Neuromotor development and mental health at 5.5 years of age of singletons born at term after intracytoplasmatic sperm injection ICSI: results of a prospective controlled single-blinded study in Germany

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Objective: To assess the neurodevelopmental health of children born after intracytoplasmatic sperm injection (ICSI).
Design: Prospective controlled blinded study.
Setting: Tertiary care center.
Patient(s): A total of 276 term-born singletons conceived by ICSI and 273 matched spontaneously conceived (SC) singletons at the age of 5.5 years.
Main Outcome Measure(s): Neuromotor development assessed by a detailed neurologic examination, including the standardized motor test MOT 4–6, and emotional/behavioral development and intelligence assessed with the Kaufman-Assessment Battery for Children.
Result(s): There were no significant differences between ICSI children and control children regarding the neurologic examination, motor skills, emotional/behavioral development, and intelligence.
Conclusion(s): The ICSI children born at term develop normally, similar to SC children. (Fertil Steril® 2009;91: 125–32. ©2009 by American Society for Reproductive Medicine.)

Key Words: ICSI, ART, children, term born, singletons, follow-up, neurologic health, neuromotor development

Assisted reproductive technologies (ART) are used worldwide every day. The techniques introduced more recently in this field include the "most invasive one," i.e. intracytoplasmic sperm injection (ICSI). The ART are by definition "unnatural," and there are theoretic considerations surrounding risks to the health of ART children. These include ovarian stimulation with the possibility of changes in follicle milieu and oocyte structure (1), sperm preparation with the theoretic possibility of exposure to substances which might change their natural function (2), manipulation of oocytes by oocyte pick-up and further processing (3,4), and the use of sperm from subfertile men with the possibility of more genetic abnormalities (5) or abnormal imprinting (6). In ICSI, even the natural selection of spermatozoa is missing, because the spermatozoa are injected into the oocyte.

Three large cohort studies on the neurologic health reported an increased risk of cerebral palsy by 1.7–2.8-fold in IVF children (7–9). The risk of being hospitalized for epilepsy is increased by 1.5-fold (7). Prospective controlled studies that were based on interviews or neurologic examinations did not find differences regarding neurologic abnormalities between children born after ART and spontaneous conception (10–16). Few of those studies assessed the neurologic outcome or the motor development of children at 5 years (14, 17–19) or 8 years (20, 21) of age. In four of those studies, preterm-born children (32–37 weeks) or multiples were included. Only Knoester et al. (17) excluded all preterm singletons. However, that study included fewer than 100 children in each group. Place and Englert (22) assessed only full-term singletons and found no difference in the intellectual abilities up to the age of 5 years after controlling for the parental education. However, the study consisted of only 66 ICSI, 52 IVF, and 59 control children.

Although all of those prospective studies did not find a higher neurologic morbidity in children born after ART compared with spontaneously conceived (SC) children, it is well recognised that prematurity and a low birth weight are risk factors for disturbed neuromotor development (23), especially because children born after ART have a higher perinatal morbidity with a higher risk for prematurity and low birth weight (24, 25).

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In the present study, we investigated neuromotor development and mental health in singletons born at term after ICSI and after SC at the age of 5.5 years. This is the first study to exclude the influence of prematurity in a large controlled study well powered to detect an equivalent mental development.

MATERIALS AND METHODS

Study Design

The aim of the study was to assess a cohort of children conceived by ICSI at the age of 4–6 years (who had been previously assessed at birth). The primary outcome measure was the intelligence measured with the Kaufman Assessment Battery for Children (K-ABC). Other measures were biometric data, health status, acute, chronic, and childhood illnesses, development, and data on family functioning.

The study was designed as a prospective controlled single blinded study with a one-sided equivalence design for the primary outcome. For sample size calculation no difference between ICSI and control was expected for the primary outcome (K-ABC), regarding a $\leq$4-unit decrease of the ICSI group to be insignificant. Setting the alpha error to .05 and statistical power to 90%, at least 250 children in each group were needed.

