Cognitive Development of Singletons Conceived by Intracytoplasmic Sperm Injection or *In vitro* Fertilization at Age 5 and 10 years

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Objective To investigate the cognitive functioning of low-risk singletons born after intracytoplasmic sperm injection (ICSI) or in vitro fertilization (IVF) at the age of 5 or 10 years. **Methods** Sixty-nine children (35 ICSI, 34 IVF) participated voluntarily in the study that had been approved by the local IRB. Their intellectual functioning was examined by the Kaufmann Assessment Battery for Children. **Results** The IQ of the study group fell in the normal range (mean = 98.2; *SD* = 12.2). ICSI children (IQ = 94.1, *SD* = 13.8) had statistically lower intellectual abilities compared to IVF children (IQ = 102.0, *SD* = 9.1; $t = -2.81$, $p = .005$), especially in simultaneous mental processing. 23.5% ICSI children, but only 2.9% IVF children ($p = .011$) had at least borderline delayed cognitive development. **Conclusions** Most artificially conceived singletons show a normal cognitive development, however the method of fertilization seems to have an impact on their IQ. ICSI might be associated with the risk for a slightly delayed cognitive development compared to IVF.

Key words assisted reproduction; child follow-up; cognitive development; intracytoplasmic sperm injection; *in vitro* fertilization.

Introduction

Since the first ''test tube baby'' Louise Brown was born in 1978, assisted human reproduction techniques (ART) are used increasingly, raising the interest in the psychological outcome of artificially conceived children. Children born after ART are a relevant group for pediatric psychologists for two reasons: First, their developmental prognosis is not yet clear, and there may be an increased risk for developmental, behavioral and/or emotional problems (Izat & Goldbeck, 2008). Secondly, parents with ART children were reported to be high utilizers of hospital care for their child independently from the child's health status (Pinborg, Rasmussen, & Nyboe, 2004) and therefore they might have special needs for reassurance and psychological counselling. Considering especially the increasing rates of intracytoplasmic sperm injection (ICSI) (Jain & Gupta, 2007), it seems very important to clarify the developmental prognosis of children after ICSI. Compared to in vitro fertilization (IVF), ICSI is the more invasive and more selective artificial reproduction technique. There are biologically plausible reasons such as a higher rate of chromosomal anomalies why ICSI children may be at increased risk for delayed mental development (Bonduelle et al., 2002; Leslie, 2004). In contrast to IVF, ICSI bypasses the natural selection process of sperm cells and therefore it has been suggested that there might be an increased risk of selecting abnormal cells, including the risk of sex chromosomal abnormalities (Bonduelle et al., 2002; In't Veld, Brandenburg, Verhoeff, Dhont, & Los, 1995) and of structural and numerical chromosomal aberrations (Bonduelle, Joris, Hofmans, Liebaers, & Van, 1998). These risks mainly represent consequences of the genetic abnormalities underlying male subfertility or infertility (Chantot-Bastaraud, Ravel, & Siffroi, 2008). Recent data suggest that assisted reproductive technology might also affect epigenetic characteristics of the male gamete, the female gamete, or might have an impact on early embryogenesis. It might be also associated with an increased risk for genomic imprinting abnormalities (Georgiou et al., 2006). In contrast to children born after IVF, whose cognitive development can be considered normal at least up to the age of 5 years according to a recent comprehensive review (Wagenaar,

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Journal of Pediatric Psychology 34(7) pp. 774–781, 2009
doi:10.1093/jpepsy/jsn120
Advance Access publication November 26, 2008

