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Matched follow-up study of 5–8-year-old ICSI singletons: child behaviour, parenting stress and child (health-related) quality of life

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BACKGROUND: Psychosocial follow-up of ICSI children is scarce. We compared child behaviour, parenting stress and quality of life for singletons aged 5–8 years born after ICSI, IVF and natural conception (NC). METHODS: All singletons born between June 1996 and December 1999 after ICSI in the Leiden University Medical Center were invited ($n = 110$). Matched singletons born after IVF and NC were recruited. Parents completed the Child Behaviour Checklist (measures problem behaviour), the Parenting Stress Index (Nijmeegse Ouderlijke Stress Index) and two quality of life questionnaires (Dux25 and TACQOL). Children completed the Dux25 Child form. RESULTS: Eighty-seven ICSI children (79%), 92 IVF children (73%) and 85 NC children enrolled. Prevalence of behavioural disorders—as reported by the parents—was comparable in the three groups. Three of 87 ICSI children had autism or an autistic spectrum disorder (ASD). Problem behaviour scores were similar for ICSI and NC children; IVF children (mainly girls) scored less problem behaviour ($P < 0.05$) and their scores were less often in the (borderline) clinical range. Parenting stress was similar for ICSI and IVF, but lower for NC than ICSI parents, mainly on the child scale. Quality of life scores were similar in the three conception groups. CONCLUSIONS: Prevalence of autism/ASD seemed higher after ICSI, but this unexpected finding should be confirmed by future studies with larger group sizes. ICSI parents experienced more stress than NC parents, although selection bias cannot be ruled out. The majority of ICSI singletons assessed at age 5–8 years showed a normal psychosocial well-being.

Keywords: ICSI; behaviour; parenting stress; quality of life

Introduction

Since the introduction of ICSI in 1992, follow-up studies on ICSI children have investigated the potential negative influences of this invasive artificial reproduction technique on health and development. Except for an increased risk of congenital malformations (Hansen *et al.*, 2005) and adverse perinatal outcomes (Schieve *et al.*, 2004), most studies report that ICSI children have similar health and development as their naturally conceived (NC) peers up to the age of 8 years (Leunens *et al.*, 2006; Belva *et al.*, 2007).

Follow-up on psychosocial development of ICSI offspring and their families is scarce (Barnes *et al.*, 2004; Ponjaert-Kristoffersen *et al.*, 2004; Sutcliffe *et al.*, 2004). Hypothetically, ICSI children might be at risk for emotional and behavioural difficulties as a result of the parental history of infertility and its potential negative sequelae. First, parental feelings of incompetence or low self-esteem, high expectations of parenthood and child's achievements, and overprotection of the precious child may reflect negatively on the child's psychosocial development. Second, ICSI children are more often born preterm and prematurity is a known risk factor for behavioural problems (Bhutta *et al.*, 2002).

The majority of these concerns are shared with the more common IVF procedure. As IVF had already been introduced in 1978, follow-up studies are more widely available involving IVF than ICSI families. Psychosocial development of the child, psychological adjustment of the parents and parent–child interaction have been found to be comparable after IVF and NC (Cederblad *et al.*, 1996; Golombok *et al.*, 1996,2002; McMahon *et al.*, 1997; van Balen, 1998; Gibson *et al.*, 2000a,b; Hahn, 2001; Colpin and Soenen, 2002; Golombok and MacCallum, 2003), or even superior after IVF (Cederblad

et al., 1996; Golombok *et al.*, 1996,2002; van Balen, 1998; Montgomery *et al.*, 1999). Two reports are in conflict with these reassuring findings. Levy-Shiff *et al.* (1998) has shown that IVF children obtained lower scores on socio-emotional adjustment and reported more anxiety, aggression and depression at age 9–10 years old, and Kallen *et al.* (2005) has found an increased rate of behavioural problems after IVF in a large register study.

The results from IVF children cannot be directly extrapolated to ICSI children, as the groups differ in conception procedure, and in type of underlying parental infertility: IVF is the treatment of choice for maternal fertility problems, whereas paternal infertility is usually treated with ICSI. This may affect psychosocial well-being as gender differences are known in coping with infertility (Wright *et al.*, 1991; Kowalcek *et al.*, 2001). The few studies that have addressed the psychosocial well-being of ICSI children and their parents showed no adverse outcomes of ICSI as compared to IVF or NC. If any differences were found, they tended to be in favour of ICSI (Barnes *et al.*, 2004; Ponjaert-Kristoffersen *et al.*, 2004; Sutcliffe *et al.*, 2004).

Except for the predominant focus on IVF families, various limitations of previous studies included small sample sizes, inadequate matching or adjustment for potential confounders and young age of the children.

At the Leiden University Medical Center, the first ICSI child was born in 1996. We designed a follow-up study with matched controls to assess the health and development of singletons born after ICSI in this centre, at the age of 5–8 years. An IVF control group served to assess a potential effect of the ICSI procedure itself, given a general background of underlying infertility, hormone treatment and fertilization *in vitro*. With a NC control group, we investigated the overall effect of ICSI, which represents the clinical question, i.e. likely to be important to future ICSI parents: what are the potential differences in health and development between children born after ICSI and their NC peers? In the current report, we focus on the psychosocial well-being of the children and their parents. We chose to assess child behaviour, parenting stress and child (health-related) quality of life. Our main research questions are: (i) do ICSI children have more behavioural problems, (ii) do ICSI parents have more stress due to parenting and (iii) will ICSI children rate a lower quality of life? Furthermore, we investigated the association (Batstra *et al.*, 2003) between our previous finding of a slight increase of minor neurological dysfunctions (Hadders-Algra, 2002,2003) in ICSI singletons (Knoester *et al.*, 2007) and problem behaviour in this group. Finally, we hypothesized that high problem behaviour scores would be associated with high parenting stress scores, because stressful parents may judge their child's behaviour more negatively and children who express problem behaviour may more likely cause stress.