We expected response rates of 50% for the ICSI children and 25% for the control children.

Children

The children born after ICSI were recruited from a cohort of children that took part in a previous prospective cohort study (26–28). In the previous study, 2,688 pregnancies after ICSI were followed prospectively and the children (n = 3,373) were examined at the age of 6–8 weeks. The study found an increased malformation rate after ICSI (odds ratio 1.25, 95% confidence interval 1.11–1.40) (26–28).

A total of 1,947 parents of the previous study had agreed to be contacted again. Among these children, there were 1,430 singletons born at term. From this cohort of ICSI children, all singletons born at term ($\geq$37+0 weeks of gestation) living in the areas of Lübeck, Kiel, Hamburg, Magdeburg, Berlin, Bremen, Hannover, Essen, and Münster were invited to take part in the study. This was designed to increase the likelihood of sociodemographic matching. In addition, the control subjects were formally matched regarding age (±3 months) and gender of the child and maternal age (±5 years).

Figures 1 and 2 illustrate the inclusion of ICSI and control children. The families of 574 term-born ICSI children were contacted by mail. If they did not respond, they were contacted by mail a second time. Only those families that agreed to participate were contacted by telephone to schedule the examination.

The control subjects were recruited via the residents' registration offices of the same areas in which the ICSI children lived (to allow for approximate sociodemographic equivalence). The families of the control subjects were contacted once by mail. Those parents that agreed to participate were contacted by telephone to schedule the examination. Those parents that did not answer to the initial contact could not be contacted again according to German law. Children who were conceived after any kind of infertility treatment were excluded.

Examination

The children were examined form September 2004 to August 2006 at the age of 4–6 years in one of the following towns: Lübeck, Kiel, Hamburg, Magdeburg, Berlin, Bremen, Hannover, Essen, or Münster. The examinations were performed in different locations to avoid a long journey for the children. However, examinations were performed in a standardized setting at each location by one of four pediatricians. The psychologic testing was performed by the same psychologist for all children. The pediatrician and the psychologist were blinded to the mode of conception, and the parents were advised not to reveal the mode of conception. Medical and psychologic examination took place on the same day and took a maximum 2 h for each child.

The neurologic examination was detailed and included the standardized Zimmer/Volkamer motor test MOT 4–6 for children aged 4–6 years (29). The MOT 4–6 measures motor abilities of children aged 4–6 years and consists of 18 items assessing balance, coordination, fine motor skills, flexibility, adroitness, reactivity, jumping power, quickness, and accuracy of movements.

The psychologic examination of intelligence and abilities was based on the K-ABC, German version (30).

Medical History of the Child

The medical history of each child was assessed by an interview and an additional questionnaire which the parents answered in a separate room while their child underwent the psychologic testing.

Statistics

The data were evaluated with the personal computer–based program SPSS 14.0 (SPSS, Chicago, IL). The association between factors and outcomes was tested using the chi-squared test, and *t* tests were used to compare the means of continuous variables. To assess equivalence for our primary outcome, Equiv Test 1.00 (Statistical Solutions, Ireland) was used. *P* values smaller than 5% were considered to be significant.

Ethics

The study was approved by the ethics committee of the University of Lübeck, Germany. Written informed consent was obtained from the parents.

