REVIEW ARTICLE

Cerebral Palsy, Autism Spectrum Disorders, and Developmental Delay in Children Born After Assisted Conception

A Systematic Review and Meta-analysis

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Objective: To assess the existing evidence of associations between assisted conception and cerebral palsy (CP), autism spectrum disorders (ASD), and developmental delay.

Data Sources: Forty-one studies identified in a systematical PubMed and Excerpta Medica Database (EMBASE) search for articles published from January 1, 1996, to April 1, 2008.

Study Selection: Studies written in English comparing children born after assisted conception with children born after natural conception assessing CP, ASD, and developmental delay, based on original data with a follow-up of 1 year or more.

Main Exposures: In vitro fertilization (IVF) with or without intracytoplasmic sperm injection or ovulation induction with or without subsequent intrauterine insemination.

Main Outcome Measures: Cerebral palsy, ASD, and developmental delay.

Results: Nine CP studies showed that children born after IVF had an increased risk of CP associated with preterm delivery. In our meta-analysis including 19 462 children exposed to IVF, we estimated a crude odds ratio of 2.18 (95% confidence interval, 1.71-2.77). Eight ASD studies and 30 studies on developmental delay showed inconsistent results. No studies assessed the risk of CP, ASD, or developmental delay in children born after ovulation induction exclusively.

Conclusions: Methodological problems were revealed in the identified studies, and the gaps in our knowledge about the long-term outcomes of children born after assisted conception are considerable, including a lack of information on the long-term consequences of ovulation induction. Possible associations with ASD and developmental delay need assessment in larger studies. Studies on assisted conception and CP from countries outside of Scandinavia are needed, including detailed information on time to pregnancy, underlying cause of infertility, and type of IVF treatment.

Arch Pediatr Adolesc Med. 2009;163(1):72-83

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In this review, we examined studies on the long-term outcomes of assisted conception, defined as in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) or ovulation induction (OI) with or without subsequent intrauterine insemination (IUI).

In vitro fertilization treatment alone now accounts for an estimated 1% to 4% of births in European countries[1] and 1% of US births.[2] There is a particular obligation to evaluate treatments offered in health care systems to guarantee their safety.

In vitro fertilization is associated with adverse perinatal outcomes such as preterm delivery (PTD, <37 weeks of gestation) and low birth weight (LBW, <2500 g) because of the strong association between IVF and multiple pregnancies and because even IVF singletons have an increased risk of PTD and LBW compared with naturally conceived (NC) singletons.[3] Likewise, OI leads to more multiple pregnancies than natural conception,[1,4] and children born after OI also have an increased risk of PTD and LBW, as reported in most studies[4-8] but not all.[9,10] Pregnancy with multiples, PTD, and LBW are strongly associated with a range of long-term child health problems[3,11,12] including admission to neonatal intensive care units and prolonged hospitalization,[13] vision impairment,[14] and cerebral palsy (CP).[15] Moderate associations between delivery of multiples, PTD, LBW, advanced parental age, and developmental disabilities such as autism spectrum disorders (ASD) have

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Table 1. MeSH Terms and Hits in Literature Search[a]

Exposures and Outcomes	No.	
	MeSH	AllFields
"Cerebral palsy" and		
"Ovulation induction"	1	3
"Fertilization in vitro"	11	24
"Reproductive techniques, assisted"	19	34
"Sperm injections, intracytoplasmic"	3	5
"Insemination, artificial"	0	1
Autism spectrum disorders, "autistic disorder" or "Aspergers syndrome" and		
"Ovulation induction"	0	0
"Fertilization in vitro"	2	2
"Reproductive techniques, assisted"	4	4
"Sperm injections, intracytoplasmic"	1	1
"Insemination, artificial"	0	0
Developmental delay, "developmental disabilities," "child development disorders," or "child development" and		
"Ovulation induction"	7	
"Fertilization in vitro"	70	
"Reproductive techniques, assisted"	93	
"Sperm injections, intracytoplasmic"	33	
"Insemination, artificial"	12	

Abbreviation: MeSH, Medical Subject Headings of the National Library of Medicine.
[a]Limits, January 1, 1996 to October 31, 2007; humans; English language. The articles on autism spectrum disorders all appear in the cerebral palsy search, except for the article by Maimburg. Articles may have appeared in more than 1 search category.

also been reported.[16-23] Advanced parental age is strongly associated with assisted conception. Additionally, possible prenatal hormonal disturbances in autism, eg, elevated levels of prenatal testosterone[24] and lower levels of oxytocin,[25] have been reported and may be linked to reproductive problems.

