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Neuromotor, cognitive, language and behavioural outcome in children born following IVF or ICSI–a systematic review

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BACKGROUND: The effect of *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) on the developing human brain is unclear. The objective of this study is to evaluate neurodevelopmental (ND) outcome of children born following these techniques. METHODS: This systematic review includes studies which compare a group of children born following IVF/ICSI to children born after natural conception by assessing outcome in terms of neuromotor development, cognition, speech/language and behaviour. Specific attention is paid to the studies' methodological quality based on study design, attrition, blinding of the assessor, validity of ND tests used, confounders included and group size or power analysis. RESULTS: Twenty-three out of 59 studies had a good methodological quality including 9 register-based (RB) and 14 controlled studies. RB studies suggested that IVF/ICSI *per se* does not increase the risk for severe cognitive impairment (i.e. mental retardation) or neuromotor handicaps such as cerebral palsy (CP), the association of IVF/ICSI and CP being brought about by the association of assisted conception with risk factors, like preterm birth. In general, controlled studies of good quality did not report an excess of ND disorders in IVF/ICSI-children. However, the majority of studies followed the children during infancy only, thereby precluding pertinent conclusions on the risk of ND disorders that come to the expression at older ages, such as fine manipulative disability or dyslexia. CONCLUSIONS: A negative effect of assisted conception on the developing human brain is not identified; however, further research of high methodological quality in children beyond pre-school age is needed.

Keywords: children; follow-up; ICSI; IVF; neurodevelopmental outcome

Introduction

The effect of assisted conception on the developing human brain is still not clear, notwithstanding the fact that *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) have been introduced more than 25 and 15 years ago, respectively (Steptoe and Edwards, 1978; Palermo *et al*., 1992). Since then many studies have been conducted on neurodevelopmental outcome (an umbrella term covering neuromotor, cognitive, speech/language and behavioural outcome) of children born following these techniques but hitherto uncertainties persist. For instance, contradicting results have been reported considering the association between assisted conception and cerebral palsy (CP), which is a neuromotor disorder that is attributed to non-progressive disturbances in the developing brain (Bax *et al*., 2005). Some studies report an association between assisted conception and CP (Ericson *et al*., 2002; Lidegaard *et al*., 2005; Strömberg *et al*., 2002), whereas others could not demonstrate such association (Pinborg *et al*., 2004; Källén *et al*., 2005; Hvidtjørn *et al*., 2006; Klemetti *et al*., 2006). The lack of clarity on potential neurodevelopmental risk after IVF/ICSI is worrying for multiple reasons. First, the number of pregnancies obtained by an assisted reproductive technology (ART) is steadily increasing. In Europe, up to 3.9% of national births are infants born after ART (Nyboe Andersen *et al*., 2007). Moreover, new and more invasive techniques are introduced at a rapid pace and are not always accompanied by extensive follow-up programmes.

Furthermore, there might be reasons to suppose that IVF/ICSI is associated with an increase in neurodevelopmental problems. Early development of the human nervous system is a complex and neatly orchestrated process which can be affected easily by external influences (De Graaf-Peters and Hadders-Algra, 2006). It has already been established that perinatal outcome of singletons born after assisted conception is worse than that of naturally conceived singletons. Artificially conceived singleton pregnancies end significantly more often preterm and with

low birth weight (Schieve *et al*., 2002; Helmerhorst *et al*., 2004; Jackson *et al*., 2004) and perinatal mortality and neonatal intensive care admission are increased (Helmerhorst *et al*., 2004; Jackson *et al*., 2004).

The lack of consensus about neurodevelopmental risk after IVF/ICSI largely stems from the fact that the results of the various follow-up studies often are difficult to interpret because of methodological shortcomings. Previous reviews mentioned methodological drawbacks but lacked a thorough methodological evaluation (Van Balen, 1998; Buitendijk, 1999; Tarlatzis and Grimbizis, 1999; Olivennes *et al*., 2002; Ludwig and Diedrich, 2002; Ludwig *et al*., 2006; Sutcliffe and Ludwig, 2007). Others focused on subgroups of children, e.g. twins (Pinborg, 2005), children born following ICSI (Van Steirteghem *et al*., 2002; Leslie, 2004), or children born following cryopreservation of embryos (Sutcliffe, 2000; Wennerholm, 2000), or took into account only a part of neurodevelopmental outcome, such as psychosocial well being (Hahn, 2001; Colpin, 2002; Golombok and MacCallum, 2003; Gibson and McMahon, 2004). Therefore, the aim of the present review is to evaluate in a systematic manner studies on neurodevelopmental outcome of children born following IVF or ICSI compared to naturally conceived children. We restricted ourselves to the techniques of IVF and ICSI as the character of these procedures is invasive and a substantial number of follow-up studies have been reported. For the still more invasive techniques, such as preimplantation genetic screening and *in vitro* maturation, follow-up information is almost completely lacking. We first evaluated the methodological quality of the studies in a strict and standardized way. The identified studies of good methodological quality are summarized and the results are presented and discussed in an age-specific manner.

Methodology

Literature search

An extensive literature search was performed for relevant studies on neurodevelopmental outcome of children born following IVF or ICSI. We searched for articles published between 1978 and 5 December 2007 in Medline, Embase (since its first coverage year: 1989), PsycINFO and the Cochrane library. A computer based search strategy with multiple combinations of terms was entered into the databases. This search strategy consisted of all combinations of (i) IVF OR ICSI OR reproductive techniques, assisted OR fertilization *in vitro* AND (ii) child development OR abnormalities OR morbidity OR psychomotor performance OR motor skills OR intelligence OR child psychology OR child behaviour OR developmental disabilities OR nervous system diseases OR CP AND (iii) infant(s) OR child(ren) OR adolescent(s) OR twins OR triplets. Note that the terms were adapted to terminology used in the various databases. In addition, the reference lists of all identified studies and review articles were reviewed for additional articles.

Inclusion and exclusion criteria

We searched for all studies which assessed neurodevelopmental outcome, i.e. neuromotor development, cognition, speech/language and behaviour as a primary outcome measure in IVF or ICSI children and a naturally conceived comparison group. Excluded from the study were studies (i) which did not include a naturally conceived control group, (ii) with a study group size of less than 25 children, (iii) in which the follow-up did not extend beyond the neonatal period, (iv) in which the study group included more than 10% of children born following ovulation induction only (without IVF or ICSI), (v) which compared outcome of children born following IVF or ICSI to children born from donor gametes, adopted children or children born from surrogate mothers and (vi) not published in English. The decision to exclude studies with a group size of less than 25 children was based on preliminary results which revealed that a small group size virtually always was associated with a poor methodological quality. Family studies were only included when a substantial part of the study was devoted to the child's neurodevelopmental outcome.

Identification

The search strategy yielded 1131 publications in Medline and Embase, 213 in PsycINFO and 181 in the Cochrane library. These were supplemented with articles found in reference lists. On the basis of abstract and title, 115 potentially relevant articles were identified and screened for retrieval. Fig. 1 shows a flow-diagram of the in and excluded studies, with reasons for exclusion. The manuscripts of the studies included in the systematic review were read in full by two independent reviewers (M.H-A. and K.J.M.). Study characteristics, data qualifying methodology and data on outcome were extracted and discussed until consensus was met.

Methodological hierarchy

Studies evaluating outcome after IVF/ICSI do not allow for a randomized clinical trial (Buck Louis *et al*., 2005). The best option for a clinical trial is the design which evaluates outcome in prospective cohorts of consecutively born IVF/ICSI children and naturally conceived controls, both recruited pre- or perinatally. Next best approaches are studies in which IVF/ICSI children are studied prospectively as a cohort, but the naturally conceived controls are matched retrospectively at nursery- or school age. In order to enhance the ability to fine grade the quality of IVF/ICSI studies, we therefore made the differentiation between prospective- and retrospective-cohort studies (respectively, PC and RC) according to the enrollment of the control children. Studies, which included IVF/ICSI children whose selection was not clearly defined, i.e. studies in which it was not clear whether the children studied represented the entire population of a region or a centre, were classified as retrospective cohort. Studies which included children with a disorder or disease (e.g. CP) and evaluated the mode of conception of children in the diseased and non-diseased groups were classified as case–control (CC).

The effect of IVF/ICSI has not only been studied in clinical trials, but also in studies based on nation-wide registers. These register-based (RB) studies are in particular valuable to detect disorders of low incidence, like CP. Hierarchically, RB studies were considered as having the same level of evidence as the PC studies.