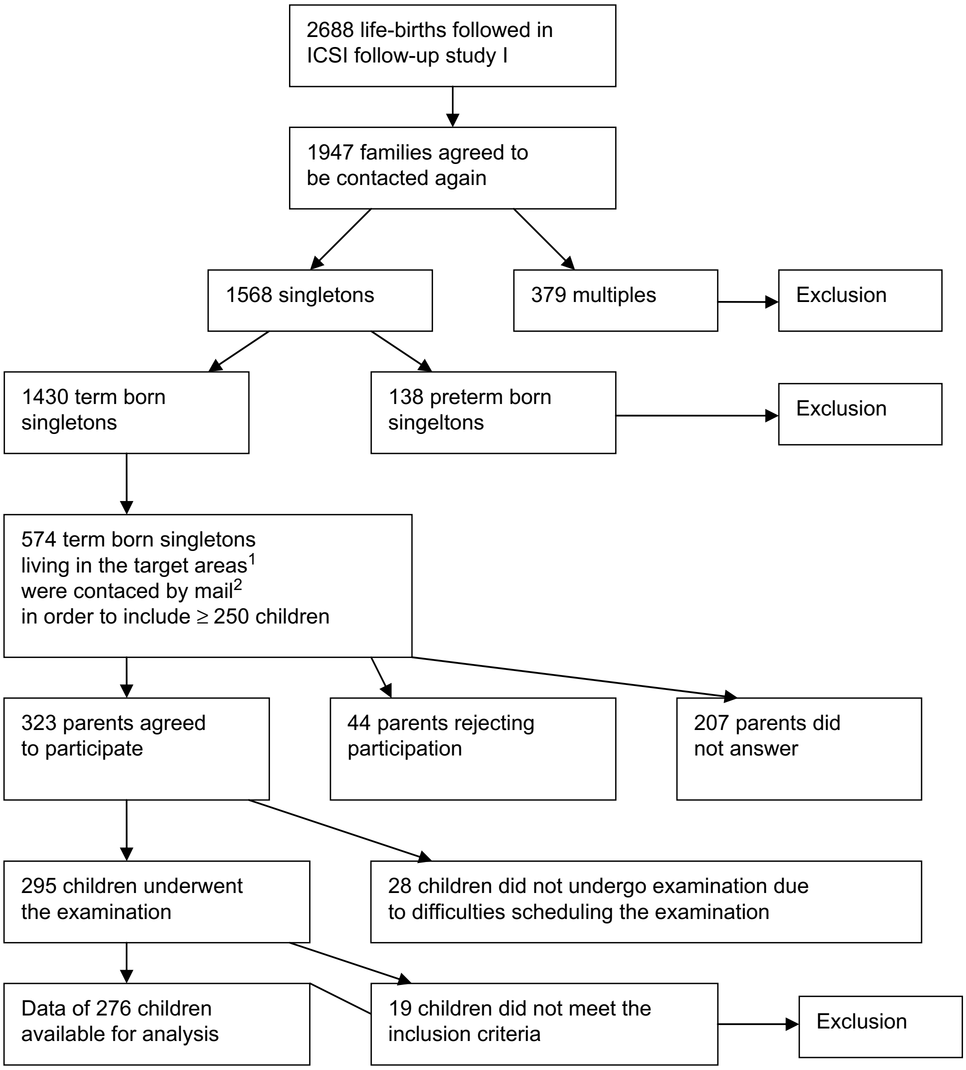
RESULTS

Participation

We asked 574 eligible ICSI and 2,577 control parents to take part in the study via postal enquiry. A total of 323 ICSI

FIGURE 1

Recruitment strategy of the ICSI group.



[1]All singletons born at term living in the areas of Lübeck, Kiel, Hamburg, Magdeburg, Berlin, Bremen, Hannover, Essen and Münster were invited to take part in the study.
[2]ICSI families were contacted by mail. If they did not answer, they were contacted a second time by mail. In case of agreement to participate, they were contacted by telephone.