We conducted a systematic review of the current evidence regarding associations between assisted conception and severe long-term outcomes, specifically CP and ASD. We also reviewed general developmental delay outcomes, as these are often the initiating diagnoses or symptoms.

METHODS

LITERATURE SEARCH

We searched PubMed using the Medical Subject Headings of the National Library of Medicine terms presented in **Table 1**. We limited our search to studies reporting human outcomes of assisted conception published from January 1, 1996, through March 31, 2008 in English and including children exposed to assisted conception (IVF, ICSI, IUI, or OI). We performed our search on April 10, 2008. The main outcome measures of interest were CP, ASD, and developmental delay.

STUDY SELECTION

A total of 130 articles met our initial search criteria. All abstracts were reviewed and 41 articles met the additional inclusion criteria of original data, follow-up time of 1 year or more, and a comparison group of unexposed NC children. Excluded articles are shown in an online appendix (http://www.nanea.dk/articles/hvidtjorn-2008-review). We examined the reference lists of all 41 articles eligible for full review, but did not identify any additional articles. We searched EMBASE using the search terms in Table 1 for CP and ASD, but did not identify any additional articles with original data. The initial screening of abstracts was conducted by an author (D.H.). Each of the articles meeting the final inclusion criteria were reviewed in full by 2 authors (D.H. and 1 coauthor; L.S., D.S., P.T., or B.J.).

Here, we present findings from the reviewed studies on CP, ASD, and developmental delay. For each outcome we discuss the main methodological strengths and limitations of the studies. Because of the elevated risk of multiple births in assisted conception, whenever possible we present the articles' findings for singletons and multiples separately, as well as all births combined, with or without adjusting for PTD.

META-ANALYSIS

We performed meta-analyses with fixed-effect models using the Mantel-Haenzel method and calculated nonadjusted summary estimates for the CP studies. Several studies included overlapping cohorts; for these we selected the study presenting the most detailed data (the necessary numbers to calculate a weighted summary). Stata software version 10.0 (Stata, College Station, Texas) was used.

We did not perform meta-analyses for the ASD studies reviewed because of the small number of studies within the specific study design types and potential methodological problems in the few studies similarly designed (see below). We did not perform meta-analyses with the developmental delay studies because a wide range of different measurements were used to assess cognitive, motor, and behavioral development. Moreover, even when 2 studies used the same instrument, child age at assessment was often variable, as were sample inclusion and/or exclusion criteria.

Of the 41 included studies, only 2 were case-control studies; the remainder were cohort studies. Nine studies assessed the risk of CP (**Table 2**) and 8 the risk of ASD (**Table 3**). Thirty studies assessed developmental delay based on various standardized scales (**Table 4**). Within all 3 outcomes there were overlapping study populations.

