using an unstandardized testing system, insufficient adjustment for demographic differences between groups, and inclusion of cryo and multiple pregnancies (4, 13, 27, 28). 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 vs. 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 with 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 with 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, including 511 ICSI 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. We used a different test instrument (RAKIT [20]) than Ponjaert-Kristoffersen et al. (Wechsler Preschool and Primary Scale of Intelligence Revised [29]) (16); however, both instruments are validated, and both studies compared the three conception groups with the same instrument. Another explanation may be that differences in parental IQ existed between the three conception groups within the two studies.

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 groups. 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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