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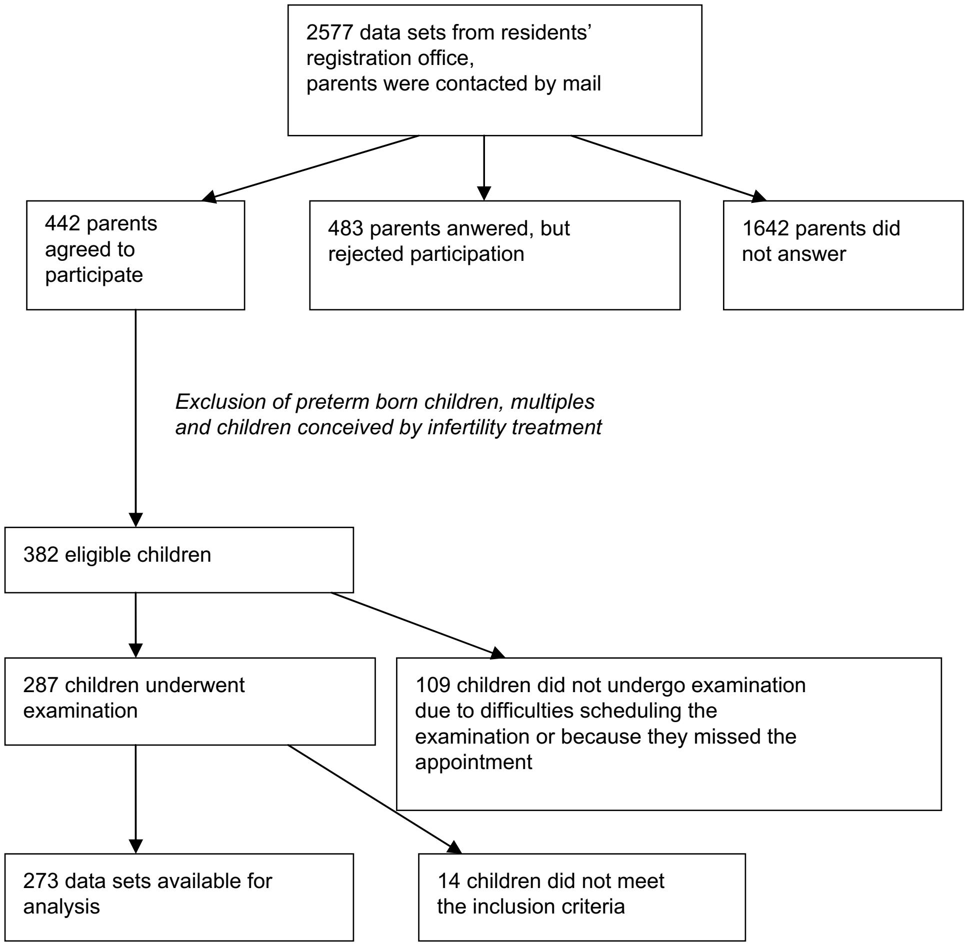
parents (56.3%) and 442 control parents (17.2%) were willing to take part in the study. The examination could be performed in 295 ICSI and 287 control children. A total of 19 ICSI children and 14 controls had to be excluded, because the examination revealed that they did not meet the inclusion criteria. Finally, the data of 276 ICSI and 273 control children were available for analysis.

Characteristics of the Families

The data of 276 ICSI children and 273 controls were available for analysis. The ICSI and control children were very closely matched regarding age at the time of the examination (Table 1). There were no differences between the families except in parental age, marital status, and number of siblings (Table 1). In spite of matching for maternal age, the parents of the ICSI children were significantly older than the parents of the control children. The ICSI parents were significantly more likely to be married and significantly less likely to be divorced than the parents of the control children. The control children had significantly more brothers and sisters than the ICSI children. There were no differences in social status and parents' education. A high percentage of parents of both groups had a high educational level with a university

FIGURE 2

Recruitment strategy of the control group.



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entry exam or higher (58.9% in the ICSI group and 58.4% in the control group) and represented the upper class according to the social class index of Deck and Röckelein (31) (60.6% and 52.9%, respectively).

Perinatal Characteristics

There were no significant differences in gestational age and birth weight (Table 1). Significantly more ICSI children had a low Apgar score at 5 min (Apgar $\leq$7) than control children (4.0% vs. 0.8%, respectively; $P<.05$), but there was no difference in the Apgar score at 10 min. The arterial pH of the umbilical cord was significantly lower in the ICSI children than in the control children (7.27 $\pm$ 0.09 vs. 7.29 $\pm$ 0.08; $P<.05$), but there was no difference regarding the neonatal admissions.

Developmental Milestones

According to the parents' reports there were no differences regarding the age at which key developmental milestones were achieved (Table 2).