Table 2. Assisted Conception and Cerebral Palsy Associations by Reference

Source, y	Country, Cohort	Follow-up: Design	Follow-up: Duration, y	Data Sources: Assisted Conception	Data Sources: Cerebral Palsy	Sample Size (Multiples, %): Exposed	Sample Size (Multiples, %): Unexposed	Associations, Not Adjusting for Preterm Delivery: Ratio (95% CI)	Associations, Not Adjusting for Preterm Delivery: Exposed Outcomes	Preterm Delivery
All Children										
Klemetti et al, 2006	Finland, 1996-1999	Retrospective cohort	2	All fertility clinics, IVF	HDR, *ICD-10* G80 and child care support register	4527 (35.7)	26 877 (2.2)	OR, 2.92 (1.63-5.26)[a]	17	88% of IVF children with CP
Hvidtjørn et al, 2006	Denmark, 1995-2000	Retrospective cohort	1-7	IVF register, IVF	NRHD, *ICD-10* G80.0-83.9	9255 (38.6)	383 919 (2.7)	HRR, 1.61 (1.13-2.30)[b]	40	HRR, 1.07 (0.76-1.52),[b] adjusting for PTD
Källen et al, 2005	Sweden, 1987-2002	Retrospective cohort	1-20	All fertility clinics, IVF	HDR, *ICD-9* or *-10* CP	16 280	All other births	OR, 1.89 (1.37-2.60)[c]	37	OR, 0.88 (0.46-1.70)[c] in children carried to term
Strömberg et al, 2002	Sweden, 1982-1995	Retrospective cohort	1.5-15	All fertility clinics, IVF	Disability centers' medical records, *ICD-10* CP	5680 (43.0)	11 360 (3.9)	OR, 3.7 (2.0-6.6)[d]	31	OR, 2.9 (1.40-6.0),[d] adjusting for PTD
Ericson et al, 2002	Sweden, 1984-1997	Retrospective cohort	1-14	All fertility clinics, IVF	HDR, *ICD-9* 343 or *ICD-10* G81	9056	1 408 110	OR, 1.69 (1.06-2.68)[e]	NS	. . .
Singletons										
Klemetti et al, 2006	Finland, 1996-1999	Retrospective cohort	2	All fertility clinics, IVF	HDR, *ICD-10* G80 and child care support register	2911	26 296	OR, 1.15 (0.40-3.27)[a]	4	. . .
Hvidtjørn et al, 2006	Denmark, 1995-2000	Retrospective cohort	1-7	IVF register, IVF	NRHD, *ICD-10* G80.0-83.9	5685	383 919	HRR, 1.28 (0.80-2.03)[b]	NS	HRR, 0.84 (0.43-1.63)[b] singletons carried to term
Lidegaard et al, 2005	Denmark, 1995-2001	Retrospective cohort	1-7	IVF register, IVF	NRHD, *ICD-10* G80.0	6052	442 349	Rate ratio, 1.8 (1.2-2.8)	25	. . .
Strömberg et al, 2002	Sweden, 1982-1995	Retrospective cohort	1.5-15	The National Board of Health and Welfare, IVF	Disability centers' medical records, *ICD-10* CP	3228	11 070	OR, 2.8 (1.3-5.8)[d]	12	OR, 2.4 (0.9-6.0),[d] adjusting for PTD
Twins										
Klemetti et al, 2006	Finland, 1996-1999	Retrospective cohort	2	All fertility clinics, IVF	HDR, *ICD-10* G80 and child care support register	1616	581	OR, 1.52 (0.43-5.40)[a]	13	. . .
Hvidtjørn et al, 2006	Denmark, 1995-2000	Retrospective cohort	1-7	IVF register, IVF	NRHD, *ICD-10* G80.0-83.9	3570	10 794	HRR, 1.08 (0.57-2.05)[b]	NS	HRR, 0.83 (0.27-2.61)[b] twins carried to term
Pinborg et al, 2004	Denmark, 1995-2000	Retrospective cohort	2-7	IVF register, IVF	NRHD, *ICD-10* G80.0-83.8	3393	10 239	OR, 0.83 (0.43-1.67)[f,g]	11	OR, 0.8 (0.4-1.6),[f] adjusting for PTD
Pinborg et al, 2003	Denmark, 1997	Retrospective cohort	3-4	IVF register, IVF	Mother questionnaires and NRHD, *ICD-10*	472	1132	OR, 0.61 (0.17-2.16)[g]	3	. . .
Strömberg et al, 2002	Sweden, 1982-1995	Retrospective cohort	1.5-15	The National Board of Health and Welfare, IVF	Disability centers' med records, *ICD-10* CP	2060	4120	OR, 0.9 (0.4-1.8)[d]	15	. . .
Triplets										
Skrablin et al, 2007	Croatia, 1986-2000	Retrospective cohort	2-12	One hospital-assisted conception	Rehabilitation centers, CP diagnosis	68	9	OR, 0.31 (0.15-0.65)[g]	9	. . .