Huismann, Cohen-Kettenis, & Adelemarre-van De Waal, 2008), there are not sufficient studies available on the psychological outcome of children conceived by ICSI, especially not until school age. The findings regarding the cognitive development of ICSI children are currently inconsistent. The first study investigating the cognitive functioning of ICSI infants compared to IVF infants (Bowen, Gibson, Leslie, & Saunders, 1998) reported significantly lower mean developmental indices of ICSI children as measured by the Bayley Scales of Infant Development compared to IVF children at the age of 12 months. Further studies with infants and toddlers found no differences on the Bayley Scales dependent of the method of fertilization (Bonduelle et al., 2003; Dittrichova et al., 2004; Papaligoura, Panopoulou-Maratou, Solman, Arvaniti, & Sarafidou, 2004). Recently several studies were published following up the cognitive development of ART children until preschool and primary school age, mostly using the Wechsler Preschool and Primary Scales of Intelligence, reporting again inconsistent findings. Some studies found no differences between mental development of children conceived by ICSI or IVF or natural conception (NC) (Leslie et al., 2003; Place & Englert, 2003; Ponjaert-Kristoffersen et al., 2005; Wennerholm et al., 2006), others showed disadvantages of ICSI children compared to IVF or NC children (Franco Junior et al., 2004; Knoester et al., 2007; Ponjaert-Kristoffersen et al., 2004). In contrast, advantageous cognitive development of ICSI children compared to NC children at 8 years was reported in a Belgian study using the Wechsler Intelligence Scale for Children Revised (WISC-R) (Leunens, Celestin-Westreich, Bonduelle, Liebaers, & Ponjaert-Kristoffersen, 2006), however, at the follow-up of the same cohort at age 10 the IQ results of ICSI and NC children converged (Leunens, Celestin-Westreich, Bonduelle, Liebars, & Ponjaert-Kristoffersen, 2008).

It is known that many factors contribute to the cognitive development of ART children, e.g. multiple pregnancies (Bonduelle et al., 2003; Dittrichova et al., 2004; Olivennes, Golombok, Ramogida, & Rust, 2005), preterm birth (Dittrichova et al., 2004; Olivennes et al., 2005), sex, parity, child age at testing (Bonduelle et al., 2003), parental education (Leunens et al., 2006; Place & Englert, 2003), and maternal age (Ponjaert-Kristoffersen et al., 2005).

In summary, the study findings on the cognitive development of ICSI children are inconclusive so far. The different results of the above cited studies may be due to several methodological factors: First, the early studies were conducted during infancy and toddlerhood, however cognitive dysfunctions and/or learning disabilities can often not be reliably detected before school age (O'Brien, 2001). Secondly, most of the studies with preschoolers and school children used the Wechsler scales, which is known to be influenced by acquired knowledge (Kline, Guilmette, Snyder, & Castellanos, 1992). ART children often stem from families with privileged socio-economic and educational background (Schmidt, 2006) and therefore findings based on the Wechsler scales may be biased by the socio-economic situation. Moreover, small sample sizes, selection effects due to different recruitment strategies, as well as the above-mentioned confounding risk factors due to inclusion of preterm births and multiples limit the conclusiveness and comparability of previous studies.

In this study we tested the hypothesis, whether ICSI singletons in the absence of relevant peri-natal risk factors show significantly and clinically relevant worse cognitive functioning compared with IVF singletons at preschool and school age. Cognitive functioning was assessed with the Kaufman Assessment Battery for Children (K-ABC). In contrast with the Wechsler Scales, the K-ABC allows to determine the child's capacity in two different cognitive styles, sequential versus simultaneous mental processing (Heath & Obrzut, 1988; Kamphuis & Reynolds, 1987; Kaufman & Kaufman, 1983b), and it was demonstrated that acquired knowledge has been widely removed from the mental processing scores of the K-ABC (Kaufman, O'Neal, Avant, & Long, 1987; Klanderman, Perney, & Kroeschell, 1985).

Participants and methods

The participants of the study were recruited between January and August 2007 using the registries of two German human reproduction clinics, located in Ulm. Two age groups were included: preschool children at the age of 5 years and school-age children at the age of 10 years. These age groups were chosen for this follow-up assessment because they are associated with decisions on education, i.e. time point of school enrolment and change to secondary school. In the German school system children enter elementary school at age 6 and are divided into three different school types at age 10 (*Hauptschule* with 9 years of education, *Realschule* with 10 years of education, and *Gymnasium* which prepares children for college/university within 12 or 13 years of education). We identified mothers who had become pregnant after IVF or ICSI according to the medical charts of the reproduction clinics and invited their children to participate in the study. To avoid a cumulation of risk factors, multiple pregnancies and children who were born before week 34 after

conception were excluded. Neither the participating children had known chromosomal disorders or neurological diagnoses, nor had any of the parents a history of learning disabilities. The cognitive functioning was assessed in the context of a study of the physical and psycho-social development of ART children. The study protocol was approved by the IRB at the University Hospital Ulm. About 321 parents (303 from one community clinic, 18 from another university clinic) fulfilled the eligibility criteria and received a written invitation to the study. About 75 parents declared their interest in the study, and finally 69 children participated (response rate 21.7%). Reasons for non-participation were lack of time, too long distance to the study centre, or lack of interest. The informed consent of parental caregivers and the assent of children were acquired according to the principles of the local IRB. Because we were not allowed to analyze data of the non-participants due to German data protection laws, we were not able to compare the medical or socio-demographic data of participants and non-participants. However, both subgroups of ART children (ICSI and IVF) were recruited according to the same strategy, thus there is no reason to assume different selection biases.