Materials and Methods

The Ethics Committee of the Leiden University Medical Center approved the study design and informed parental consent was obtained. Data sampling was carried out between March 2004 and May 2005.

Participants

ICSI singletons born between June 1996 and December 1999 after fertility treatment in the Leiden University Medical Center were selected. Exclusion criteria were: oocyte or sperm donation, cryopreservation of the embryo and selective embryo reduction with medical indication. Similar criteria were used in the inclusion of IVF children, who were matched person-to-person to ICSI participants for gender, socio-economic status, gestational age (preterm/term), maternal age at the time of pregnancy (± 3 years) and birth date (closest). Socio-economic status low, medium or high was ascribed using the zip-code/socio-economic status indicator of Statistics Netherlands (Van Duijn and Keij, 2002), based on home price and income. If no match was available within the maternal age range of ± 3 years, larger deviations were permitted.

Regular pre-schools and primary schools (i.e. schools not providing special education) with zip-codes that indicated social class distributions similar to the ICSI cohort assisted in the sampling of NC singletons. We applied group matching on gender, socio-economic status and birth date. The composition of the NC control group from regular schools was justifiable as only one ICSI child attended special education.

The assessment of the psychological well-being of ICSI children and their parents was part of a larger study in which all children have undergone a neurological examination and intelligence testing in the hospital. As neuromotor outcome (minor neurological dysfunction; Hadders-Algra, 2002,2003) and intelligence quotient (IQ) have been associated with behaviour (Batstra *et al.*, 2003; Chen *et al.*, 2006; Goodman *et al.*, 1995), we entered the prevalence of minor neurological dysfunctions (Knoester *et al.*, 2007) and mean IQ scores in the current study as potential confounding factors. Mean IQ scores are not shown in Table I, as these data will be published separately (accepted for publication). Demographic characteristics of the parents and children were obtained through questionnaires.

Measures

Behaviour

The Child Behaviour Checklist (CBCL/4–18) (Achenbach, 1991; Verhulst *et al.*, 1996) is a parental measurement of emotional and behavioural problems in 4–18-year-old children. The 113 items are categorized under nine syndrome scales: (i) withdrawn, (ii) somatic complaints, (iii) anxious/depressed, (iv) social problems, (v) thought problems, (vi) attention problems, (vii) rule-breaking behaviour, (viii) aggressive behaviour and (viii) other problems. Syndrome scales i–iii comprise internalizing behaviour, vii and viii externalizing behaviour; all items together comprise the total problem score. Problem scores of the CBCL are classified as normal ($\leq$85th percentile), borderline clinical (85–90th percentile) and clinical ($\geq$90th percentile), for boys and girls separately (Verhulst *et al.*, 1997).

In the CBCL, parents were asked if their child has a (mental) handicap. With this information, in combination with a more general questionnaire on child's health that contained questions on, e.g. consulting a paediatrician/psychiatrist, we have evaluated behavioural disorders 'as reported by the parents'.

The CBCL was completed at home after it had been sent to all children at the same time.

Parental stress

The Nijmeegse Ouderlijke Stress Index (NOSI; de Brock *et al.*, 1992) is the Dutch version of the Parenting Stress Index (Abidin, 1983) and measures stress due to parenting on the basis of 123 items in two domains: the parent domain and the child domain. The parent domain includes the subscales sense of competence, restriction of

Table I. Demographic characteristics of parents and children: ICSI versus IVF and ICSI versus NC.

	ICSI $n = 81$	IVF $n = 81$	ICSI $n = 87$	NC $n = 85$
Gender: male, *n* (%)	40 (49)	40 (49)	44 (51)	47 (55)
Parity: first-born, *n* (%)	61 (75)	59 (73)	65 (75)*	31 (37)*
Gestational age: <37 weeks, *n* (%)	0 (0)	0 (0)	6 (7)*	0 (0)*
Birth weight: <2500 g, *n* (%)	3 (4)	3 (4)	7 (8)*	1 (1)*
Child education, *n* (%)	[a]		[a]	
Regular pre-/primary school	70 (88)	69 (85)	76 (88)	79 (93)
Regular school, repeat class	7 (9)	8 (10)	7 (8)	4 (5)
Regular school, remedial teaching	2 (3)	2 (2)	2 (2)	2 (2)
special education	1 (1)	2 (2)	1 (1)	0 (0)
Minor neurological dysfunction, *n* (%)	53 (66)[a]	49 (61)[a]	57 (66)[a,]*	43 (51)*
Parental age at pregnancy, mean (range)				
Mother	32.8 (22–41)	33.4 (24–42)	32.8 (22–41)*	30.6 (20–41)*
Father	36.9 (23–65)	37.3 (27–60)	36.9 (23–65)*	32.6 (20–49)*
Ethnicity, *n* (%)[b]				
Mother: non-Caucasian	7 (9)	9 (11)	9 (10)	8 (9)
Father: non-Caucasian	8 (10)	8 (10)	10 (12)	11 (13)
Level of education, *n* (%)				
Mother		[a]		
No education	0 (0)	1 (1)	0 (0)*	0 (0)*
Low	25 (31)	25 (31)	27 (31)*	11 (13)*
Medium	28 (35)	27 (34)	29 (33)*	37 (44)*
High	28 (35)	27 (34)	31 (36)*	37 (44)*
Father	[a]		[a]	
No education	0 (0)	2 (3)	0 (0)	1 (1)
Low	28 (35)	26 (32)	31 (36)	22 (26)
medium	26 (33)	16 (20)	26 (30)	26 (31)
high	26 (33)	37 (46)	29 (34)	36 (42)
Diagnosed infertility factor, *n* (%)				
Mother	13 (16)*	37 (46)*	15 (17)*	0*
Father	64 (79)*	11 (14)*	70 (80)*	0*
Smoking during pregnancy, *n* (%)				
Mother	[a]		[a]	
No	70 (88)	70 (86)	76 (88)	75 (88)
Yes, <10 per day	9 (11)	10 (12)	9 (11)	8 (9)
Yes, >10 per day	1 (1)	1 (1)	1 (1)	2 (2)
Father		[c]		[a]
No	57 (70)	61 (77)	61 (70)	62 (74)
Yes, <10 per day	7 (9)*	11 (14)*	9 (10)*	15 (18)*
Yes, >10 per day	17 (21)*	7 (9)*	17 (20)*	7 (8)*
Family situation, *n* (%)				
Parents live together	71 (88)	77 (95)	77 (89)	75 (88)
Parents live separated	9 (11)	4 (5)	9 (10)	10(12)
One parent has passed away	1 (1)	0 (0)	1 (1)	0 (0)
Family size, median (range)	2 (1–4)	2 (1–4)	2 (1–4)*	3 (1–10)*
Daily care-taking, *n* (%)	[a]		[a]	[a]
Mother and father equally	24 (30)	14 (17)	26 (30)*	14 (17)*
Mainly mother	51 (64)	63 (78)	55 (64)*	69 (82)*
Mainly father	5 (6)	4 (5)	5 (6)*	1 (1)*
Socio-economic status, *n* (%)				
Low	8 (10)	8 (10)	10 (12)	7 (8)
Medium	26 (32)	26 (32)	27 (31)	18 (21)
High	47 (58)	47 (58)	50 (58)	60 (71)