Abbreviations: CP, cerebral palsy; CI, confidence interval; *ICD-8*, *-9*, or *-10*, *International Classification of Diseases, Eighth, Ninth, or Tenth Revision*; IVF, in vitro fertilization; HDR, Hospital Discharge Register; HRR, hazard rate ratio; NRHD, National Register of Hospital Discharges; NS, not shown; OR, odds ratio; PTD, preterm delivery.

[a] Adjusted for mother's socioeconomic position.
[b] Adjusted for parity, sex, maternal age, and educational level.
[c] Adjusted for year of birth.
[d] Adjusted for sex, year of birth, and birth hospital.
[e] Adjusted for year of birth, maternal age, parity, and smoking.
[f] Adjusted for sex and year of birth.
[g] Calculated from raw numbers presented in the article.

RESULTS

CEREBRAL PALSY

Generalizability

Results for CP are shown in Table 3. Of the 9 studies assessing the risk of CP in children born after IVF, only 1 was conducted outside of Scandinavia (a Croatian study of triplets).[26] The Scandinavian studies were population-based, diminishing any selection bias. However, the Scandinavian countries are very similar in demographic factors, socioeconomic status, ethnicity (mainly white), and free access to health care (including fertility treatment), and this uniformity might limit extrapolation of the findings to populations of different ethnic profiles, demography, and health care systems.

Table 3. Assisted Conception and Autism Spectrum Disorders Associations by Reference

Source, y	Country, Cohort	Follow-up: Design	Follow-up: Duration, y	Data Source: Assisted Conception	Data Source: Autism Spectrum Disorders	Sample Size (Multiples, %): Exposed	Sample Size (Multiples, %): Unexposed	Associations: Ratio (95% CI)	Associations: Exposed Outcomes
All Children									
Maimburg and Vaeth, 2007	Denmark, 1990-1999	Case-control		Birth records, assisted conception	DPCRR, *ICD-8* 299.0 or *ICD-10* F84.0	473	473	OR, 0.37 (0.14-0.98)[a]	10
Stein et al, 2006	Israel, 1970-1998	Case-control		Interviews, infertility medical intervention	Autism treatment organization, *ICD-8* or *DSM III-IV* Autism	206	152	OR, 1.91 (0.94-3.88)[b]	29
Klemetti et al, 2006	Finland, 1996-1999	Retrospective cohort	2	All fertility clinics, IVF	HDR, *ICD-10* F80-98 and child care support register (more than ASD)	4527 (35.7)	26 877 (2.2)	OR, 1.68 (1.11-2.53)[c]	>ASD
Strömberg et al, 2002	Sweden, 1982-1995	Retrospective cohort	1.5-15	National Board of Health and Welfare, IVF	Disability centers' medical records, *ICD-10* infantile autism	5680 (43.0)	11 360 (1.3)	Too infrequent	NS
Ericson et al, 2002	Sweden, 1984-1997	Retrospective cohort	1-14	All fertility clinics, IVF	HDR, *ICD-9* and *ICD-10* (more than ASD)	9056	1 408 110	OR, 1.35 (0.86-2.11)[d]	>ASD
Singletons									
Klemetti et al, 2006	Finland, 1996-1999	Retrospective cohort	2	All fertility clinics, IVF	HDR, *ICD-10* F80-98 and child care support register (more than ASD)	2911	26 296	OR, 1.05 (0.57-1.91)[c]	>ASD
Lidegaard et al, 2005	Denmark, 1995-2001	Retrospective cohort	1-7	IVF register, IVF	DPCRR, *ICD-10* F84	6052	442 349	Rate ratio, 1.2 (NS)	13
Twins									
Klemetti et al, 2006	Finland, 1996-1999	Retrospective cohort	2	All fertility clinics, IVF	HDR, *ICD-10* F80-98 and child care support register (more than ASD)	1616	581	OR, 3.05 (0.70-13.29)[c]	>ASD
Pinborg et al, 2004	Denmark, 1995-2000	Retrospective cohort	2-7	IVF register, IVF	DPCRR: *ICD-10* F84 and F84.5	3393	10 239	OR, 0.82 (0.23-2.95)[b]	3
Pinborg et al, 2003	Denmark, 1997	Retrospective cohort	3-4	IVF register, IVF	Maternal questionnaires and discharge records, *ICD-10* F84 and F84.5	472	1132	NA	0