The Kaufman Assessment Battery for Children (Kaufman & Kaufman, 1983a) is a clinical instrument for assessing cognitive development. Based on research and theory in cognition and neuropsychology, the K-ABC defines intelligence as a child's ability to solve problems using simultaneous and sequential mental processes (Kaufman & Kaufman, 1983b). The K-ABC measures intelligence separately from achievement. The 16 subtests are grouped into a mental processing set and achievement set, which yield separate global scores (mean = 100, $SD = 15$). The mental processing set is then grouped into those requiring primarily sequential processing of information and those requiring simultaneous processing, with separate global scores (mean = 100, $SD = 15$) for each. The K-ABC has good to excellent reliability and validity (Melchers & Preuss, 1992). We used the German version of the K-ABC (Kaufman & Kaufman, 2001) with age-specific reference data from German speaking children in Germany, Switzerland, and Austria. Norms are based on administration of the tests to representative samples of >100 children at each 6-month age interval from 2.5 to 12.5 years, a total of 3098 individuals. The assessment in this study was performed by two trained and supervised research assistants.

Data on the medical history were taken from the mothers' medical records. Additionally, parents were interviewed on the history of pregnancy, birth, and early development of their children. Socio-economic data were gathered by structured interviews with parents. Socio-economic status (SES) was determined by parental education, the highest degree within a couple indicated the classification of the family.

Statistical analyses

Raw scores of the K-ABC were transformed into standard scores according to the norm tables of the German test manual. Mean scores, ranges and standard deviations of the sequential mental processing index, the simultaneous mental processing index, the mental processing composite and the achievement index were calculated. According to a series of exploratory *t*-tests for independent samples, there was no effect of age group on the K-ABC results (p between .34 and .93), therefore the two age cohorts were primarily analyzed together, and in a second step the analyses were repeated for both age groups. The group differences of the mean scores were analyzed by *t*-tests for independent samples. About 95% confidence intervals of mean differences were determined. A significance level of $\alpha = .05$ (two tailed) was considered sufficient to accept the alternative hypothesis. According to a statistical power analysis, a sample size of $n \geq 34$ per group was considered sufficient (power = .80) to detect group differences of ≥10 IQ points. To estimate effect sizes, Cohen's d was calculated for all group comparisons.

Results

Thirty-four singletons conceived by ICSI and 35 singletons conceived by IVF participated in the study. Details of the sample characteristics are shown in Table I. No significant differences appeared between ICSI singletons and IVF singletons with respect to socio-demographic, socio-economic, and medical variables except the method of fertilization. So both groups can be considered comparable.

Most of the participants reached scores in the normal range of the reference population (mental processing composite (IQ): mean = 98.2; $SD = 12.2$, range: 47–124). However, singletons born after ICSI had consistently lower scores in all sub-scales of the K-ABC compared to singletons born after IVF (Table II). These differences were statistically significant in the domains mental processing composite, simultaneous mental processing, and achievement. The mean difference of the domain sequential mental processing failed the significance level, but can be considered a statistical trend ($p = .106$). The mean difference of 7.9 points in the mental processing composite, which represents the IQ, is about half a standard deviation. The most prominent difference (10.5 points) was found in

Table I. Sample Characteristics (No Significant Differences between ICSI and IVF Groups)