Attrition is an important problem in follow-up studies. We classified studies according to their degree of post-natal attrition. This means that attrition due to perinatal mortality is not taken

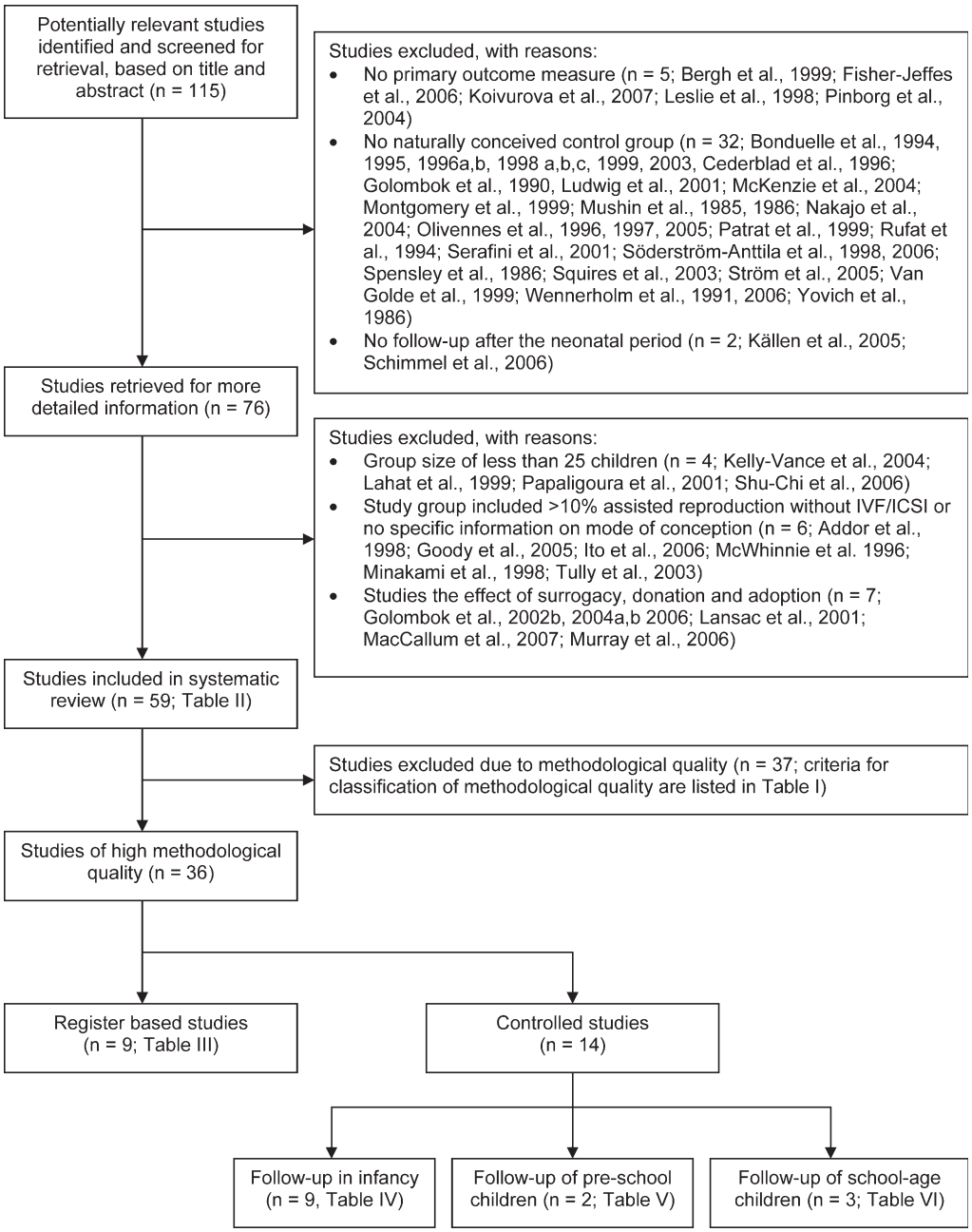

Figure 1: Flow-diagram for included studies.

into account. A low rate of attrition indicates that the chance of selection bias will be kept to a minimum. Blind evaluation of outcome is another important criterion for validity. We only considered a study blind if this was explicitly mentioned in the paper or if data were collected for a purpose other than the evaluation of the effect of IVF/ICSI treatment. A case in point is data collected in Child Welfare Clinics or in habilitation centres.

Neurodevelopmental outcome is affected by multiple factors. Studies dealing with the effect of IVF/ICSI should take into account these confounding factors, either by matching study- and control groups or by including the confounders in multivariate statistics evaluating outcome. We evaluated whether studies took the following confounding variables into account: plurality, gestational age or low birthweight, parity, maternal age, parental education, parental profession or other indicators of social–economical class and the age at which the child had been tested. We did not list gender amongst the confounders, as we were interested in particular whether boys or girls might have a specific vulnerability for sequelae after ART. It is well known that the prevalence of neurodevelopmental disorders is higher in boys than in girls (Hadders-Algra *et al*., 1988a,b). Therefore, we chose to explicitly report the results if studies did stratify for gender.

Quality assessment was performed by the two independent reviewers and took into account internal validity (quality of the study) and external validity (generalizability of the study; Moher

Table I. Criteria for classification of methodological quality of controlled studies.

Criteria for	Assessed criteria	Qualification
Confounders accounted for	Either by matching in study protocol including report of success of matching, or by means of multivariate statistical analysis: (i) plurality (ii) gestational age/low birthweight (iii) parity (iv) maternal age (v) parental education or social–economical class (vi) testing age	$+++ = \geq 5$ parameters $++ = 4$ parameters $+ = 3$ parameters $- = \leq 2$ parameters
Internal validity	(i) prospective cohort study or register based study (ii) post-natal attrition $\leq 10\%$ (iii) blindness of the assessor (iv) good validity of the neurodevelopmental test (either generally acknowledged or documented in paper) (v) ≥ 4 confounders taken into account	$+++ = 4$ or 5 criteria fulfiled $++ = 3$ criteria fulfiled $+ = 2$ criteria fulfiled $- = 0$–1 criteria fulfiled
Power of study to assess neurodevelopmental (ND) outcome	(i) power analysis (ii) sample size	$+ =$ power analysis provided, or samples evaluated larger than 2500 individuals $- =$ power analysis not provided and samples evaluated smaller than 2500 individuals
External validity	(i) qualification of internal validity (ii) qualification of power of study to assess neurodevelopmental outcome	$+++ =$ internal validity $+++$ and power $+$ $++ =$ (internal validity $++$ and power $+$) or (internal validity $+++$ and power $-$ with sample sizes ≥ 50 subjects) $+ =$ (internal validity $+$ and power $+$) or (internal validity $+++$ and power $-$ with samples sizes < 50 subjects) or (internal validity $++$ and power $-$ with sample sizes ≥ 50 subjects) $- =$ not fulfiling the criteria for $+++/++/+$

et al., 1999). Internal validity was based on (i) design of the study, (ii) attrition, (iii) blinding at evaluation, (iv) validity of the neurodevelopmental tests applied in the study and (v) the degree to which confounders were taken into account. External validity was based on internal validity, the size of the samples studied and/or the presence of a power calculation. When results of a study had been reported in two different papers, only the paper which described the study most extensively was taken into account for the review. Criteria for classification of methodological quality of controlled studies, i.e. internal and external validity, are listed in Table I.

Presentation of the results

We first report the methodological quality of the retrieved studies (Table II). Thereafter, we present the data of the studies with a good methodological quality ($\geq ++$ external validity). A differentiation was made between RB (Table III) and controlled studies (Tables IV, V, VI). For the controlled studies, infants, pre-school children and school-age children are reported separately as neurological dysfunction in these age groups is expressed differently. This is for instance reflected by the existence of specific neurological assessments for infants, pre-schoolers and school-age children (Hadders-Algra, 2005). Owing to the plasticity of the brain dysfunctions that exist at a young age may disappear when the child grows older. But the reverse may also occur: with increasing age increasingly complex brain functions become functionally expressed, which may be accompanied by the emergence of dysfunctions in the novel functions. A case in point is the development of dyslexia at school age (Hadders-Algra, 2005).

In the different age-groups, neuromotor development (including neuromotor handicaps), cognition, language and behaviour are reported separately. Ages of the infants at evaluation, neurodevelopmental tests used and study outcome were recorded. Owing to the heterogeneity in tests used and child age a meta-analysis on the effect of IVF/ICSI could not be performed.

Results

Methodological quality of the studies

Fifty-nine studies fulfiled the selection criteria, including 9 RB studies and 50 controlled studies. Study characteristics are summarized in Table II. Sample size of the study groups ranged from 26 to 16 280 children. There was a considerable amount of overlap of children between studies. We decided to report the studies separately as they in general used different developmental outcome parameters. Most studies included children born following conventional IVF or a mixture of IVF and ICSI (denoted by S; 33 out of 59 studies, i.e. 56%). Twenty-four studies reported results of children born following ICSI only (S_1; 41%) and two studies reported on children born following cryopreservation as embryos (S_2; 3%).

Twenty-three of the controlled studies used a prospective study design for both study and control group. In these studies, the control group was formed as a cohort either prenatally, neonatally or from a hospital delivery register. Twenty-seven cohort studies

Table II. Study characteristics. Full table to be found as Supplementary data Table 1.