Neurologic Examination and Motor Skills

There were no differences between ICSI and control children in the neurologic examination, except for a higher incidence of strabismus in the control children (2.9% vs. 0.4%; $P<.05$; Table 2).

The overall motor skills of both groups were rated as normal. The ICSI and control children were comparable in the overall test result (standard value in MOT 4–6: 107.12 $\pm$ 13.31 vs. 106.15 $\pm$ 14.03, respectively; ns) as well as in the single items of the test (Table 2). In their subjective assessment of the motor skills, the pediatricians rated the motor skills as subnormal in 6.3% of the ICSI children and in 7.8% of the control children (ns).

A total of 6.2% (17 of 274) of the ICSI parents and 5.5% (15 of 271) of the control parents rated their child's physical strength as being lower than other children of the same age (ns).

Behavioral and Emotional Development

The K-ABC showed normal behavioral and emotional development for both groups (Table 3). The ICSI and control children

TABLE 1

Family characteristics and perinatal data.

	ICSI group (n = 276)	Control group (n = 273)	*P*
Child's age (months)			
Mean age ± SD	64.72 ± 6.70	65.41 ± 7.04	
Median	64.0	65.0	
Minimum	48.0	48.0	
Maximum	82.0	82.0	
Maternal age (years)	34.31 ± 3.62	31.7 ± 4.6	<.001
Paternal age (years)	36.93 ± 5.4	34.43 ± 6.28	<.001
Marital status			<.001
Married	246/256 (96.1%)	188/249 (75.8%)	
Divorced	5 (1.9%)	20 (8.1%)	
Brothers and sisters	0.57 ± 0.65	1.18 ± 0.85	<.001
Parental education: university entry exam or higher	159/269 (59.1%)	159/270 (58.9%)	ns
Social status index[a]			ns
Upper class[a]	154/254 (60.6%)	137/259 (52.9%)	
Middle class[a]	99/254 (39.0%)	121/259 (46.7%)	
Lower class[a]	1/254 (0.4%)	1/259 (0.4%)	
Social status index[a]	6.86 ± 1.09	6.66 ± 1.31	ns
Perinatal characteristics			
Gestational age (weeks)	39.87 ± 1.33	39.88 ± 1.3	ns
Birth weight (g)	3441.43 ± 450.66	3513.61 ± 445.67	ns
Apgar 5′ ≤7	11/272 (4.0%)	2/266 (0.8%)	<.05
Apgar 10′ ≤7	2/272 (0.7%)	—	ns
Arterial pH of umbilical cord	7.27 ± 0.09	7.29 ± 0.08	<.05
Neonatal admission required	24/273 (8.8%)	19/272 (7.0%)	ns

[a] According to social status index of Deck and Röckelein (29).

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were equivalent regarding sequential processing, simultaneous processing, learning abilities, and planning abilities. The ICSI and control children showed normal intelligence as represented by the learning abilities scale. A sensitivity analysis with adjustment for maternal age and social status also showed equivalent results for all subscales of the K-ABC.

Clinical significant differences between two scales (≥10-point differences) would indicate specific problems or deficits (Table 4). The percentage of children showing significant differences was within the normal range in both groups and did not differ between the groups. A total of 21.0% of the ICSI children and 23.9% of the control children had significantly lower scores in the sequential processing scale compared with the simultaneous processing scale. This could indicate problems regarding memory or deficits in the ability to concentrate.

DISCUSSION

We could show that the ICSI singletons born at term showed normal development with good neurologic health and good motor skills at the age of 5.5 years.

Except for a higher incidence of strabismus in the control children, we did not observe any difference in the detailed neurologic examination between the groups. Our neurologic examination included a detailed standardized motor test with 18 different subtests. Most other studies have assessed only fine and gross motor skills, and only a few performed a more detailed assessment (17, 20).