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval; DPCRR, The Danish Psychiatric Central Research Register; *DSM-IIII or -V, Diagnostic and Statistical Manual of Mental Disorders* (Third or Fourth Edition); HDR, Hospital Discharge Register; *ICD-8*, *-9*, or *-10*, *International Classification of Diseases, Eighth, Ninth, or Tenth Revision*; IVF, in vitro fertilization; NA, not available; NS, not shown; OR, odds ratio.

[a] Adjusted for parity, multiplicity, birth weight, gestational age, birth defect, maternal age, and country of origin.

[b] Calculated from raw numbers presented in the article.

[c] Adjusted for mother's socioeconomic position.

[d] Adjusted for year of birth, maternal age, parity, and smoking.

Methodological Quality of Included Studies

Sample Size and Precision. The Scandinavian studies were based on data from registers comprising health status on the whole population and information on IVF treatments from all fertility clinics retrieved via the unique identification number given to each citizen, resulting in large cohorts reporting fairly precise risk estimates. Risk estimates were less precise in the strata of multiplicity because of reduced sample sizes and lower expected prevalence within the group of singletons only.

Exposure Data. One study assessed the risk of CP in triplets born after all types of assisted conception, identified through a single hospital.[26] The remaining 8 studies evaluated children born after IVF using specific population-based data on exposure and identified either through an IVF register (in Denmark) or through all fertility clinics in the specific country (Sweden or Finland); they likely included practically all children born after IVF. However, no study specifically examined OI and only 1 study specified that pregnancies resulting from OI (OI children) were excluded from the comparison group of children born after natural conception.[27] Thus for most studies, some misclassification of the unexposed group likely occurred, as OI children were counted as NC children. This would presumably lead to bias toward the null hypothesis, as OI is strongly associated with multiple pregnancies.[28,29] In the studies of twins, Pinborg et al[30,31] reported that 17.3% of pregnancies in the unexposed groups were the result of OI.

Outcome Data. Cerebral palsy was defined as a diagnosis of *International Statistical Classification of Dis-*

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Table 4. Assisted Conception and Developmental Delay Associations by Reference