Author and publication year	Study group* (n=)	Control group (n=)	Study design‡	Post-natal attrition follow-up	Blind‖	Validity of ND tests used¶	Conf. acc. for**	Internal validity**	Power ND test**	External validity**
Agarwal *et al*. (2005)	S_1=76	261	PC	3–10%	yes	++	++	+++	+	+++
Audiens *et al*. (1995)	S=50	50	RC	0%	?	++	-	+	−	−
Barnes *et al*. (2004)	S=301, S_1=345	310	RC	4–66%	no	++	++	+	−	−
Belva *et al*. (2007)	S_1=150	147	RC	39–62%	no	++	++	+	−	−
Bonduelle *et al*. (2004)	S_1=300	266	RC	12.5–70%	partially	+	−	−	−	−
Bonduelle *et al*. (2005)	S=437, S_1=540	538	RC	4–75%	partially	+	++	−	−	−
Bowen *et al*. (1998)	S=84, S_1=89	80	PC	2–3%	no	++	+++	+++	−	++
Brandes *et al*. (1992)	S=116	116	PC	0–13%	yes	++	+++	+++	−	++
Colpin *et al*. (1995)	S=31	31	PC	11%	no	+	++	+	−	−
Colpin and Soenen (2002)	S=27	23	PC	P: 13–25% T: 34–52%	P: no T: yes	++	++	P: ++ T: +++	−	P: + T: +
D'Souza *et al*. (1997)	S=278	278 sin	PC	?	?	++	−	+	−	−
Ericson *et al*. (2002)	S=9056	1417166	RB	<1%	yes	++	+	+++	+	+++
Gershoni-Baruch *et al*. (1991)	S_A=33 (HFTVS), S_B=45	33+45	RC	~0%	?	++	+	+	−	−
Gibson *et al*. (1998)	S=65	62	PC	2–7%	?	++	+++	+++	−	++
Gibson *et al*. (2000)	S=65	61	PC	3–7%	yes	++	+++	+++	−	++
Golombok *et al*. (1995)	S=41	43	PC	≥5–38%	P: no T: yes	++ Rutter + Interv. − m SAT + PC&SA	++	++	−	+
Golombok *et al*. (1996)	S=116	120	RC	≥33%	P: no T: yes	++ Rutter + PC&SA	++	+	−	−
Golombok *et al*. (2001)	S=34	38	PC	≥11–17%	P: no T: yes C: ?	+ Psych. Interv ++ SDQ + SAICA	++	++	−	+
Golombok *et al*. (2002)	S=102	102	RC	≥12–15%	P: no T: yes C: ?	++ SDQ + CAFÉ	++	+	−	−
Hahn and DiPietro (2001)	S=54	59	RC	≥24%	P: no T: yes	++ ECBI ++ PBCL + SESBI − TRRLS	++	+	−	−
Hvidtjørn *et al*. (2006)	S=9255	394713	RB	<1%	yes	++	+++	+++	+	+++
Källén *et al*. (2005)	S=16 280	population	RB	<1%	yes	++	++	+++	+	+++
Klemetti *et al*. (2006)	S=4559	26 877	RB	<1%	yes	++	+	+++	+	+++
Knoester *et al*. (2007a)	S=81, S_1=87	85	RC	21–33%	yes	++	+++	++	+	++
Knoester *et al*. (2007b)	S=81, S_1=87	85	RC	21–27%	no	++	+	−	−	−
Knoester *et al*. (2008)	S=86, S_1=83	85	RC	21–33%	yes	++	+++	++	+	++
Koivurova *et al*. (2003)	S_A=299 (all) S_B=250 (sin, tw)	C_A=558 C_B=380	PC B= sin	10–15%	yes	+	−	+	+	+
La Sala *et al*. (2004)	S_1=50	51	RC	40–58%	yes	++	++	++	−	+
Leslie *et al*. (2003)	S=80, S_1=97	110	RC	5–88%	yes	++	++	++	+	++
Leunens *et al*. (2006)	S_1=151	153	RC	39–62%	no	++	+++	+	WISC:+mABC:−	WISC:+mABC:−
Leunens *et al*. (2008)	S_1=109	90	RC	41–56%	no	++	++	+	−	−
Levy-Shiff *et al*. (1998)	S=51	51	RC	0–8%	yes	++	++	+++	−	++
Lidegaard *et al*. (2005)	S=6052	442349	RB	<1%	yes	++	−	+++	+	+++

Continued

Table II. *Continued*

Author and publication year	Study group* (n=)	Control group (n=)	Study design‡	Post-natal attrition follow-up	Blind‖	Validity of ND tests used¶	Conf. acc. for**	Internal validity**	Power ND test**	External validity**
Maimburg and Væth (2007)	S=461	461	RB	0%	yes	++	++	+++	−	++
McMahon *et al*. (1997)	S=65	62	PC	<5%	yes SFP no Q	++ SFP + Q	+++	+++ SFP ++ Q	−	++ SFP + Q
McMahon and Gibson (2002)	S=70	63	PC	<10%	yes SSP no Q	++ SSP + Q	++	+++SSP ++ Q	−	++ SSP + Q
Morin *et al*. (1989)	S=83	93	PC	11–25%	yes	++	++	+++	−	++
Neri *et al*. (2004)	S_1=101	57	RC	?	?	++	−	−	−	−
Papaligoura *et al*. (2004)	S=26, S_1=34	29	RC	0–7%	yes	++	+++	+++	−	+
Pinborg *et al*. (2003)	S_A=634 sin S_B=472 tw	1132 tw	PC	11–23%	no	+	+++	+	−	−
Pinborg *et al*. (2004)	S_A=5130 sin S_B=3393 tw	10 239 tw	RB	<1%	yes	++	++	+++	+	+++
Place and Englert (2003)	S=52, S_1=66	59	PC	30–60%	no	++	+++	++	−	+
Ponjaert-Kristoffersen *et al*. (2004)	S_1=300	260	RC	12–70%	?	++	++	+	−	−
Ponjaert-Kristoffersen *et al*. (2005)	S=424, S_1=511	488	RC	4–66%	partially	++	++	+	−	−
Raoul-Duval *et al*. (1993, 1994)	S=33	33	PC	6–67%	yes	++	++	+++	−	+
Ron-El *et al*. (1994)	S=32	32	PC	3–19%	yes	++	+++	+++	−	+
Sanchez-Albisua *et al*. (2007)	S_1=34	39	PC	~50–72%	?	+	++	+	−	−
Saunders *et al*. (1996)	S=289	146	PC	≥27–88%	no	++	+	+	−	−
Strömberg *et al*. (2002)	S=5680	15 397	RB	<1%	yes	++	++	+++	+	+++
Sutcliffe *et al*. (1995a,b)	S_2=91	83	RC	~0%	no	++	−	+	−	−
Sutcliffe *et al*. (1999)	S_1=123	123	RC	10%	?	++	++	++	+	++
Sutcliffe *et al*. (2001)	S_1=208	221	RC	1–10%	no	++	+++	++	+	++
Sutcliffe *et al*. (2003)	S_1=264	260	RC	10–15%	no	++	+	−	+	−
Sutcliffe *et al*. (2004)	S_1=140	101	RC	7–10%	no	++	−	+	−	−
Sutcliffe *et al*. (2005)	S=425 S_1=525	523	RC	0–75%	yes	++	−	+	−	−
Sun *et al*. (2007)	S=1958	50 396	RB	~10%	yes	++	+++	+++	−	++
Sydsjö *et al*. (2002)	S=121	110	PC	2%	no	+	++	++	−	+
Van Balen (1996)	S=45	35	PC	31–65%	no	+	+++	+	−	−
Wennerholm *et al*. (1998)	S=255, S_2=255	252	PC	0–2%	yes	+	−	++	−	+

*S, studygroup; children born following IVF or a combination of IVF and ICSI; S_1, children born following ICSI; S_2, children born following cryopreservation as embryos. HFTVS, High-frequency transvaginal ultrasonography. †sin, singletons; tw, twins; tri, triplets; all, children of all pluralities. ‡PC, prospective cohort study; RC, retrospective cohort study; CC, case–control study; RB, register-based study. §Post-natal attrition follow-up, *P*, parent; T, teacher. ‖*P*=parent, T=teacher, C=child. ¶Neurodevelopmental (ND) tests used: rutter, Rutter's behaviour scale; Interv., Interview; mSAT, modified Seperation Anxiety Test; PC&SA, Pictural Scale for Perceived Competence and Social Acceptance for Young Children; SDQ, Strengths and difficulties questionnaire; SAICA, Social Adjustment Inventory for Children and Adolescents; CAFÉ, Child and Adolescent functioning and Environment Schedule; ECBI, Eyberg Child behaviour Inventory; PBCL, Pre-school Behaviour Checklist; SESBI, Sutter-Eyberg Student Behaviour Inventory; TRRLS, Teachers report on response to limit setting; SFP, Still-face Procedure; Q, Questionnaire; SSP, Strange Situation Procedure. **for criteria see Table I.