[a]one missing value; [b]Turkey classified under non-Caucasian; [c] two missing values. *$P < 0.05$.

role, attachment, depression, parent's health, social isolation and relationship with spouse; the child domain consists of adaptability, mood, distractibility/hyperactivity, demandingness, 'reinforces parent' and acceptability. A total stress score can be calculated by adding up the parent and child domain scores. The NOSI is the only test with separate norms for mothers and fathers. This parental questionnaire was filled out during the examination in the hospital.

(Health-related) quality of life

To measure quality of life, we used two different questionnaires: the Dutch Children TNO AZL Quality of Life questionnaire (Dux25) and the TNO AZL Child Quality of Life questionnaire (TACQOL) (Theunissen *et al.*, 1998; Vogels *et al.*, 1998; Verrips *et al.*, 1999). The difference between the questionnaires is that the Dux25 measures quality of life based on general questions of 'happiness' and the TACQOL relates these questions to the child's health status. Example question of the Dux25: 'How much do you (does your child) like school?' Example question of the TACQOL: 'Did your child have headaches in the past weeks?/How did she feel at that time?'. Thus, the TACQOL measures the health status of the child as well as his/her coping strategy.

The Dux25 contains 25 items on four domains of life quality: physical, home, emotion and social. The instrument is child-friendly and was completed by both the child and the parent, in the hospital during the examination. The child form was assisted by one investigator blinded to the conception mode of the child.

The TACQOL covers health-related quality of life (HRQoL) with 56 items in seven domains: physical complaints, motor functioning, autonomy, cognitive functioning, social functioning, positive moods and negative moods. This questionnaire was completed by the parents in the hospital during the examination of their child.

The Dux25 and TACQOL are designed for children aged 6–16 years. To promote reliability we asked the parents of the children who were still 5 years old at the time of the examination to fill out the Dux25 Parent and TACQOL forms for a second time, when the children had turned 6. The questionnaires were completed at home and returned by mail. To ensure that no bias was introduced, we compared the scores of the first completion with the scores of the second. Furthermore, we compared ICSI with IVF and ICSI with NC using the first and second completions. The Dux25 Child could not be filled out at home when children had reached age 6, as objective instructions by the parents would not be guaranteed. Instead, we performed a subanalysis among children aged 6 years and older.

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences 12.0 for Windows package (SPSS Inc., Chicago, IL). If values were missing within a questionnaire, we followed the user's manual instructions on missing values of the particular test. Continuous data were analysed with an independent *t*-test if a normal distribution was likely. Categorical data were analysed using Pearson's chi-square test. Statistical significance was reached if $\alpha < 0.05$. Differences in continuous data were presented as a mean difference and 95% confidence interval (95% CI). Differences in categorical data (2×3) were expressed in terms of *P*-values. We performed regression analysis (General Linear Model) to adjust for confounders. Potential confounders were identified by combining three sources of information: (i) baseline differences between the study groups, (ii) univariate associations of variables with the outcome scales and (iii) prior knowledge on associations: plausibility and direction. Two types of exceptions were made. First, we did not adjust for differences in type of infertility (paternal/maternal) as the choice for ICSI or IVF is largely determined by type of infertility. Second, in the ICSI–NC comparison we did not adjust for factors that chronologically followed conception and might be in the causal pathway from conception mode to outcome, such as prematurity, low birth weight, IQ and minor neurological dysfunction. In this way we examined the total difference between ICSI and NC children, an important issue from the perspective of future parents.

It is likely that the perception of psychological well-being in child-rearing differs some between mothers and fathers. The NOSI has separate norms for both parents. Regarding the other three questionnaires, we compared the proportions of mothers and fathers who completed the forms between the three conception groups and considered whether this variable was a confounding factor or not. These data are not shown, but if we adjusted for 'parent who completed the form', it is indicated by a footnote in the table.

Although IQ scores are not reported in Table I, we adjusted for IQ if this variable met the abovementioned criteria for confounding.