The larger registry-based studies reporting an increased neurologic morbidity in children born after ART (7–9) are in contrast to the prospective controlled studies that are based on interviews and neurologic examinations. In one registry-based study, Pinborg et al. showed no difference regarding severe neurologic disabilities such as mental retardation and cerebral palsy between IVF twins, IVF singletons, and SC twins (32). Low birth weight or prematurity and male gender were independent risk factors for neurologic sequelae in all three cohorts and for twins alone. After adjustment for low birth weight and prematurity, the incidence of neurologic disabilities was not influenced by IVF, maternal age >35 years, or being a twin (32). These risk factors have been suggested by others to increase the risk for cerebral palsy and contact with childhood disability services (8).

TABLE 2

Motor skills, abnormalities in neurologic examination, and age at which developmental milestones were reached.

	ICSI group (n = 276)	Control group (n = 273)	*P*
Results of MOT 4–6			
Motor skills (total points in test)	22.06 ± 4.95	22.01 ± 5.18	ns
Motor skills (standard value)	107.12 ± 13.31	106.15 ± 14.03	ns
Subnormal motor skills (subjective assessment of pediatrician)	17/272 (6.7%)	21/271 (7.8%)	ns
Lower physical stength than other children of same age (assessment of parents)	17/274 (6.3%)	5/271 (5.5%)	ns
Neurologic examination			
Abnormality in facial expression	1/272 (0.4%)	1/273 (0.4%)	ns
Abnormality in ability to follow with eyes	1/272 (0.4%)	1/273 (0.4%)	ns
Strabismus	1/270 (0.4%)	8/272 (2.9%)	<.05
Age at which milestone was reached (months)			
Sitting	7.44 ± 1.69	7.43 ± 1.58	ns
Walking	13.41 ± 2.18	13.08 ± 2.03	ns
Talking first words	12.89 ± 3.98	13.51 ± 4.64	ns
Without diapers	33.48 ± 8.72	35.29 ± 10.19	ns

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Neurologic sequelae such as cerebral palsy or childhood epilepsy are rare events. Therefore, sample sizes of several thousand children, which can only be attained in registry-based studies, are needed to show a relevant increase in the risk. Those registry-based studies included children up to the ages of 4–14 years; the very few prospective studies on older children are available only up to the age of 8 years. On the other hand, it must also be noted that these registries were not established to monitor specifically the neurologic health of ART children. Another problem of the registries is that the number of preterm-born children is higher after ART compared with SC, which would influence the study results, even in studies controlled for plurality.

The increased risk of neurologic problems, especially cerebral palsy, observed in the registry-based studies can largely be explained, though not completely, by the higher frequency of twins, low birth weight, and low gestational age, but an effect of IVF, parental infertility, or other factors not adjusted for in the studies cannot be excluded.

The ICSI children in the present study showed a normal emotional and behavioral development with a normal intelligence at the age of 5.5 years. This was true not only for the isolated test results but also for comparison with the control group. The groups were very similar regarding sociodemographic factors. Both groups show a mean social status and parental education level that exceeded the national average. This indicates that families taking part in clinical studies do not represent the average society. This has to be taken into account when assessing the children and interpreting the data.

The cognitive function of children can be influenced by various factors, such as parental education and parental

TABLE 3

Test results of the Kaufman Assessment Battery for Children.

	ICSI group (n = 276)	Control group (n = 273)	*P* value to reject nonequivalence[a]
Sequential processing	101.90 ± 11.53	101.71 ± 11.72	>.01
Simultaneous processing	104.57 ± 11.03	104.59 ± 10.91	>.01
Learning ability/intelligence	102.87 ± 9.19	102.78 ± 9.04	>.01
Planning ability	102.97 ± 11.32	101.60 ± 11.25	>.01

Note: Complete test results were available for 271 ICSI children and 268 control children.
[a] Null hypothesis for equivalence: μ (control) $-$ μ (ICSI) $>$ 4 units.

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TABLE 4

Number and percentage of children with significant differences between two scales.