Table III. Register based studies on neurodevelopmental outcome of children born following IVF/ICSI.

Study	Methodological quality*		Age†	Register used‡	Variables controlled for§	Neurodevelopmental outcome‖	
	Int.	Ext.				Outcome after first correction for confounders	Outcome after final correction for confounders
Pinborg *et al.* 2004	+++	+++	2–7	National patient/psychiatric register (ICD-10)	Maternal age, ART procedure, plurality, LBW, preterm birth, gender, year of birth.	$S_{sin}=S_{tw}=C_{tw}$ Mental retardation: $S_{sin}=S_{tw}=C_{tw}$	CP: $S_{sin}=S_{tw}=C_{tw}$
Strömberg *et al.* 2002	+++	+++	1.5–14	National register of diagnosis at CDC (ICD-10)	Maternal age, ART procedure, plurality, LBW, preterm birth, gender, year of birth, birth hospital	CP: S>C (sin), S=C (tw) Mental retardation: S=C Dev. delay S=C Behav. dis.: S=C	CP: S>C (all), S=C (sin) Dev.delay: S>C (all), S=C (sin)
Klemetti *et al.* 2006	+++	+++	2–4	National hospital discharge register (ICD-10)	Maternal profession, plurality	CP: S>C (all) Behav. dis.: S=C (all) Epilepsy: S>C (all)	CP: S=C (sin), S=C (tw) Behav. dis.: S=C (sin), S=C (tw) Epilepsy: S=C (sin), S=C (tw)
Hvidtjørn *et al.* 2006	+++	+++	1–7	National hospital discharge register (ICD-10)	Maternal age, maternal educational level, parity, plurality, preterm birth, SGA status, gender.	CP: S>C	CP: S=C
Källén *et al.* 2005	+++	+++	1–20	National hospital discharge register (ICD-9/10)	Maternal age, smoking, parity, years of unwanted childlessness, preterm birth, year of birth.	CP: S>C Mental retardation: S=C Behavioural problems: S>C Epilepsy: S>C Convulsion: S>C	CP: S=C Mental retardation: S=C Behavioural problems: S=C Epilepsy: S=C Convulsion: S>C
Ericson *et al.* 2002	+++	+++	1–14	National hospital discharge register (ICD-9/10)	Maternal age, smoking, parity, year of birth.	Not reported.	CP: S>C Mental retardation: S=C Dev. disturbances: S=C Epilepsy: S>C
Lidegaard *et al.* 2005	+++	+++	1–7	National patient/psychiatric register (ICD-10)	Plurality	CP: S>C Mental retardation: S=C Behavioural disturbance: S=C Sleeping disturbance: S>C Speech/language retardation: S=C Motor retardation: S=C	n.a.
Sun *et al.* 2007	+++	++	0–6	National hospital discharge register (ICD-10)	Maternal+paternal age, maternal social status, smoking, BMI, parental epilepsy, parity, plurality, preterm birth, year of birth.	Epilepsy: S>C Febrile seizures: S=C	Epilepsy: S=C Febrile seizures: S=C
Maimburg & Væth 2007	+++	++	0–11	National patient/psychiatric register (ICD-8/10)	Maternal age, maternal origin, parity, plurality, preterm birth, birth weight, birth defects.	Infantile autism: S<C	Infantile autism: S<C

*Methodological quality: see table II.; Int., Internal validity; Ext., External validity; †Age of included children in years, ‡CDC, Childhood disability center; ICD-9/10, International Classification of Diseases, 9th/10th revision; §ART, assisted reproductive technology; LBW, low birth weight; SGA, small for gestational age; BMI, body mass index, ‖CP, Cerebral Palsy; Behav. dis., behavioural disorder; Dev., developmental; S, study group; C, control group; sin, singletons; tw, twins; all, all pluralities; S=C, no statistically significant differences between study and control group; S>C, significantly more problems in study than in control group; S<C: significantly less problems in study than in control group; n.a.=not applicable

Table IV. Controlled studies with neurodevelopmental outcome in infancy (1 month–$2\frac{1}{2}$ year) and good external validity.

Study	Age	Methodological quality*		Neuromotor development/handicaps		Cognition		Speech/language		Behaviour	
		Int.	Ext.	test used†	outcome‡	test used†	outcome‡	test used†	outcome‡	test used†	outcome‡
Agarwal *et al.* (2005)	2 years	+++	+++	Bayley	S_1=C	Bayley	S_1=C	-		VABS	S_1=C
Gibson *et al.* (2000)	1 years	+++	++	−		−		−		SSP EAS	S=C S=C
Gibson *et al.* (1998)	1 years	+++	++	Bayley	S=C	Bayley	S=C	REEL-2; expressive: receptive:	 S=C S<C	Bayley STST BCL VABS; soc. domain	S=C S<C S<C S=C
McMahon *et al.* (1997)	4 months	+++	++	−		−		−		SFP STSI NPI	S<C S<C S=C
McMahon and Gibson (2002)	1 years	+++	++	−		−		−		SFP SSP	S<C S=C
Morin *et al.* (1989)	1–$2\frac{1}{2}$ years	+++	++	Bayley Neuro-paed. exam.	S>C S=C	Bayley	S=C	−		Bayley; vocalization and energy levels:	S=C S>C
Bowen *et al.* (1998)	1 years	+++	++	Bayley	S=S_1=C	Bayley	S_1<(S=C) ♀: S=S_1=C ♂: S_1<(S=C)	-		-	
Sutcliffe *et al.* (1999)	1–2 years	++	++	Griffiths; eye–hand coord.:	S_1=C S_1<C	Griffiths	S_1=C	Griffiths	S_1=C	−	
Sutcliffe *et al.* (2001)	1–2 years	++	++	Griffiths Neuro-paed. exam.	S_1=C S_1 =C	Griffiths	S_1=C	Griffiths	S_1=C	-	

*Methodological quality: see Table II. Int., Internal validity; Ext., External validity. †Neurodevelopmental tests used: neuro-paed. Exam, general neuro-paediatric examination; Bayley, Bayley's Scale of Infant Development (second edition; BSID-II); Griffiths, Griffiths scales of mental development; REEL-2, Receptive-Expressive Emergent Language Test, 2nd edition; VABS, Vineland Adaptive Behaviour Scale; SSP, Strange Situation Procedure; EAS, Emotional Availability Scales; STST, Short Temperament Scale for Toddlers; BCL, Behaviour Checklist; SFP, Still-face procedure (mother–child interaction); STSI, Short Temperament Scale for Infants; NPI, Neonatal Perception Inventory. ‡S, study group; infants born following IVF or IVF/ICSI; S_1, study group; infants born following ICSI; C, control group; S=C, no statistically significant differences between study and control group; S>C, Study group performs significantly better than control group; S<C, Study group performs significantly worse than control group.

were performed retrospectively. This always meant that at least a part of the control group had been recruited retrospectively, e.g. via nurseries or schools. A CC design was not used in the controlled studies. Information on attrition was available in 97% of the studies; it varied from 0 to 88%.

Thirty-three of the identified studies had good (++ or +++) internal validity and 23 studies had good external validity. Only outcome of studies with good external validity are reported in detail, separately for RB studies (9; 100%) and controlled studies (14; 28%).

RB studies

In some Scandinavian countries, national registers of fertility treatment have been linked to national registers of hospital diagnoses or registers of psychiatric disorders to calculate the odds for adverse outcome in children born following fertility treatment. Nine of these RB studies focused on neurodevelopmental outcome (Table III). Three studies included only children aged at least $1\frac{1}{2}$ or 2 years to ensure accurate neurological diagnosis (Strömberg *et al*., 2002; Pinborg *et al*., 2004; Klemetti *et al*., 2006). With respect to risk for CP, this is very appropriate as the diagnosis CP cannot be established prior to the age of $1\frac{1}{2}$–2 years of age (Bax *et al*., 2006). Strömberg *et al*. (2002) identified IVF as an independent risk factor for development of CP, but the effect disappeared when only singletons were taken into account. Pinborg *et al*. (2004) reported that twins born following IVF/ICSI had a similar risk of CP as naturally conceived twins and singletons born following IVF/ICSI. Klemetti *et al*. (2006) reported an increased risk of CP for children born after IVF/ICSI when all pluralities were taken into account, but not for singletons only. Studies that included also younger children (Ericson *et al*., 2002; Källén *et al*., 2005; Lidegaard *et al*., 2005; Hvidtjørn *et al*., 2006) showed that IVF/ICSI might be associated with a higher prevalence of CP, but when the results had been adjusted for important confounders such as preterm birth and plurality the increased risk usually disappeared. Interestingly, epilepsy and/or the occurrence of convulsions remained associated with IVF/ICSI in some studies even after correction for confounders (Ericson *et al*., 2002; Kallén *et al*., 2005).