We tested our hypothesis of a correlation between problem behaviour and parenting stress by drawing a scatter plot and calculating the regression coefficient for the various scales and conception modes.

Results

Participants

One hundred and ten ICSI children met the inclusion criteria, 87 of whom enrolled on the study (79%). Of the 257 eligible IVF children 126 potential matches were selected and 92 (73%) participated. Two IVF controls were available for five ICSI children, and the best match was selected ($n = 87$). Extension of the range of maternal age beyond ± 3 years was required in eleven cases. Among the total cohort of ICSI children, eight had been born prematurely, six of whom entered the study. Proper IVF matches could only be found for two of six preterm children. We decided to restrict the ICSI–IVF comparison to children born at term ($n = 81/81$), because the two preterm ICSI/IVF couples could not represent all preterm ICSI and IVF children. Matching preterm ICSI children with term IVF children would have introduced confounding.

Eighty-seven NC children from 16 schools were enrolled, of whom one was excluded for being a twin and one for being conceived with intrauterine insemination ($n = 85$). The ICSI–NC comparison was not restricted to term children because we wanted to assess the overall effect of ICSI on the outcome measures. This included the potentially negative effect of prematurity ($n = 87/85$).

Characteristics

Characteristics of the parents and children are shown in Table I. The ICSI and IVF group were comparable except for the prevalence of maternal and paternal infertility factors, and smoking behaviour of the father during pregnancy (ICSI fathers smoked more heavily). ICSI and NC children were less similar: differences existed on parity (more first-born children in the ICSI group), gestational age, birth weight, minor neurological dysfunction (all in favour of NC), parental age (ICSI parents were older), maternal education (NC mothers were more highly educated), infertility factors (present with ICSI, absent with NC), paternal smoking (ICSI fathers smoked more heavily), family size (smaller with ICSI) and daily care for the child (ICSI parents more often shared daily care).

Behaviour

Table II lists behavioural disorders in children born after ICSI, IVF and NC, as reported by the parents. No marked differences in behavioural disorders were found between ICSI and IVF children or ICSI and NC children. However, the prevalence of ICSI children with autism or an autistic spectrum disorder (ASD) was 3/87 (3.4%), which seemed unexpectedly high in comparison with the general population estimate of $\pm 0.3\%$ (Williams *et al.*, 2006).

Tables III and IV show the group results on the CBCL, stratified by gender. On the problem scales, no differences were found between ICSI and IVF boys, ICSI and NC boys or ICSI and NC girls. ICSI girls however had higher problem scores than IVF girls on internalizing, externalizing and total score, allowing for the potential confounders (Table III). All the mean scores were in the $\leq$85th percentile range of normal behaviour. Table IV shows the frequencies of children with scores in the normal, borderline clinical and clinical ranges. ICSI children more often scored in the (borderline) clinical range than IVF children; a difference that was larger within girls than boys. Outcomes of ICSI and NC children were comparable. We found no correlation between minor

Table II. Behavioural problems in children born after ICSI, IVF, and NC: as reported by parents.

Type of disorder	ICSI $n = 81$	IVF $n = 81$	ICSI $n = 87$	NC $n = 85$
Mean age years (range)	6.1 (5.3–7.7)	6.2 (5.3–8.3)	6.1 (5.3–7.7)	6.3 (5.1–8.0)
Autism/ASD	2[a]	–	3[a]	1
Anxiety disorder	1	–	1	–
Fear of failure	1	–	1	–
Aggressive behaviour	1	–	1	–
ADHD/attention deficit disorder	1[a]	1	1[a]	2
Auditory hypersensitivity	–	1	–	–
Concentration problems	2	2	2	1
Mild cross-gender role	–	1	–	1
Not specified	–	1	–	1

[a]one child with autism and Attention-Deficit/Hyperactivity Disorder (ADHD).

neurological dysfunctions and problem behaviour (data not shown).

Parenting stress

The raw parenting stress score was equally high among ICSI and IVF parents on the parent, child and total scales (Table V). No differences appeared after adjustment for IQ of the children. ICSI parents reported higher stress rates than NC parents, with mean differences (95% CI) of 6 (−3, 16) points on the parent total scale, 12 (1, 23) points on the child total scale, and 18 (−1, 37) points on the total stress score. Adjustment for child age, maternal educational level, socio-economic status and parent who completed the questionnaire resulted in minor changes (Table V). On the subscale level we found a significant difference on distractibility/hyperactivity [mean difference between ICSI and NC = 4 (1, 6)].

Parenting stress was positively correlated with problem behaviour regardless of problem scale or conception mode. Regression coefficients for parenting stress as a function of problem behaviour were: 2.8 (2.3, 3.3) for total problem score, 7.5 (5.8, 9.2) for internalizing and 5.9 (4.7, 7.1) for externalizing; 3.4 (2.5, 4.2) for total problem score in ICSI children, 2.7 (1.6, 3.8) in IVF children and 2.6 (1.9, 3.4) in NC children.

Quality of life

Dux25 child

Quality of life was rated very similarly by ICSI, IVF and NC children (Table VI). Adjustment for IQ in the ICSI–IVF comparison and for parity and socio-economic status in the ICSI–NC comparison did not result in substantial differences. In the subanalysis of children aged 6 years and older (ICSI $n = 37$, IVF $n = 42$; ICSI $n = 41$, NC $n = 56$), ICSI children obtained a higher score than both IVF children and NC children on the emotion scale [6% (0, 12) and 6% (0, 12); adjusted values 6% (0, 12) and 5% (−2, 13)].

We checked the reasons for missing forms in the different conception categories to assess whether this was a result of behavioural or concentration problems and if this was similar in the three groups. In the ICSI–IVF comparison, 3/6 ICSI children failed to complete the form due to behaviour or concentration loss versus 2/4 IVF children. In the ICSI–NC

Table III. CBCL: syndrome scale scores ICSI versus IVF and ICSI versus NC.