Source, y	Country, Cohort	Follow-up: Design	Follow-up: Duration, y	Exclusions	Data Source: Assisted Conception	Data Source: Outcomes	Sample Size (Multiples, %): Exposed	Sample Size (Multiples, %): Unexposed	Measurement Scale	Associations	Adjusting or Matching
All Children											
Kallen et al, 2005	Sweden, 1987-2002	Retrospective cohort	1-20		All fertility clinics, IVF	HDR, *ICD-9* or -10	16 280	All other births	Behavioral problems	OR, 1.74 (95% CI, 1.11-2.74)	Maternal age, birth year, parity, and smoking
Leslie et al, 2003	Australia, 1993-1995	Retrospective cohort	5		1 Fertility clinic, ICSI	Psychological examination	97 (23)	110 (13)	WPPSI	NS findings in cognitive development at age 5 y	Parental education and language
Agarwal et al, 2005	Singapore, 1998-1999	Retrospective cohort	2		1 Fertility clinic, ICSI	Parent report and neurological examination	76 (46)	261 (46)	BSID-II, WABS	NS findings in mental and motor development and adaptive behavior at age 2 y	Maternal age, sex, race, plurality, parity, and date of delivery
La Sala et al, 2004	Italy, 1998-2001	Retrospective cohort	2	Congenital abnormalities, cerebral palsy	1 Fertility clinic, ICSI	Psychological examination	50 (40)	51 (24)	BSID-II, Videotaped interacting between parents and child	NS findings in mental development at ages 1 and 2 y, statistically significant lower scores in motor development and in cooperation with parents at age 1 and 2 y	No
Papaligoura et al, 2004	Greece, 1998-2000	Retrospective cohort	1	Born second or later	1 Fertility clinic, ICSI	Psychological examination	34 (23)	29 (21)	BSID	NS findings in mental and motor development at age 1 y	GA, maternal age, and birth weight (g)
Koivuroa et al, 2003	Finland, 1990-1995	Retrospective cohort	3		2 Fertility clinics, IVF	Psychological examination	299	558	Psychomotor developmental milestone (modified Bayley scale)	NS findings in psychomotor development at ages 1, 2, and 3 y	Sex, maternal age and occupation, parity, and year of birth
Bowen et al, 1998	Australia, 1993-1995	Prospective cohort	1		1 Fertility clinic, ICSI	Psychological examination	89 (22)	80 (25)	BSID-II	Statistically significant lower scores in mental development at age 1, NS findings in motor development at age 1 y	Maternal age, parity, and multiplicity
Levy-Shiff et al, 1998	Israel	Retrospective cohort	10	PTD < 36	2 Fertility clinics, IVF	Psychological examination, self-report	51	51	WPPSI state-trait anxiety, depression, aggression, and behavior inventories for children	NS findings in cognitive development at ages 9 and 10 y, statistically significant lower scores in behavior development at ages 9 and 10 y	Sex, age, parity, and parental education and social level
D'Souza et al, 1997	Great Britain, 1984-1991	Prospective cohort	4		1 Fertility clinic, IVF (fresh)	Medical examination	278 (46)	278 (0)	Developmental delay (Griffiths score with DQ)	2 IVF multiples, 0 IVF singletons, and 0 NC children had adverse developmental outcome	Sex and father's occupation
Twins											
Minakami et al, 2008	Japan	Prospective cohort	1	Singletons	Assisted conception	Medical examination	136 (100)	72 (100)	Physical and neurological development	Statistically significantly less assisted conception, twins had adverse outcome (death, cerebral palsy, and mental retardation)	
Ito et al, 2006	Japan, 1994-2000	Retrospective cohort, corrected for age	3	Birth weight >1500 g, singletons	1 Fertility clinic, assisted conception	Psychological examination	28 (100)	16 (100)	Kyoto scale of psychological development DQ for posture, cognition, and language	6 IVF and 0 NC twins had borderline or lower total DQ, statistically significantly more IVF twins had borderline or lower DQ for cognition and language, NS findings in DQ for posture at age 3 y	

(continued)

eases, 10th Revision (ICD-10) code G80.0-G83.9, stated as "*ICD-10* diagnosis CP," or described in 1 study as "children diagnosed with CP by a pediatric neurologist."[26] Six studies obtained information about CP diagnoses from hospital discharge registers[27,31-35]; the remaining 3 used records from rehabilitation centers[26,36] or questionnaires confirmed by discharge registers.[30] However, the validity and completeness of the CP diagnoses in hospital discharge registers have been questioned.[37] Klemetti et al[27] supplemented their information on CP diagnosis using registers reporting child care support. Only Strömberg et al[36] obtained the CP diagnoses from the medical records of all disability centers in Sweden.