	ICSI group (n = 276)	Control group (n = 273)	*P* value
Sequential processing < simultaneous processing	57 (21.0%)	64 (23.9%)	ns
Sequential processing > simultaneous processing	27 (10.1%)	27 (10.0%)	ns
Sequential processing < planning ability	31 (11.6%)	25 (9.3%)	ns
Sequential processing > planning ability	36 (13.5%)	25 (9.3%)	ns
Simultaneous processing < planning ability	25 (9.4%)	26 (9.6%)	ns
Simultaneous processing < planning ability	47 (17.6%)	45 (16.7%)	ns
Learning ability < planning ability	21 (7.9%)	25 (9.3%)	ns
Learning ability > planning ability	39 (14.6%)	26 (9.6%)	ns

Note: A clinically significant difference is defined as ≥10-point difference between two scales. *P* values were calculated for the comparison of ICSI and control children. Complete test results were available for 271 ICSI children and 268 control children.

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age. It has been shown that parental educational level plays a crucial role. Place and Englert found a lower mean IQ in IVF and ICSI children compared with SC children aged 0–5 years, but this difference disappeared after adjusting for parental education. The fact that the between-group differences disappeared after adjustment for the levels of education of the parents shows how crucial it is not to underestimate the influence of such factors when evaluating child development. In a European study, Ponjaert-Kristoffersen et al. (18) showed that, although there were no differences in the IQ of IVF/ICSI and control children at age 5 years, older maternal age at birth was significantly linked to lower full-scale IQ and verbal IQ as well as lower abilities on a subtest of the performance scale (object assembly) in IVF/ICSI children. Higher maternal educational level was linked to better abilities on the object assembly scale, whereas lower maternal educational level was linked to lower scores on spatial visualization analysis (18). Leunens et al. (20) found a slightly, but significantly, higher IQ in ICSI children compared with SC children at the age of 8 years, probably because of a higher maternal educational level in the ICSI group (20). The present groups were very similar regarding social status and parental education, but they differed significantly—as in almost all controlled studies (14, 18, 20)—in parental age. Owing to a period of unwanted childlessness, subfertile couples generally conceive at an older age than fertile couples. However, adjustment for the maternal age did not change the results.

Other factors apart from sociodemographic characteristics that play an important role are low gestational age and low birth weight. In a registry-based cohort study, Strömberg et al. found an increased risk for suspected developmental delays in children aged 1.5–14 years, but when singletons and twins were analyzed separately this increase was no longer statistically significant different, neither for singletons nor for twins (8). Those data were generated from records of rehabilitation services. Risk factors for suspected developmental delay were low birth weight and low gestational age.

The strength of the present study is that we reassessed at 5 years a cohort of German post-ICSI born children, the study being well powered for our primary outcome. Although this is one of the largest studies on this topic, cohort sizes such as in registry based studies cannot be reached. Only four different pediatricians examined the children in a standardized manner. Compared with other studies, mainly multicenter studies, with different recruitment strategies within the study, both groups were matched as closely as possible, with all children of each group being recruited in the same way. A weakness of this study lies in the low response rate in the control group. In recruiting a control group from the general population with the limitation of only one postal contact by the German law, a higher response rate cannot be expected. Studies recruiting control children through schools and nurseries have reached response rates of 30%–40%, if mentioned at all. However, recruitment through schools implies a selecting bias that we wanted to exclude by this complex population-based design.

Because the aim was to assess whether ICSI has an effect on the children, only term-born singletons were assessed to exclude the confounding influence of multiple births and prematurity. Therefore, the reassuring results are only applicable to term-born singletons. The neuromotor health of children born as multiples or prematurely will be influenced by those factors. However, with regard to the present results it is not likely that ICSI itself has an effect on the neurologic health of multiples or premature born children.

Overall, our findings suggest that factors other than mode of conception influence the long-term cognitive development of ICSI children, such as parental educational levels, low birth weight, and prematurity. Parents of term-born infants conceived by ICSI can be counseled that their child will develop in the same way as children born after SC, at least up to the age of 5–6 years. And because it has been shown that at this age ability is strongly correlated with adult ability ($r = -0.7$), this represents valuable news.

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