Gender	Syndrome scale	Norm p50 (range)[a]	ICSI $n = 72$	IVF $n = 70$	Mean diff. (95% CI)	Adj. mean diff. (95% CI)[b]
Mean age (range)			6.7 (5.3–8.8)	6.8 (5.3–8.9)	−0.1 (−0.5, 0.2)	
Boys			$n = 36$	$n = 37$		
	Internalizing	3–4 (0–62)	5	4	1 (−1, 3)	1 (−1, 3)
	Externalizing	7 (0–66)	8	7	0 (−3, 3)	0 (−3, 3)
	Total score	19 (0–236)	22	18	4 (−2, 10)	3 (−4, 10)
Girls			$n = 36$	$n = 33$		
	Internalizing	4 (0–62)	6*	4*	2 (0, 4)*	2 (0, 4)*
	Externalizing	4–5 (0–66)	9*	5*	4 (1, 6)*	3 (1, 6)*
	Total score	16 (0–236)	23*	14*	9 (4, 15)*	8 (3, 14)*
Gender	Syndrome scale	Norm p50 (range)[a]	ICSI $n = 78$	NC $n = 75$	Mean diff. (95%CI)	Adj. mean diff. (95%CI)[c]
Mean age (range)			6.7 (5.3–8.8)	6.7 (5.2–8.8)	0.0 (−0.3, 0.3)	
Boys			$n = 40$	$n = 40$		
	Internalizing	3–4 (0–62)	5	5	0 (−1, 2)	0 (−1, 2)
	Externalizing	7 (0–66)	8	7	0 (−2, 3)	0 (−3, 2)
	Total score	19 (0–236)	22	20	2 (−5, 8)	1 (−5, 7)
Girls			$n = 38$	$n = 35$		
	Internalizing	4 (0–62)	6	6	0 (−2, 2)	−1 (−3, 1)
	Externalizing	4–5 (0–66)	8	7	1 (−1, 4)	0 (−3, 3)
	Total score	16 (0–236)	22	20	2 (−4, 8)	−1 (−8, 5)

[a]higher score means more problem behaviour; [b] adjustment for IQ, paternal smoking during pregnancy and paternal educational level; [c] adjustment for paternal smoking during pregnancy, paternal educational level, and socio-economic status. *$P < 0.05$. CI, confidence interval.

Table IV. CBCL: numbers and prevalences of children scoring in the normal, borderline clinical and clinical range.

Gender	Syndrome scale	Range	ICSI *n* (%)	IVF *n* (%)	*P*-value	ICSI *n* (%)	NC *n* (%)	*P*-value
All	Internalizing		*n* = 72	*n* = 70		*n* = 78	*n* = 75	
		Normal (≤p85)	50 (69)	63 (90)		55 (71)	56 (75)	
		Borderline clinical (p85–p90)	14 (19)	2 (3)		15 (19)	10 (13)	
		Clinical (≥p90)	8 (11)	5 (7)		8 (10)	9 (12)	
					0.004			0.604
	Externalizing							
		Normal (≤p85)	51 (71)	61 (87)		56 (72)	59 (79)	
		Borderline clinical (p85–p90)	12 (17)	3 (4)		12 (15)	7 (9)	
		Clinical (≥p90)	9 (13)	6 (9)		10 (13)	9 (12)	
					0.032			0.499
	Total score							
		Normal (≤p85)	54 (75)	63 (90)		59 (76)	59 (79)	
		Borderline clinical (p85–p90)	6 (8)	5 (7)		6 (8)	8 (11)	
		Clinical (≥p90)	12 (17)	2 (3)		13 (17)	8 (11)	
					0.019			0.492
Boys	Total score		*n* = 36	*n* = 37		*n* = 40	*n* = 40	
		Normal (≤p85)	27 (75)	33 (89)		30 (75)	32 (80)	
		Borderline clinical (p85–p90)	4 (11)	2 (5)		4 (10)	5 (13)	
		Clinical (≥p90)	5 (14)	2 (5)		6 (15)	3 (8)	
					0.281			0.556
Girls	Total score		*n* = 36	*n* = 33		*n* = 38	*n* = 35	
		Normal (≤p85)	27 (75)	30 (91)		29 (76)	27 (77)	
		Borderline clinical (p85–p90)	2 (6)	3 (9)		2 (5)	3 (9)	
		Clinical (≥p90)	7 (19)	0 (0)		7 (18)	5 (14)	
					0.027			0.786

$P < 0.05$. ≤p85:≤85th percentile range etc.

comparison, these numbers were 3/7 and 0/2. The other main reason why children did not complete the form was poor understanding.

By asking the parents of 5-year-old children to complete the Dux25 Parent and TACQOL once again at age 6 (ICSI *n* = 39, IVF *n* = 34; ICSI *n* = 41, NC *n* = 25), the mean child age at testing rose from 6.1 to 6.6 in the ICSI group, and from 6.3 to 6.7 in the IVF and NC group. The number of children younger than 6.0 years of age was reduced to 7 in both the ICSI and IVF group (9%). The corresponding numbers were 8 (10%) and 3 (4%) in the ICSI–NC comparison. We found slight differences that did not influence our conclusions when comparing the raw scores of the first and second completion or the differences between ICSI, IVF and NC in the two selections.

Dux25 parent

Parents of ICSI children rated the quality of life of their children slightly lower than IVF parents, but the differences did not reach statistical significance (Table VI). Child quality

Table V. Parenting stress outcomes in children born after ICSI, IVF and NC.