Table V. Controlled studies with neurodevelopmental outcome in pre-school children (3–5½ years) and good external validity.

Study	Age	Methodological quality*		Neuromotor development/ handicaps		Cognition		Speech/language		Behaviour	
		Int.	Ext.	test used†	outcome‡	test used†	outcome‡	test used†	outcome‡	Test used†	Outcome‡
Brandes *et al*. 1992	1–4 y	+++	++	Neuro-paed. exam.	S=C	Bayley Stanford-Binet	S=C S=C	−	−	−	−
Leslie *et al*. 2003	5 y	++	++	−	−	WPPSI—R	S=S_1=C	−	−	−	−

*Methodological quality: see Table II. Int.=Internal validity, Ext.=External validity. †Neurodevelopmental tests used: neuro-paed. exam=general neuro-paediatric examination, Bayley=Bayley's Scale of Infant Development (second edition; BSID-II), Stanford-Binet=Stanford-Binet intelligence scale, WPPSI-*R*=Wechsler Pre-school and Primary Scales of Intelligence- Revised. ‡S=study group; infants born following IVF or IVF/ICSI, S_1=study group; infants born following ICSI, C=control group, S=C: no statistically significant differences between study and control group. S>C=Study group performs significantly better than control group, S<C Study group performs significantly worse than control group.

Table VI. Controlled studies with neurodevelopmental outcome in school-age children (>6 years) and good external validity.

Study	Age	Methodological quality*		Neuromotor development/handicaps		Cognition		Speech/language		Behaviour	
		Int.	Ext.	Test used†	Outcome‡	Test used†	Outcome‡	Test used†	Outcome‡	Test used†	Outcome‡
Levy-Shiff *et al*. (1998)	9–10 years	+++	++	Bender. Neuro-paed. exam	S=C S=C	WISC-R Benton	S=C S=C	Reading comprehension	S=C	RSSA; learning problems: socioemotional: hyperactivity: CSR; anxiety: depression: aggression:	S=C ♀: S=C ♂: S<C S=C ♀: S=C ♂: S<C ♀: S=C ♂: S<C ♀: S=C ♂: S<C
Knoester *et al*. (2007a)	5–8 years	++	++	Touwen; MND:	$S=S_1$ S_1=C	−	−	−	−	−	−
Knoester *et al*. (2008)	5–8 years	++	++	−	−	RAKIT	S_1=S ♀: S_1=S ♂: S_1=S S_1<C ♀: S_1<C ♂: S_1<C	RAKIT; verbal meaning:	S_1=S S_1<C	−	−

*Methodological quality: see Table II. Int., Internal validity; Ext., External validity. †Neurodevelopmental tests used: neuro-paed. exam, general neuro-paediatric examinationl; WISC-R, Wechsler Intelligence Scale for Children-Revised; Benton, Visual Retention Test; RSSA, Rating Scale for School Adjustment; CSR, Child Self Report-forms; Bender, Visual Motor Gestalt Test; Touwen, Neurological examination according to Touwen; MND, minor neurological dysfunction; RAKIT, Revised Amsterdam Child Intelligence Test. ‡S, study group; infants born following IVF or IVF/ICSI. S_1, study group; infants born following ICSI; C, control group; S=C, no statistically significant differences between study and control group, S>C, study group performs significantly better than control group; S<C, study group performs significantly worse than control group.

The association of IVF/ICSI and mental retardation was investigated in five papers. These studies reported a consistent absence of a relationship between IVF/ICSI and mental retardation. Speech/language retardation was only investigated by Lidegaard *et al*. (2005); no differences between IVF/ICSI children and naturally conceived children were demonstrated. Four studies reported on behaviour, three of them found no differences and one—the CC study of Maimburg and Væth (2007)—surprisingly reported that children born after assisted conception had a lower risk of developing infantile autism.

None of the RB studies reported different outcomes after IVF/ICSI for boys and girls.

Controlled studies with follow-up in infancy

Nine studies with good external validity (41%) investigated neurodevelopmental outcome of infants born following assisted conception (Table IV). Five evaluated children born following routine IVF (or a combination of IVF and ICSI) and four studies focused on infants conceived by ICSI. The age of the infants at

the time of assessment varied from 4 months to two and a half years. In four studies, the same group of infants was examined (McMahon *et al*., 1997; Gibson *et al*., 1998, 2000; McMahon and Gibson, 2002).

Neuromotor development was assessed in six studies either with the help of the Bayley Scales of Infant Development (second edition: BSID-II; Bayley, 1993) or with the Griffiths mental development scales (Griffiths, 1996). Four studies found no differences between infants born following assisted and natural conception. One study reported that children born after ICSI had significantly worse eye–hand coordination than naturally conceived infants (Sutcliffe *et al*., 1999). Another study indicated that children born after IVF had a better psychomotor development than naturally conceived controls (Morin *et al*., 1989). Two studies provided information on neurological handicap. They found similar rates of handicap in children born following IVF/ICSI and controls.

Cognition was assessed in six studies: four used the Bayley scales and two the Griffiths scales. Five out of the six studies reported no differences between the study and the control group in mental development. Only the study of Bowen *et al*. (1998) reported significantly lower mental scores in 1-year-old infants born after ICSI than in age matched infants born after IVF and naturally conceived infants. Stratification for gender revealed that lower mental development index scores were only found in boys but not in girls (Table IV).

Speech and language were tested in three studies. The results were inconsistent: two studies showed no differences between study and control group and one study found lower scores on receptive language development in infants born following IVF, but no differences in expressive language skills (Gibson *et al*., 1998).

Behaviour was assessed in six studies. It is good to realize that many different inventories are available to test behaviour. Most objective evaluation procedures are observational measures in which scores are based on observed behaviour during testing. Four of the six studies evaluated behaviour of the same group of infants, be it at different ages (McMahon *et al*., 1997; Gibson *et al*., 1998, 2000; McMahon and Gibson, 2002). These four studies in general showed little difference between study and control infants, but on some inventories the IVF-infants were rated as having a more difficult temperament than naturally conceived infants (McMahon *et al*., 1997; Gibson *et al*., 1998; McMahon and Gibson, 2002). Two of the six studies reported no differences in behaviour and one of the six studies reported higher energy levels and vocalization in infants born after IVF (Morin *et al*., 1989).

In summary, the controlled studies with follow-up in infancy do not indicate that neuromotor or cognitive development, including handicapping neurological conditions, of infants born after IVF/ICSI differs from that of non-IVF/ICSI controls. Nor do these studies indicate that infants born following IVF/ICSI show a higher prevalence of language- or behaviour problems than naturally conceived controls.

Controlled studies with follow-up of pre-school children

Only two studies on neurodevelopmental outcome at pre-school age had a good external validity (Brandes *et al*., 1992; Leslie *et al*., 2003; Table V). The other 13 studies with follow-up at pre-school age did not fulfil the criteria for good external validity, mainly because of a retrospective design, high attrition and non-blinded testing. The study of Leslie *et al*. (2003) was a follow-up of the children described by Bowen *et al*. (1998). It revealed that the previously reported difference in cognitive development at 18 months between children born after ICSI compared to those born after IVF or after natural conception had disappeared at 5 years. The other study with follow-up at pre-school age did not find a difference in neurological handicap and cognition between children born after IVF and controls (Brandes *et al*., 1992). Neither of the studies stratified for gender.

Controlled studies with follow-up of school-age children

Three studies with good external validity reported on neurodevelopmental outcome of school-age children (Levy-Shiff *et al*., 1998; Knoester *et al*., 2007a, 2008; Table VI). Major reasons for insufficient external validity of the other 10 studies were high attrition—a generally recognized problem in long term follow-up studies—and the use of non-validated outcome measures. The study of Levy-Shiff *et al*. (1998) reported that children born after IVF/ICSI in general do not differ from their naturally conceived peers. Nevertheless, the data indicated that children born after IVF had more socioemotional problems, aggression, anxiety and depression than naturally conceived peers. This was especially true for boys. The studies performed by Knoester *et al*. (2007a, 2008) could not identify a difference in neuromotor outcome between ICSI and either IVF or naturally conceived children, but cognitive development was slightly worse, i.e. IQ was lower, in singletons born after ICSI than in naturally conceived singletons; this was true for boys and girls.

Discussion

In general, the follow-up studies of good methodological quality showed no consistent differences in neuromotor, cognitive, language and behavioural development between children born following IVF/ICSI and natural conception. We made a great effort to assess methodological quality as a good methodological quality is a prerequisite for generalization of the results of a study. Only 23 papers (39%) met our predefined criteria for good external validity. Thus, our study stresses the need for research with a high methodological quality, i.e. RB studies or truly prospective studies in which all consecutive pregnancies of a hospital or fertility clinic and their naturally conceived controls are followed carefully.