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Table 4. Assisted Conception and Developmental Delay Associations by Reference (continued)

Source, y	Country, Cohort	Follow-up: Design	Follow-up: Duration, y	Exclusions	Data Source: Assisted Conception	Data Source: Outcomes	Sample Size (Multiples, %): Exposed	Sample Size (Multiples, %): Unexposed	Measurement Scale	Associations	Adjusting or Matching
					Singletons						
Leunens et al, 2008	Belgium, 1993-1995	Retrospective cohort	10	PTD < 32, multiples	1 Fertility clinic, ICSI	Psychological examination	109 (0)	90 (0)	WISC, MABC	NS findings in cognitive and motor development at age 10 y	
Knoester et al, 2007	Netherlands, 1996-1999	Retrospective cohort	5-8	Oocyte or sperm donation, cryopreservation, multiples	1 Fertility center, ICSI	Questionnaires to parents	87 (0)	85 (0)	Child behavior checklist	NS findings in behavioral development at ages 5-8 y, 3/87 (3.4%) of ICSI children had an ASD diagnosis	
Knoester et al, 2007	Netherlands, 1996-1999	Retrospective cohort	5-8	Oocyte/sperm donation, cryopreservation, multiples	1 Fertility center, ICSI	Neurological examination	87 (0)	85 (0)	Neurological parameters, Touwen criteria	NS findings in neuromotor development at ages 5-8 y	Maternal age and parity
Knoester et al, 2007	Netherlands, 1996-1999	Retrospective cohort	5-8	Oocyte/sperm donation, cryopreservation, multiples	1 Fertility center, ICSI	Psychological examination	86 (0)	85 (0)	RAKIT	Statistically significant lower scores in cognitive development at ages 5-8 y	
Sanchez-Albisua et al, 2007	Germany, 1996-2001	Retrospective cohort	1.5 and 3	PTD < 35, multiples, perinatal complications	1 Fertility clinic, ICSI	Parent report, neurological examination	34 (0)	39 (0)	Developmental milestones	No difference in mental and motor development at ages 18 mo and 3 y	GA, age at examination, sex, and management of perinatal complications
Belva et al, 2006	Belgium, 1993-1995	Retrospective cohort	8	PTD < 32, multiples	1 Fertility clinic, ICSI	Neurological examination	150 (0)	147 (0)	Neurological parameters, Touwen criteria	NS findings in motor development at age 8 y except for coordination, ICSI children had statistically significant lower score	Sex, age at examination, and maternal education level
Leuens et al, 2006	Belgium, 1993-1995	Retrospective cohort	8	PTD < 32, multiples	1 Fertility clinic, ICSI	Psychological examination	151 (0)	152 (0)	WISC, MABC	Statistically significant higher scores in cognitive development at age 8 y, NS findings in motor development at age 8 y	Sex, age at examination, and maternal education level
Ponjaert-Kristoffersen et al, 2005	International, 1993-1995	Retrospective cohort	5	PTD < 32, multiples	Multicenter, IVF and ICSI	Psychological examination	ICSI, 511 (0); IVF, 424 (0)	488 (0)	WPPSI, McCarthy Scales of Children's Abilities Motor Scale	NS findings in cognitive and motor development at age 5 y	Sex, maternal education level, and birth order
Ponjaert-Kristoffersen et al, 2004	International, 1993-1995	Retrospective cohort	5	PTD < 32, multiples	Multicenter, ICSI	Psychological examination	300 (0)	260 (0)	WPPSI, PDMS	NS findings in cognitive development at age 5 y, statistically significant lower scores in motor development at age 5 y	Sex, age at examination, and maternal age
Barnes et al, 2004	International	Retrospective cohort	5	PTD < 32, not white, multiples	Multicenter, IVF and ICSI	Parental question-naires	ICSI, 514 (0); IVF, 424 (0)	488 (0)	The McDevitt and Carey temperament questionnaires, Childs Behavior Checklist	NS findings in behavioral development at age 5 y	Sex, maternal age and education, and parental socioeco-nomic status
Bonduelle et al, 2004	International	Retrospective cohort	5	PTD < 32, multiples	Multicenter, ICSI	Neurological examination	300 (0)	266 (0)	Walking, running, jumping	12 in each group had walking, running, or jumping disorders at age 5 y	Sex, age at examination, and maternal age
Sutcliffe et al, 2003	International	Retrospective cohort	1	Multiples	Multicenter, ICSI	Medical examination	264 (0)	260 (0)	Griffiths Mental Development Scales	NS findings in mental development at age 1 y	Sex, age, maternal age, and social and educational level