NOSI scale	ICSI *n* = 76	IVF *n* = 76	Mean diff. (95% CI)	Adj. mean diff. (95% CI)[a]	ICSI *n* = 81	NC *n* = 80	Mean diff. (95% CI)	Adj.mean diff. (95% CI)[b]
Mean age years (range)	6.1 (5.3–7.7)	6.2 (5.3–8.3)	−0.1 (−0.4, 0.1)		6.1 (5.3–7.7)	6.3 (5.3–8.0)	−0.2 (−0.4, 0.0)	
Parent total[c]	108	107	1 (−10, 12)	3 (−8, 14)	107	101	6 (−3, 16)	8 (−3, 19)
Competence	22	21			22	21		
Restriction of role	16	16			16	14		
Attachment	10	10			10	10		
Depression	21	22			21	21		
Parent's health	12	12			12	11		
Social isolation	11	10			11	10		
Relationship with spouse	16	15[d]			16	14[e]		
Child total[c]	133	131	2 (−11, 14)	1 (−12, 13)	132*	121*	12 (1, 23)*	11 (0, 23)
Adaptability	29	29			29	27		
Mood	18	19			18	17		
Distractibility/hyperactivity	33	31			32*	29*		
Demandingness	20	19			20	18		
Reinforcement	15	14			15	14		
Acceptability	18	19			18	17		
Stress total[c]	241	238	3 (−19, 25)	3 (−19, 25)	239	221	18 (−1, 37)	19 (−1, 40)

[a]adjustment for IQ; [b]adjustment for age child, maternal educational level, socio-economic status, parent who completed form; [c]higher score means more stress; norm values—form completed by mother: parent total (104–130), child total (123–162), stress total (227–292); form completed by father: parent total (94–115), child total (122–157), stress total (215–270); [d]one missing value due to divorce; [e]three missing values due to divorce. *$P < 0.05$. NOSI, the Nijmeegse Ouderlijke Stress Index.

Table VI. Quality of life outcome for ICSI, IVF and NC children.

DUX 25 child subscale score[a]	ICSI $n = 75$	IVF $n = 77$	Mean diff. (95% CI)[b]	ICSI $n = 80$	NC $n = 83$	Mean diff. (95% CI)[c]
Mean age (range)	6.1 (5.3–7.7)	6.3 (5.3–8.3)	−0.1 (−0.3, 0.1)	6.2 (5.3–7.7)	6.3 (5.3–8.0)	−0.2 (−0.4, 0.0)
Physical	82 (58–100)	80 (33–100)	2 (−3, 6)	83 (58–100)	81 (54–100)	2 (−2, 6)
Home	83 (35–100)	85 (50–100)	−1 (−6, 3)	84 (35–100)	84 (45–100)	0 (−4, 5)
Emotion	77 (43–100)	73 (36–96)	3 (−1, 8)	77 (43–100)	73 (39–100)	4 (−1, 8)
Social	79 (21–100)	79 (50–100)	−1 (−5, 4)	79 (21–100)	77 (32–100)	2 (−2, 7)
DUX 25 parent subscale score[a]	ICSI $n = 77$[d]	IVF $n = 76$	Mean diff. (95% CI)[e]	ICSI $n = 82$[d]	NC $n = 80$	Mean diff. (95% CI)[f]
Mean age (range)	6.6 (5.3–7.7)	6.7 (5.5–8.3)	−0.1 (−0.2, 0.1)	6.6 (5.3–7.7)	6.7 (5.6–8.0)	0.0 (−0.2, 0.1)
Physical	79 (29–100)	82 (46–100)	−3 (−8, 2)	79 (17–100)	79 (50–100)	−1 (−6, 4)
Home	85 (60–100)	88 (60–100)	−3 (−7, 0)	85 (35–100)	85 (45–100)	0 (−4, 4)
Emotion	79 (32–100)	82 (39–100)	−3 (−7, 1)	80 (32–100)	80 (46–100)	0 (−4, 4)
Social	81 (50–100)	82 (46–100)	−1 (−4, 3)	81 (43–100)	80 (46–100)	1 (−3, 5)

[a]scores are mean percentages of maximum quality of life score; [b]crude difference, no changes with adjustment for IQ; [c]crude difference, no changes with adjustment for parity and socio-economic status; [d]one ICSI parent completed the 'home' scale only: physical, emotion and social $n = 76$ in ICSI versus IVF and $n = 81$ in ICSI versus NC; [e]crude difference, no changes with adjustment; physical for paternal education; home for paternal education and family situation; [f]crude difference, no changes with adjustment: physical for socio-economic status and paternal education; home for parity and paternal age, socio-economic status and paternal education; emotion for socio-economic status; social for socio-economic status and family size. No significant differences ($p < 0.05$) found.

of life scores as assigned by the parents were very similar for the ICSI and NC group. Adjustment for potential confounders resulted in irrelevant changes.

TACQOl

Table VII shows the sum scores and the corresponding percentages of the maximum score on health status and HRQoL. No differences in health status or HRQoL were found between ICSI and IVF children. ICSI and NC children had comparable scores with a small but significant difference on social functioning [health status 0 (−1, 0), HRQol −1 (−2, 0)]. Adjustment for confounding factors (ICSI/IVF: maternal age and IQ, ICSI/NC: maternal age, family size, socio-economic status and parent who completed the form) did not change the results, except that the difference between ICSI and NC on social functioning was no longer statistically significant.

Discussion

At 5–8 years of age, we found no differences in behavioural disorders between children born after ICSI, IVF and NC. The prevalence of autism/ASD in the ICSI group was higher than expected (3.4% versus the general population ±0.3%) (Williams *et al.*, 2006). ICSI girls had higher problem scores than IVF girls on the CBCL and more often scored in the clinical range. However, problem behaviour scores of ICSI and NC children were comparable. ICSI parents reported similar stress rates as IVF parents, but NC parents reported less stress. We found no differences in (health-related) quality of life as measured with the Dux25 Child, Dux25 Parent and TACQOL. We found no correlation between minor neurological dysfunctions and problem behaviour; parenting stress was positively correlated with problem behaviour regardless of problem scale or conception mode.