The data from RB studies indicate that IVF/ICSI *per se* does not increase the risk for CP, but that an increased risk for CP is induced by the association of assisted conception with other risk factors, like preterm birth. Children born following assisted conception are more likely to be born premature and with low birthweight. The increased risk for adverse perinatal outcome cannot solely be attributed to the higher rate of multiplicity following assisted conception. For singletons, the relative risk for preterm and very preterm birth is also found to be increased (Helmerhorst *et al*., 2004; Jackson *et al*., 2004). Prematurity and multiple gestations are both strongly associated with the risk of CP (Strömberg *et al*., 2002; Hvidtjørn *et al*., 2006). Therefore, these strong risk factors might hide a potential additionally milder effect of IVF/ICSI as causative factor for CP (Dahlquist *et al*., 2002), if present at all.

It is reassuring that the RB studies did not report an increase in mental retardation or clinically relevant behaviour problems. Since this information is based on large nation-wide registers the chance of a possible non-detected association probably is small. However, a matter of concern is the contradictory findings in the association between IVF/ICSI and epilepsy or convulsions.

To study more subtle differences between IVF/ICSI children and naturally conceived children, such as a minor reduction in IQ, minor neurological or behavioural dysfunction, the controlled studies are most appropriate. In general, these studies did not report an excess of neuromotor, cognitive, language and behavioural disorders in children born following IVF/ICSI. However, two points should be taken into consideration. First, in the case of neuromotor and cognitive development, most studies used evaluation tools such as the Bayley Scales of Infant Development. These tests have been well standardized and validated as tools for clinical assessment. This means that these instruments are reliable in detecting gross pathology, but they do not evaluate neuromotor and cognitive outcome in a detailed sense. Second, the number of studies of high methodological quality that continued follow-up after infancy is rather limited, while most so-called 'minor' neurodevelopmental disorders are first diagnosed beyond that age.

ICSI

The procedure of ICSI is more invasive in nature than IVF only; natural sperm selection is passed by and spermatozoa with impaired mobility, morphology or genetic abnormalities may be used (Bowen *et al*., 1998; Sutcliffe *et al*., 1999, 2001; Knoester *et al*., 2007a, 2008). In addition, the origin of infertility preceding the fertility therapy is usually different for IVF and ICSI and we do not know how this may affect neurodevelopmental outcome. Overall, the controlled studies included in this review which focused explicitly on follow-up after ICSI showed similar neuromotor, cognitive, language and behavioural outcome after ICSI and natural conception. However, two studies reported a mild IQ reduction in children born after ICSI. The study of Bowen *et al*. (1998) reported significantly lower mental scores in ICSI-boys than IVF- and naturally conceived boys. However, for the generalizability of this study it has to be taken into account that a substantial proportion of infants included in this study were born after the transfer of cryopreserved embryos (Sutcliffe *et al*., 1998). Recently, Knoester *et al*. (2008) reported lower IQ-scores in 5- to 8-year-old ICSI children when compared to naturally conceived children. This blinded study used a validated test instrument and extensively adjusted for confounders, however, response rate and reasons for non-participation were unclear in the naturally conceived control group. Therefore, ascertainment bias could have emerged: parents who believe that their child is intelligent are probably more willing to let their child cooperate in an intelligence-test, which could have resulted in relatively high IQ-scores in the naturally conceived group. Nevertheless, the results of these two studies warrant more research of high methodological quality and long-term follow-up.

Some studies compared children born following IVF only to children born following IVF with ICSI (Bowen *et al*., 1998, Leslie *et al*., 2003; Pinborg *et al*., 2004; Källén *et al*., 2005; Hvidtjørn *et al*., 2006; Knoester *et al*., 2007a, 2008). The risk of CP between the two treatments did not differ (Pinborg *et al*., 2004; Källén *et al*., 2005; Hvidtjørn *et al*., 2006). The limited data available from controlled studies also did not suggest that other neurodevelopmental outcome parameters differed for the two treatments (Bowen *et al*., 1998; Leslie *et al*., 2003; Knoester *et al*., 2007a, 2008).

Perspectives for future research

This review demonstrated a clear need for follow-up studies of good methodological quality and with continuation of follow-up after infancy, ideally continuing into adulthood. So far only few studies with solid methodology addressed gender specific vulnerability for neurodevelopmental disorders after IVF or ICSI (Bowen *et al*., 1998; Levy-Shiff *et al*., 1998; Knoester *et al*., 2008). As two of these studies suggest a larger risk for cognitive and emotional problems in boys, we suggest that future studies continue to pay attention to the gender issue.

Another issue which needs evaluation in future research is the long-term effect of cryopreservation of embryos on developmental outcome. Until now very few studies have addressed this problem, while this technique has already been applied on routine base for years. Similar careful and long-term follow-up is warranted for other technologies, such as preimplantation genetic screening or *in vitro* maturation. We underline the ESHRE Task Force recommendation that with the introduction of new technologies a plan for follow-up should accompany the clinical trial, as the interests of future offspring should be emphasized (ESHRE Task Force on Ethics and Law, 2007).

Conclusion

The majority of studies on neurodevelopmental outcome after IVF/ICSI did not have a robust methodological quality. The exception to this rule was formed by the RB studies. The latter studies suggest that IVF/ICSI per se does not increase the risk for mental retardation or CP. However, the association of assisted conception with risk factors such as multiple gestation and preterm birth does result in an indirect association of IVF/ICSI with CP. The controlled studies which met the criteria of good methodological quality did not show an increase in neuromotor, cognitive, language and behavioural problems in children born after IVF/ICSI. It should be realized that the majority of these studies evaluated outcome in infancy, which precludes a conclusion about the risk of minor neurodevelopmental disorders, which in general first become expressed after infancy.

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References

Agarwal P, Loh SK, Lim SB, Sriram B, Daniel ML, Yeo SH, Heng D. Two-year neurodevelopmental outcome in children conceived by intracytoplasmic sperm injection: prospective cohort study. *BJOG* 2005;**112**:1376–1383.

Audiens H, Denayer E, Ahlenajafie N, Troch E, Bonduelle M, Ramet J, Vandenplas Y. Sleep apnoea in babies born after in vitro fertilization. *Eur J Pediatr* 1995;**154**:454–457.

Barnes J, Sutcliffe AG, Kristoffersen I, Loft A, Wennerholm U, Tarlatzis BC, Kantaris X, Nekkebroeck J, Hagberg BS, Madsen SV *et al*. The influence of assisted reproduction on family functioning and children's socio-emotional development: results from a European study. *Hum Reprod* 2004;**19**:1480–1487.

Bayley N. *Bayley Scales of Infant Development.* 2nd edn. San Antonio, USA: The psychological Corporation, 1993.

Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N, Dan B, Jacobsson B, Damiano D. Executive Committee for the definition of Cerebral Palsy. Proposed definition and classification of cerebral palsy, April 2005. *Dev Med Child Neurol* 2005;**47**:571–576.

Bax M, Tydeman C, Flodmark O. Clinical and MRI correlates of cerebral palsy. The European cerebral palsy study. *JAMA* 2006;**296**:1602–1608.

Belva F, Henriet S, Liebaers I, Van Steirteghem A, Celestin-Westreich S, Bonduelle M. Medical outcome of 8-year-old singleton ICSI children (born ≥32 weeks' gestation) and a spontaneously conceived comparison group. *Hum Reprod* 2007;**22**:506–515.

Bonduelle M, Bergh C, Niklasson A, Palermo GD, Wennerholm UB. Medical follow-up study of 5-year-old ICSI children. *Reprod Biomed Online* 2004;**9**:91–101.

Bonduelle M, Wennerholm UB, Loft A, Tarlatzis BC, Peters C, Henriet S, Mau C, Victorin-Cederquist A, Van Steirteghem A, Balaska A *et al*. A multi-centre cohort study of the physical health of 5-year-old children conceived after intracytoplasmic sperm injection, in vitro fertilization and natural conception. *Hum Reprod* 2005;**20**:413–419.

Bowen JR, Gibson FL, Leslie GI, Saunders DM. Medical and developmental outcome at 1 year for children conceived by intracytoplasmic sperm injection. *Lancet* 1998;**351**:1529–1534.

Brandes JM, Scher A, Itzkovits J, Thaler I, Sarid M, Gershoni-Baruch R. Growth and development of children conceived by in vitro fertilization. *Pediatrics* 1992;**90**:424–429.

Buck Louis GM, Schisterman EF, Dukic VM, Schieve LA. Research hurdles complicating the analysis of infertility treatment and child health. *Hum Reprod* 2005;**20**:12–18.

Buitendijk SE. Children after in vitro fertilization. An overview of the literature. *Int J Technol Assess Health Care* 1999;**15**:52–65.