Variable	ICSI singletons ($n = 34$)	IVF singletons ($n = 35$)
Gender of child		
Female, *n* (%)	16 (47.1)	15 (42.9)
Male, *n* (%)	18 (52.9)	20 (57.1)
Age of child		
Age group 5 years, *n* (%)	20 (58.8)	21 (60)
Age group 10 years, *n* (%)	14 (41.2)	14 (40)
M (*SD*)	7.1 (2.4)	7.3 (2.5)
Age of father, *M* (*SD*)	43.6 (4.1)	43.0 (4.6)
Age of mother, *M* (*SD*)	40.7 (4.1)	40.9 (4.7)
Age of mother at birth, *M* (*SD*)	33.7 (3.7)	33.6 (3.5)
Socio-economic status (by parental profession)		
Low, *n* (%)	19 (55.9)	19 (55.9)
Moderate/high, *n* (%)	15 (44.1)	15 (44.1)
Number of brothers/sisters		
0	11 (32.4)	14 (40.0)
1	13 (38.2)	12 (34.3)
2	5 (14.7)	7 (20.0)
>2	5 (14.7)	2 (5.7)
Pregnancy duration (weeks), *M* (*SD*)	39.5 (1.8)	38.7 (1.6)
Birth weight (g), *M* (*SD*)	3.352 (547)	3.192 (593)
Birth length (cm), *M* (*SD*)	51.2 (2.3)	50.8 (3.3)
Indication for fertilization		
Azo-/oligospermia, *n* (%)	8 (23.5)	4 (11.4)
Tubular problem, *n* (%)	3 (8.8)	5 (14.3)
Sperm quality, *n* (%)	6 (17.6)	1 (2.9)
Sterilization, *n* (%)	2 (5.9)	1 (2.9)
Uterus problem, *n* (%)	0 (0)	2 (5.7)
Other, *n* (%)	1 (2.9)	2 (5.7)
Unknown, *n* (%)	14 (41.2)	20 (57.1)

the simultaneous mental processing index. Effect sizes were moderate ($d > .50$), with the exception of a small effect size in the domain sequential mental processing. Even after elimination of an outlier with a mental processing composite score (IQ) of 47, the results of the between-group comparisons remained stable. Figure 1 illustrates the distribution of IQ scores in both groups, indicating a general shift towards lower IQ scores in the ICSI group. Below average results (<85) in the mental processing composite were found in eight children (23.5%) conceived by ICSI, but only in one child (2.9%) conceived by IVF.

The analyses by age demonstrated the same direction of differences in mental processing and achievement between ICSI and IVF children in both age groups (Table II). However, only in the 5-year-old children the differences by fertilization method reached statistical significance. Effect sizes were large for the 5-year-old

Table II. Results of the Kaufman Assessment Battery for Children for the Total Study Sample, and by Age Groups

	Total study group ($n = 69$)					Age group 5 years ($n = 41$)			Age group 10 years ($n = 28$)		
Variable	ICSI ($n = 34$) *M* (*SD*)	IVF ($n = 35$) *M* (*SD*)	Δ mean 95% CI ES	*t*	*p*	ICSI ($n = 20$) *M* (*SD*)	IVF ($n = 21$) *M* (*SD*)	*p* *ES*	ICSI ($n = 14$) *M* (*SD*)	IVF ($n = 14$) *M* (*SD*)	*p* *ES*
Mental processing composite	94.1 (13.8)	102.0 (9.1)	−7.9 −13.6 to −2.3 −0.64	−2.81	.006	93.8 (10.1)	102.4 (8.3)	.005 −.85	94.5 (18.3)	101.4 (10.5)	ns −.46
Sequential mental processing	93.3 (15.1)	98.4 (10.3)	−5.1 −11.3 to 1.2 −0.39	−1.63	ns	94.9 (13.3)	99.0 (9.6)	ns −.35	91.1 (17.6)	97.5 (11.6)	ns −.43
Simultaneous mental processing	95.0 (17.5)	105.5 (12.1)	−10.5 −17.8 to −3.3 −0.66	−2.90	.005	93.6 (14.6)	106.4 (10.5)	.003 −.91	97.0 (21.3)	104.1 (14.4)	ns −.39
Achievement	97.7 (12.3)	104.3 (9.1)	−6.6 −11.8 to −1.4 −0.59	−2.52	.014	96.9 (7.5)	103.0 (9.3)	.026 −.68	99.0 (17.2)	106.3 (8.8)	ns −.52
	n (%)	*n* (%)		χ^2	*p*	*n* (%)	*n* (%)	*p*	*n* (%)	*n* (%)	*p*
Children with mental processing composite <85	8 (23.5)	1 (2.9)		6.50	.011	5 (25)	0 (0)	.014	3 (21.4)	1 (14.3)	ns