Interpretation of the results

Behaviour

Our sample size was too small to draw firm conclusions on differences in behavioural disorders as reported by the parents of ICSI, IVF and NC children. Although we did not have enough statistical power to detect a significant difference between the ICSI and NC group on autism/ASD, we mention the high prevalence of autism/ASD after ICSI (3.4%) compared with the estimated frequency of 0.3–0.4% in the general population (Williams *et al.*, 2006). This is a remarkable but uncertain finding that may deserve attention in future research, especially so as ICSI children have a background of parental infertility and often advanced paternal age at birth, factors which have been associated with autism (Croughan *et al.*, 2006; Henderson, 2006; Reichenberg *et al.*, 2006). Causal pathways are suggested to involve epigenetics (Niemitz and Feinberg, 2004; Schanen, 2006).

The CBCL measures the parental judgement of children's behaviour. We found similar outcomes for ICSI and NC children, which is in line with the results of two large follow-up studies conducted among 5-year-old singletons (Barnes *et al.*, 2004; Ponjaert-Kristoffersen *et al.*, 2004). We may safely conclude that ICSI children do not show more problem behaviour than NC children.

The finding of lower problem behaviour scores in the IVF as compared to the ICSI group is in conflict with the results of the main other study comparing problem behaviour of ICSI and IVF children using the CBCL. Barnes *et al.* (2004) has found ICSI and IVF children to be comparable with large group sizes ($n = 345/n = 301$) at five years of age. As follow-up studies in ICSI children are rare, we explored whether IVF children have been reported to have less problem behaviour than NC children, an indirect conclusion from our study. Cederblad *et al.* (1996) compared 73 IVF children with a Swedish population group and found no differences in CBCL problem scores; neither in boys nor in girls. The increased rate of multiples and preterm born children in the IVF group did not affect the results. At 8–9 years of age, Colpin and Soenen (2002) assessed problem behaviour in 27 IVF children and 23 NC controls, and showed no significant differences either. Only Montgomery *et al.* (1999) found that IVF children less often scored in the (borderline) clinical range, when assessing 494 IVF children older than 4 years of age with the CBCL and comparing their scores with norm values.

The lack of stratification by gender in the majority of studies limits the comparison of the present study with the literature, as the difference that we found between ICSI and IVF was mainly attributable to a difference among the girls. As compared to the norm values, ICSI and NC girls score slightly high in the present study, whereas IVF girls score equal to the norm or slightly lower. When comparing our data with those of Colpin and Soenen (2002) and Ponjaert-Kristoffersen *et al.* (2004), the raw problem scores of our NC control group and theirs were very similar (Colpin—mother norms, considering that 96% of the forms had been filled out by the mother in our NC group: internalizing behaviour 5.1, externalizing behaviour 7.9 and total problem behaviour 21.2; Ponjaert-Kristoffersen: internalizing behaviour 4.3, externalizing behaviour 8.2 and total problem behaviour 20.0). Apparently, the IVF scores in the present study were particularly low rather than the ICSI and NC scores being high.

It remains unclear why IVF children would show less problem behaviour than their ICSI or NC counterparts. The majority of CBCL forms were completed by the mother in the present study. Based on the differences in background of infertility, we could hypothesize that IVF mothers—who will often have been subfertile—judge their child more positively as compared to ICSI and NC mothers—who did not have fertility problems. Why this would particularly involve girls is unclear. We suggest further assessment of problem behaviour in ICSI, IVF and NC children in future research with stratification by gender of the child as well as by parent who completed the form.

Parenting stress

We showed that problem behaviour and parenting stress are positively correlated, with comparable regression coefficients in the three conception groups. However, the differences between the three groups regarding problem behaviour are not reflected in similar differences in parental stress. We would have expected to find the stress scores of ICSI and NC parents higher than those of IVF parents, but instead, ICSI and IVF were comparable and NC parents indicated less stress.

Lower levels of stress on the child domain suggest that NC parents experience less stress due to particular characteristics of the child (see subscales in Materials and Methods section) in the parent–child relationship. The stress levels of NC parents were around the lower border of the norm. It is possible that the participating NC parents have unwittingly been a selection of NC parents who experience little stress. ICSI and IVF parents may have been less prone to such a selection as they were more committed to the study and would have participated anyway. Selection bias based on the level of stress would explain the difference between our outcomes and previous reports: no difference in stress has been found between IVF and NC parents (Colpin and Soenen, 2002; McMahon *et al.*, 2003) or ICSI, IVF and NC parents (Barnes *et al.*, 2004). Golombok *et al.* (1996) has even shown lower stress rates in mothers of 4–8-year-old singletons born after artificial reproduction as compared to NC, results that have been supported by the follow-up study of ICSI and NC children at age 5 of Ponjaert-Kristoffersen *et al.* (2004). Whether ICSI parents were indeed more tolerant or had answered the questionnaires in a more socially desirable way could not be distinguished.

For future research, we recommend measuring parenting stress in a survey separate from time-consuming examinations. This may prevent (mainly NC) parents who experience a lot of stress from refusing to cooperate.

Quality of life

To our knowledge, (health-related) quality of life of ICSI children has not been assessed previously. The lack of differences between ICSI and IVF children or between ICSI and NC children on quality of life as scored by the child and parent separately was very reassuring, as well as the lack of differences on health status and HRQoL.