Colpin H. Parenting and psychological development of IVF children: Review of the research literature. *Dev Rev* 2002;**22**:644–673.

Colpin H, Soenen S. Parenting and psychosocial development of IVF children: a follow-up study. *Hum Reprod* 2002;**17**:1116–1123.

Colpin H, Demyttenaere K, Vandemeulebroecke L. New reproductive technology and the family: the parent-child relationship following in vitro fertilization. *J Child Psychol Psychiatry* 1995;**36**:1429–1441.

Dahlquist G, Finnström O, Köster M, Strömberg B. Neurological sequelae in in-vitro fertilisation babies. *Lancet* 2002;**360**:719.

De Graaf-Peters VB, Hadders-Algra M. Ontogeny of the human central nervous system: what is happening when? *Early Hum Dev* 2006;**82**:257–266.

D'Souza SW, Rivlin E, Cadman J, Richards B, Buck P, Lieberman BA. Children conceived by in vitro fertilisation after fresh embryo transfer. *Arch Dis Child* 1997;**76**:70–74.

ESHRE Task Force on Ethics Law including Pennings G, de Wert G, Shenfield F, Cohen J, Tarlatzis B, Devroey P. ESHRE Task Force on Ethics and Law 13: the welfare of the child in medically assisted reproduction. *Hum Reprod* 2007;**22**:2585–2588.

Ericson A, Nygren KG, Olausson PO, Källén B. Hospital care utilization of infants born after IVF. *Hum Reprod* 2002;**17**:929–932.

Gershoni-Baruch R, Scher A, Itskovitz J, Thaler I, Brandes JM. The physical and psychomotor development of children conceived by IVF and exposed to high-frequency vaginal ultrasonography (6.5 MHz) in the first trimester of pregnancy. *Ultrasound Obstet Gynecol* 1991;**1**:21–28.

Gibson F, McMahon C. Parenting and child psychosocial development after infertility management. *Int Congr Ser* 2004;**1266**:351–358.

Gibson FL, Ungerer JA, Leslie GI, Saunders DM, Tennant CC. Development, behaviour and temperament: a prospective study of infants conceived through in-vitro fertilization. *Hum Reprod* 1998;**13**:1727–1732.

Gibson FL, Ungerer JA, McMahon CA, Leslie GI, Saunders DM. The mother-child relationship following in vitro fertilisation (IVF): infant attachment, responsivity, and maternal sensitivity. *J Child Psychol Psychiatry* 2000;**41**:1015–1023.

Golombok S, Cook R, Bish A, Murray C. Families created by the new reproductive technologies: quality of parenting and social and emotional development of the children. *Child Dev* 1995;**66**:285–298.

Golombok S, Brewaeys A, Cook R, Giavazzi MT, Guerra D, Mantovani A, van Hall E, Crosignani PG, Dexeus S. The European study of assisted reproduction families: family functioning and child development. *Hum Reprod* 1996;**11**:2324–2331.

Golombok S, MacCallum F, Goodman E. The test-tube generation: parent-child relationships and the psychological well-being of in vitro fertilization children at adolescence. *Child Dev* 2001;**72**:599–608.

Golombok S, Brewaeys A, Giavazzi MT, Guerra D, MacCallum F, Rust J. The European study of assisted reproduction families: the transition to adolescence. *Hum Reprod* 2002;**17**:830–840.

Golombok S, MacCallum F. Practitioner review: outcomes for parents and children following non-traditional conception: what do clinicians need to know? *J Child Psychol Psychiatry* 2003;**44**:303–315.

Griffiths R. *The Griffiths Mental Development Scales 1996 Revision (Revised by Huntley M).* Henley: Association for research in infant and child development, Test agency, 1996.

Hadders-Algra M, Huisjes HJ, Touwen BC. Perinatal correlates of major and minor neurological dysfunction at school age: a multivariate analysis. *Dev Med Child Neurol* 1988a;**30**:472–481.

Hadders-Algra M, Huisjes HJ, Touwen BC. Perinatal risk factors and minor neurological dysfunction: significance for behaviour and school achievement at nine years. *Dev Med Child Neurol* 1988b;**30**:482–491.

Hadders-Algra M. The neuromotor examination of the preschool child and its prognostic significance. *Ment Retard Dev Disabil Res Rev* 2005;**11**:180–188.

Hahn CS. Review: psychosocial well-being of parents and their children born after assisted reproduction. *J Pediatr Psychol* 2001;**26**:525–538.

Hahn CS, DiPietro JA. In vitro fertilization and the family: quality of parenting, family functioning, and child psychosocial adjustment. *Dev Psychol* 2001;**37**:37–48.

Helmerhorst FM, Perquin DAM, Donker D, Keirse MJNC. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. *BMJ* 2004;**328**:261–265.

Hvidtjørn D, Grove J, Schendel DE, Væth M, Ernst E, Nielsen LF, Thorsen P. Cerebral palsy among children born after in vitro fertilization: the role of preterm delivery- a population-based, cohort study. *Pediatrics* 2006;**118**:475–482.

Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. *Obstet Gynecol* 2004;**103**:551–563.

Källén B, Finnström O, Nygren KG, Olausson PO. In vitro fertilization in Sweden: child morbidity including cancer risk. *Fertil Steril* 2005;**84**:605–610.

Klemetti R, Sevón T, Gissler M, Hemminki E. Health of children born as a result of in vitro fertilization. *Pediatrics* 2006;**118**:1819–1827.

Knoester M, Vandenbroucke JP, Helmerhorst FM, Van der Westerlaken LAJ, Walther FJ, Veen S. Matched follow-up study of 5-8 year old ICSI-singletons: comparison of their neuromotor development to IVF and naturally conceived singletons. *Hum Reprod* 2007a;**22**: 1638–1646.

Knoester M, Helmerhorst FM, Van der Westerlaken LAJ, Walther FJ, Veen S. Matched follow-up study of 5-8-year-old ICSI singletons: child behaviour, parenting stress and child (health related) quality of life. *Hum Reprod* 2007b;**22**:3098–3107.

Knoester M, Helmerhorst FM, Vandenbroucke JP, Van der Westerlaken LAJ, Walther FJ, Veen S. Cognitive development of singletons born after intracytoplasmic sperm injection compared with in vitro fertilization and natural conception. *Fertil Steril* 2008, in press.

Koivurova S, Hartikainen AL, Sovio U, Gissler M, Hemminki E, Järvelin MR. Growth, psychomotor development and morbidity up to 3 years of age in children born after IVF. *Hum Reprod* 2003;**18**:2328–2336.

La Sala GB, Gallinelli A, Fagandini P, Bevolo P, Landini A, Ballabeni A, Gasparini F, Leni M, Torricelli L. Developmental outcomes at one and two years of children conceived by intracytoplasmic sperm injection. *Int J Fertil Womens Med* 2004;**49**:113–119.

Leslie GI, Gibson FL, McMahon C, Cohen J, Saunders DM, Tennant C. Children conceived using ICSI do not have an increased risk of delayed mental development at 5 years of age. *Hum Reprod* 2003;**18**:2067–2072.

Leslie GI. Mental development of children conceived using intracytoplasmic sperm injection. *Minerva Ginecol* 2004;**56**:247–257.

Leunens L, Celestin-Westreich S, Bonduelle M, Liebaers I, Ponjaert-Kristoffersen I. Cognitive and motor development of 8-year-old children born after ICSI compared to spontaneously conceived children. *Hum Reprod* 2006;**21**:2922–2929.

Leunens L, Celestin-Westreich S, Bonduelle M, Liebaers I, Ponjaert-Kristoffersen I. Follow-up of cognitive and motor development of 10-year-old singleton children born after ICSI compared with spontaneously conceived children. *Hum reprod* 2008;**23**:105–111.

Levy-Shiff R, Vakil E, Dimitrovsky L, Abramovitz M, Shahar N, Har-Even D, Gross S, Lerman M, Levy I, Sirota L *et al*. Medical, cognitive, emotional, and behavioral outcomes in school-age children conceived by in-vitro fertilization. *J Clin Child Psychol* 1998;**27**:320–329.

Lidegaard Ø, Pinborg A, Andersen AN. Imprinting diseases and IVF: Danish national IVF cohort study. *Hum Reprod* 2005;**20**:950–954.

Ludwig M, Diedrich K. Follow-up of children born after assisted reproductive technologies. *Reprod Biomed Online* 2002;**5**:317–322.

Ludwig AK, Sutcliffe AG, Diedrich K, Ludwig M. Post-neonatal health and development of children born after assisted reproduction: A systematic review of controlled studies. *Eur J Obstet Gynecol Reprod Biol* 2006;**127**:3–25.

Maimburg RD, Væth M. Do children born after assisted conception have less risk of developing infantile autism? *Hum Reprod* 2007;**22**:1841–1843.