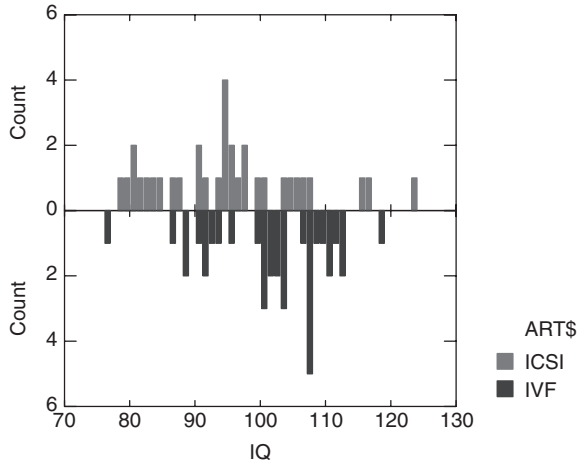

Figure 1. Distribution of IQ scores (mental processing composite) in both study groups.

children regarding mental processing composite and simultaneous mental processing, moderate for the achievement index, and small for the sequential mental processing indices. Effect sizes for the 10-year-old children were moderate for the achievement index, and small for the three mental processing indices.

Discussion

This study makes an importantly new contribution to our understanding of the developmental prognosis of children conceived by ICSI or IVF. So far, there are only few studies which follow up these children until school-age, and the main results of our study challenge the findings of several previous studies. Our study included 5- and 10-year-old singletons without concurrent high-risk factors with known effects on developmental outcome, besides method of fertilization.

Our results indicate that singletons born after ICSI might have an elevated risk of borderline delayed cognitive development compared with singletons conceived by IVF. Almost every fourth ICSI child in the study sample, but only one of 35 IVF children had a low-intelligence level of more than one standard deviation below the age norm, thus demonstrating a clinically relevant cognitive impairment for a considerable subgroup of singletons conceived by ICSI. These children probably need some special education and/or cognitive training. Moreover, it is known that these children are on risk to develop elevated behavioral, emotional, and social problems (Kavale & Forness, 1996). We found statistically significant mean differences of simultaneous mental processing and of the mental processing composite as measured by the K-ABC between ICSI and IVF children across the two age groups of 5 and 10 years. The average cognitive functioning of ICSI singletons was about half a standard deviation below the average level of IVF singletons. Analyses by age subgroups demonstrated significantly less mental processing abilities in the ICSI children compared with IVF children at age 5 years. Similar differences at age 10 years failed to reach the significance level. Effect sizes between groups in the different scores of cognitive functioning and across age groups varied between large and small, with a tendency toward larger effect sizes at 5 years.

It is important to note that simultaneous mental processing was the primary domain of difference between ICSI and IVF children. This means that ICSI children in our study group demonstrated some difficulties to integrate multiple dimensions of perceptions and cognitions at the same time, referred to as a component of fluid intelligence (Kaufman & Kaufman, 1983b). Neuropsychological testing is required to detect these specific cognitive problems. So, the differential results of our study propose that rather specific cognitive difficulties based on a mild neuropsychological dysfunction are associated with the method of fertilization. The most likely explanation would be a genetic base of these cognitive problems, as ICSI excludes the natural selection process during conception (Gekas et al., 2001), although none of the children in our study group had known chromosomal abnormalities. However, no cytogenetic examination of the study participants was performed, and therefore this assumption remains speculative. Alternatively, epigenetic characteristics of the gametes or genomic imprinting abnormalities (Georgiou et al., 2006) may be responsible for the elevated risk of impaired cognitive development of ICSI children.

The results of this study are consistent with the study of Bowen et al. (1998), who described a developmental risk of ICSI children at age 12 months compared to IVF children, with the recent findings of Knoester et al. (2007), who demonstrated lower IQ scores in ICSI singletons compared with IVF and NC singletons, and with the findings of Ponjaert-Kristoffersen et al. (2004), who found lower scores of ICSI children in some Performance subtests of the Wechsler Scales at age five compared with NC children. The replication of these previous findings with another method to assess cognitive functioning, the K-ABC, validates the results of these previous studies and adds further specific information on the type of cognitive difficulties that ICSI children might develop. On the other hand, our findings are inconsistent with the results of the International Collaborative Study (Ponjaert-Kristoffersen et al., 2005; Wennerholm et al., 2006) that demonstrated