Methodology

We carried out a follow-up study with matched controls, in a single centre. Participation rates in the IVF and ICSI groups were 73 and 79%, respectively, and we therefore assume to have included a representative sample of these populations. To what extent the NC control group represents its reference population cannot be measured. Selection bias most likely occurred in the low socio-economic status group, as participation rates were low: from the nine schools with a low socio-economic status in the catchment area only seven NC children applied.

As we did not succeed in finding preterm IVF children to match all six preterm ICSI children, we limited the ICSI–IVF comparison to children born at term. This did not conflict with our design, as we aimed to investigate the extra effect of ICSI as compared to IVF; both methods of artificial reproduction, of which prematurity is a well-known complication (Helmerhorst *et al.*, 2004; Jackson *et al.*, 2004). Preterm children were indeed included in the ICSI–NC comparison as the total difference in psychological well-being between children born after ICSI and NC includes the negative consequences of the higher rate of prematurity.

The comparison of ICSI and IVF children is complicated by the groups not only differing in the variable under study, i.e. conception mode, but also in the type of underlying infertility. Men and women are known to cope differently with their infertility (Wright *et al.*, 1991; Kowalcek *et al.*, 2001), but it is unknown whether this affects child-rearing up to the child age of 5–8 years. Therefore, differences between ICSI and IVF children were carefully interpreted. Because it is difficult to separate method of artificial reproduction from its indication, a suggestion for future research may be to have the questionnaires filled out by both parents of each child. In this way, each child will be judged by both a mother and a father, and by both a fertile and an infertile parent.

We did not succeed in obtaining a 100% completion rate of the questionnaires. The large amount of forms to fill out may have played a role in parents accidentally skipping questions or pages. Besides, the CBCL, NOSI and TACQOL are rather long forms that are not easy to complete for parents who are less familiar with the Dutch language (proportions of children with Dutch as the primary language spoken at home were similar in the three groups, data not shown). Because we handled missing values within questionnaires according to the test manuals and

Table VII. HRQoL and health status; parents' reports ICSI versus IVF and ICSI versus NC.

TACQOL scales	ICSI, mean	$n = 74$, %[a]	IVF, mean	$n = 77$, %[a]	Mean diff. (95% CI)[b]
Mean age years (range)	6.6 (5.3–7.7)		6.7 (5.5–8.3)		0.0 (−0.2, 0.2)
Physical complaints					
Health status	13	80	13	83	0 (−1, 0)
HRQoL	27	84	27	86	0 (−2, 1)
Motor functioning					
Health status	15	95	15	93	0 (0, 1)
HRQoL	31	96	30	95	0 (0, 1)
Autonomy					
Health Status	15	93	14	90	0 (0, 1)
HRQoL	31	96	30	95	0 (0, 1)
Cognitive functioning					
Health status	14	85	14	86	0 (−1, 1)
HRQoL	29	91	29[c]	91	0 (−1, 1)
Social functioning					
Health status	14	88	14	89	0 (−1, 0)
HRQoL	29	91	29[d]	92	0 (−1, 1)
Positive emotions	15	93	15	94	0 (−1, 0)
Negative emotions	11	71	11	69	0 (0, 1)
Scales	ICSI, mean	$n = 79$, %[a]	NC, mean	$n = 79$, %[a]	Mean diff. (95% CI)[e]
Mean age (range)	6.6 (5.3–7.7)		6.7 (5.6–8.0)		0.0 (−0.2, 0.1)
Physical complaints					
Health status	13	80	13	83	0 (−1, 0)
HRQoL	27	84	28	87	−1 (−2, 0)
Motor functioning					
Health status	15	95	15	96	0 (−1, 0)
HRQoL	31	97	31	97	0 (−1, 0)
Autonomy					
Health status	15	93	15	95	0 (−1, 0)
HRQoL	31	95	31	96	0 (−1, 0)
Cognitive functioning					
Health status	14	85	14	88	−1 (−1, 0)
HRQoL	29	91	30	93	−1 (−2, 0)
Social functioning					
Health status	14*	87*	14*	90*	0 (−1, 0)*
HRQoL	29*	91*	30*	93*	−1 (−2, 0)*
Positive emotions	15	93	15	96	0 (−1, 0)
Negative emotions	11	71	12	74	0 (−1, 0)

[a]percentages of maximum quality of life score: 16 for health status and emotion scales, 32 for HRQoL scales; [b]crude mean difference of sum scores, no changes after adjustment: physical HRQoL for maternal age; motor HRQoL for maternal age; cognitive HRQoL for IQ; [c]two missing values; [d]one missing value; [e]crude mean difference of sum scores, no changes after adjustment: physical HRQoL for maternal age, family size and completing parent; motor HRQoL for maternal age and completing parent; cognitive HRQoL for socio-economic status and completing parent; social HRQoL for socio-economic status and completing parent; positive emotions for completing parent; negative emotions for socio-economic status. *$P < 0.05$.

because the numbers of missing forms were fairly equally distributed between ICSI and IVF or ICSI and NC, we assume that our conclusions are not biased by these omissions.

Although the results of IQ testing of the children will be published separately, we chose to adjust for IQ differences between the groups if IQ was univariately associated with an outcome variable of the present study. This improved the precision of the results, but caused no material changes.

In summary, besides an unexpected increase in the prevalence of autism/ASD in ICSI children, which is uncertain and will need more research, ICSI children showed no rise in problem behaviour as compared to NC children. IVF children had lower behavioural problem scores than ICSI children and less often scored in the (borderline) clinical range. An increase in parenting stress was found in ICSI versus NC parents; however, this may have resulted from selection bias. (Health-related) quality of life was similar in the three conception groups. We conclude that the majority of ICSI singletons assessed at 5–8 years of age show a normal psychosocial well-being.

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