McMahon CA, Ungerer JA, Tennant C, Saunders C. Psychosocial adjustment and the quality of the mother-child relationship at four months postpartum after conception by in vitro fertilization. *Fertil Steril* 1997;**68**:492–500.

McMahon C, Gibson F. A special path to parenthood: parent-child relationships in families giving birth to singleton infants through IVF. *Reprod Biomed Online* 2002;**5**:179–186.

Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analysis of randomised controlled trials: the QUOROM statement. *Lancet* 1999;**354**:1896–1900.

Morin NC, Wirth FH, Johnson DH, Frank LM, Presburg HJ, Van de Water VL, Chee EM, Mills JL. Congenital malformations and psychosocial development in children conceived by in vitro fertilization. *J Pediatr* 1989;**115**:222–227.

Neri QV, Tanaka N, Wang A, Katagiri Y, Takeuchi T, Rosenwaks Z, Palermo GD. Intracytoplasmic sperm injection. Accomplishments and qualms. *Minerva Ginecol* 2004;**56**:189–196.

Nyboe Andersen A, Goossens V, Gianaroli L, Felberbaum R, de Mouzon J, Nygren KG. Assisted reproductive technology in Europe, 2003. Results generated from European registers by ESHRE. *Hum Reprod* 2007;**22**:1513–1525.

Olivennes F, Fanchin R, Lédée N, Righini C, Kadoch IJ, Frydman R. Perinatal outcome and developmental studies on children born after IVF. *Hum Reprod Update* 2002;**8**:117–128.

Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. *Lancet* 1992;**340**:17–18.

Papaligoura Z, Panopoulou-Maratou O, Solman M, Arvaniti K, Sarafidou J. Cognitive development of 12 month old Greek infants conceived after ICSI and the effects of the method on their parents. *Hum Reprod* 2004;**19**:1488–1493.

Pinborg A. IVF/ICSI twin pregnancies: risks and prevention. *Hum Reprod Update* 2005;**11**:575–593.

Pinborg A, Loft A, Schmidt L, Andersen Nyboe A. Morbidity in a Danish national cohort of 472 IVF/ICSI twins, 1132 non-IVF/ICSI twins and 634 IVF/ICSI singletons: health-related and social implications for the children and their families. *Hum Reprod* 2003;**18**:1234–1243.

Pinborg A, Loft A, Schmidt L, Greisen G, Rasmussen S, Andersen AN. Neurological sequelae in twins born after assisted conception: controlled national cohort study. *BMJ* 2004;**329**:311.

Place I, Englert Y. A prospective longitudinal study of the physical, psychomotor, and intellectual development of singleton children up to 5 years who were conceived by intracytoplasmic sperm injection compared with children conceived spontaneously and by in vitro fertilization. *Fertil Steril* 2003;**80**:1388–1397.

Ponjaert-Kristoffersen I, Tjus T, Nekkebroeck J, Squires J, Verté D, Heimann M, Bonduelle M, Palermo G, Wennerholm UB. Psychological follow-up study of 5-year-old ICSI children. *Hum Reprod* 2004;**19**:2791–2797.

Ponjaert-Kristoffersen I, Bonduelle M, Barnes J, Nekkebroeck J, Loft A, Wennerholm UB, Tarlatzis BC, Peters C, Hagberg BS, Berner A *et al*. International collaborative study of intracytoplasmic sperm injection-conceived, in vitro fertilization-conceived, and naturally conceived 5-year-old child outcomes: cognitive and motor assessments. *Pediatrics* 2005;**115**:283–289.

Raoul-Duval A, Bertrand-Servais M, Frydman R. Comparative prospective study of the psychological development of children born by in vitro fertilization and their mothers. *J Psychosom Obstet Gynaecol* 1993;**14**:117–126.

Raoul-Duval A, Bertrand-Servais M, Letur-Könirsch H, Frydman R. Psychological follow-up of children born after in-vitro fertilization. *Hum Reprod* 1994;**9**:1097–1101.

Ron-El R, Lahat E, Golan A, Lerman M, Bukovsky I, Herman A. Development of children born after ovarian superovulation induced by long-acting gonadotropin-releasing hormone agonist and menotropins, and by in vitro fertilization. *J Pediatr* 1994;**125**:734–737.

Sanchez-Albisua I, Borell-Kost S, Mau-Holzmann UA, Licht P, Krägeloh-Mann. Increased frequency of severe major anomalies in children conceived by intracytoplasmic sperm injection. *Dev Med Child Neurol* 2007;**49**:129–134.

Saunders K, Spensley J, Munro J, Halasz G. Growth and physical outcome of children conceived by in vitro fertilization. *Pediatrics* 1996;**97**:688–692.

Schieve LA, Meikle SF, Ferre C, Peterson HB, Jeng G, Wilcox LS. Low and very low birth weight in infants conceived with use of assisted reproductive technology. *N Engl J Med* 2002;**346**:731–737.

Steptoe PC, Edwards RG. Birth after the reimplantation of a human embryo. *Lancet* 1978;**2**:366.

Strömberg B, Dahlquist G, Ericson A, Finnström O, Köster M, Stjernqvist K. Neurological sequelae in children born after in-vitro fertilisation: a population-based study. *Lancet* 2002;**359**:461–465.

Sun Y, Vestergaard M, Christensen J, Zhu JL, Bech BH, Olsen J. Epilepsy and febrile seizures in children of treated and untreated subfertile couples. *Hum Reprod* 2007;**22**:215–220.

Sutcliffe AG. Follow-up of children conceived from cryopreserved embryos. *Mol Cell Endocrinol* 2000;**169**:91–93.

Sutcliffe AG, Ludwig M. Outcome of assisted reproduction. *Lancet* 2007;**370**:351–359.

Sutcliffe AG, D'Souza SW, Cadman J, Richards B, McKinlay IA, Lieberman B. Minor congenital anomalies, major congenital malformations and development in children conceived from cryopreserved embryos. *Hum Reprod* 1995a;**10**:3332–3337.

Sutcliffe AG, D'Souza SW, Cadman J, Richards B, McKinlay IA, Lieberman B. Outcome in children from cryopreserved embryos. *Arch Dis Child* 1995b;**72**:290–293.

Sutcliffe AG, Taylor B, Grudzinskas G, Thornton S, Lieberman B. Children conceived by intracytoplasmic sperm injection. *Lancet* 1998;**352**:578–579.

Sutcliffe AG, Taylor B, Li J, Thornton S, Grudzinskas JG, Lieberman BA. Children born after intracytoplasmic sperm injection: population control study. *BMJ* 1999;**318**:704–705.

Sutcliffe AG, Taylor B, Saunders K, Thornton S, Lieberman BA, Grudzinskas JG. Outcome in the second year of life after in-vitro fertilisation by intracytoplasmic sperm injection: a UK case-control study. *Lancet* 2001;**357**:2080–2084.

Sutcliffe AG, Saunders K, McLachlan R, Taylor B, Edwards P, Grudzinskas G, Leiberman B, Thornton S. A retrospective case-control study of developmental and other outcomes in a cohort of Australian children conceived by intracytoplasmic sperm injection compared with a similar group in the United Kingdom. *Fertil Steril* 2003;**79**:512–516.

Sutcliffe AG, Edwards PR, Beeson C, Barnes J. Comparing parents' perceptions of IVF conceived children's behaviour with naturally conceived children. *Infant Ment Health J* 2004;**25**:163–170.

Sutcliffe AG, Barnes J, Wennerholm UB, Loft A, Tarlatzis BC, Ponjaert-Kristoferson I, Bonduelle M. Laterality in five-year-olds conceived by intracytoplasmic sperm injection, standard in vitro fertilisation and natural conception: a European study. *BJOG* 2005;**112**:1397–1401.

Sydsjö G, Wadsby M, Kjellberg S, Sydsjö A. Relationships and parenthood in couples after assisted reproduction and in spontaneous primiparous couples: a prospective long-term follow-up study. *Hum Reprod* 2002;**17**:3242–3250.

Tarlatzis BC, Grimbizis G. Pregnancy and child outcome after assisted reproduction techniques. *Hum Reprod* 1999;**14**:231–243.

Van Balen F. Child-rearing following in vitro fertilization. *J Child Psychol Psychiatry* 1996;**37**:687–693.

Van Balen F. Development of IVF Children. *Dev Rev* 1998;**18**:30–46.

Van Steirteghem A, Bonduelle M, Devroey P, Liebaers I. Follow-up of children born after ICSI. *Hum Reprod Update* 2002;**8**:111–116.

Wennerholm UB. Cryopreservation of embryos and oocytes: obstetric outcome and health in children. *Hum Reprod* 2000;**15**:18–25.

Wennerholm UB, Albertsson-Wikland K, Bergh C, Hamberger L, Niklasson A, Nilsson L, Thiringer K, Wennergren M, Wikland M, Borres MP. Postnatal growth and health in children born after cryopreservation as embryos. *Lancet* 1998;**351**:1085–1090.

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