above average levels of cognitive functioning of ICSI children and no differences compared with IVF children, and they contradict the results of a Belgian study with Dutch speaking children (Leunens et al., 2006, 2008) indicating higher IQ scores of 8-year-old ICSI children compared to NC singletons and similar IQ levels of both groups at age 10 years. Methodological effects and sample effects might be responsible for these discrepancies. The choice of the instrument to assess cognitive functioning might explain inconsistent findings between studies. So far, no study had used the K-ABC to assess the cognitive development of ART children, and almost all studies were based on the Bayley Scales or the Wechsler Scales. However, the Wechsler Scales measure a more complex construct of intelligence than the mental processing scales of the K-ABC (Kline et al., 1992), whereas the K-ABC is able to describe cognitive functioning on a more basic neuropsychological level. The domain of simultaneous mental processing is not explicitly included in the WISC-C. Additionally, the K-ABC measures achievement separately from mental processing, whereas the Wechsler scales include aspects of achievement and are therefore known to be sensitive to environmental stimulation (Tong, Baghurst, Vimpani, & McMichael, 2007). However, these effects may be valid only for the former versions of the Wechsler scales, and the recent revision (WISC-IV) may be less dependent of environmental factors having an impact on the test results. Anyway, interpretation of the results of cognitive testing has to take into account that children conceived by ART are known to stem from primarily positive environmental conditions, compared to average NC children. The positive social environment due to above-average economic living conditions and good educational level of ART parents might provide a set of stimulating developmental conditions that is able to compensate some cognitive delay, especially if cognitive functioning is assessed on a more complex level. So, to detect milder and more specific forms of delayed cognitive development in ART children it seems useful to use instruments which measure problem solving and achievement separately and which are able to differentiate between different cognitive styles, including simultaneous mental processing. Consistent with the results of Leunens et al. (2006, 2008), our results could indicate a tendency of equalizing differences of cognitive developmental outcome between methods of fertilization with age, and this effect might be due to the stimulation and training provided by the parents of ART children. However, this is a still very speculative assumption that should be investigated in further longitudinal studies.

Some limitations of the present study have to be considered in interpreting the findings. Both the sampling technique and the small sample size limit the generalization of our findings. There was a low response rate of about 22%, and therefore selection effects might have had an impact on the results. It may be that parents with developmentally delayed children were over-represented in our study, because they expected some assistance by the diagnostic procedure. However, this effect would probably have determined both subgroups and would not explain the difference between ICSI and ICF children. Anyway, a within group selection bias towards lower IQ levels should be considered possible. Unfortunately, we were not able to compare basic medical or socio-demographic data of the responding and non-responding families, therefore other within-group selection biases cannot be excluded. Additionally, the small sample size requires a replication of our finding with larger samples. The low-statistical power due to the small size, especially in the subgroup of children aged 10 years may have limited the detection of further significant age specific differences. Another limitation refers to the fact that the recruitment for this study was based on only two ART clinics, thus specific technical procedures or other sample effects may have influenced the results. Therefore the results of this study should be interpreted cautiously, and more large-scale multi-site follow-up studies tracking children into school-age and adolescence are necessary to determine the developmental outcome of ART children. Further studies should follow up the children into late school age and include neuropsychological measures. Additionally, the inclusion of measures of school achievement would be important to describe the possible cognitive difficulties of ICSI children more detailed and to determine whether these children are on risk to develop school problems. Also genetic analyses and the correlation of genotype and phenotype in terms of cognitive function should be considered to broaden our understanding why some ICSI children demonstrate cognitive dysfunctions and others develop normally.

This study adds some evidence to the previously demonstrated concerns regarding the developmental outcome of ICSI children. Considering the pervasive consequences of cognitive functioning for behavioral and social adaptation as well as for school achievement, it is crucial to identify cognitive developmental delays as early as possible.

Although most of the ART children seem to develop normally, there might be a specific elevated risk of borderline delayed cognitive development due to the method of fertilization. Couples considering different methods of ART should be informed about this potential risk.

Parental concerns about the development of their ART child should be taken seriously and accounted for by a thorough psychological assessment. Considering the variability of study findings, a comprehensive follow-up assessment including psychometric testing of the cognitive functioning of all ART children should be provided to identify children with special needs and refer these children to early behavioral interventions and special education.

Conflicts of interest: None declared.

Received April 19, 2008; revisions received October 22, 2008; accepted October 23, 2008

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