(continued)

Table 4. Assisted Conception and Developmental Delay Associations by Reference (continued)

Source, y	Country, Cohort	Follow-up: Design	Follow-up: Duration, y	Exclusions	Data Source: Assisted Conception	Data Source: Outcomes	Sample Size (Multiples, %): Exposed	Sample Size (Multiples, %): Unexposed	Measurement Scale	Associations	Adjusting or Matching
Singletons (continued)											
Place et al, 2003	Belgium, 1998-2000	Retrospective cohort	3 and 5	PTD < 37, multiples, birth weight <2500 g	1 Fertility clinic, IVF and ICSI	Psychological examination	ICSI, 66 (0); IVF, 52 (0)	59 (0)	The revised Brunet-Lezine scale, WPPSI	NS findings in motor and behavioral development at age 18 mo, NS findings in cognitive development at ages 3 and 5 y	Sex, age, maternal age, and demographic factors
Colpin et al, 2002	Belgium, 1990-1991	Retrospective cohort	8-9	Multiples	1 Fertility clinic, IVF	Questionnaires to parents, teachers	27 (0)	23 (0)	Child Behavior Checklist, Teacher's Report Form	NS findings in behavioral development at age 8-9 y	No
Golombok et al, 2002	International	Retrospective cohort	11-12	Perinatal problems, multiples	Multicenter, IVF	Questionnaires to mothers and teachers, interviews with children	ICSI, 102 (0); IVF, 94 (0)	102 (0)	SDQ, Child and adolescent functioning and environment schedule	NS findings in behavioral development at age 11-12 y	Sex, age, age of mother, social class, and family size
Golombok et al, 2001		Retrospective cohort	11-12	Perinatal problems, multiples	IVF	Maternal interview and questionnaires, child interview, questionnaires to mothers and teachers	34 (0)	38 (0)	The social adjustment inventory for children and adolescents, SDQ	3 IVF and 3 NC showed a psychiatric disorder, NS findings in behavioral development at age 12 y	
Sutcliffe et al, 2001	Great Britain, 1995-1997	Retrospective cohort	1	Multiples	Multicenter, ICSI	Medical examination	208 (0)	221 (0)	Griffiths mental development scales	NS findings in mental development at age 1-2 y	Sex, maternal race, social and educational level
Sutcliffe et al, 1999	Great Britain	Retrospective cohort	1.5	Multiples	Multicenter, ICSI	Medical examination	123 (0)	123 (0)	Griffiths mental development scales	NS findings in mental development at age 17 mo	Sex, maternal race, social and educational level
Golombok et al, 1996	International	Retrospective cohort	5-6	Perinatal problems, multiples	Multicenter, IVF	Questionnaires from mothers and teachers	ICSI, 116 (0); IVF, 111 (0)	120 (0)	Rutter A and B scale	NS findings in behavioral development at ages 5-6 y	Sex, age, age of mother, social class, and family size
Wennerholm et al, 1998	Sweden, 1990-1995	Retrospective cohort	1.5	Stillborn twin, trisomy 13	2 Fertility clinics, IVF, cryopreserved	Medical examination	255 (0)	252 (0)	Psychomotor development	No difference in psychomotor development at age 18 mo	No

Abbreviations: ASD, autism spectrum disorder; BSID, The Bayley Scale of Infant Development; CI, confidence interval; DQ, Developmental Quotient; GA, gestational age; HDR, Hospital Discharge Register; *ICD-9, International Classification of Diseases, Ninth Revision;* ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; MABC, Movement Assessment Battery for Children; NC, naturally conceived; NS, not significant; OR, odds ratio; PDMS, Peabody Developmental Motor Scales; PTD, preterm delivery; RAKIT, Revised Amsterdam Child Intelligence Test; SDQ, Strength and Difficulties Questionnaires; WABS, Vineland Adaptive Behavior Scale; WISC, Wechsler Intelligence Scale for Children; WPPSI, Wechsler Preschool and Primary Scales of Intelligence.

All Birth Findings

All studies of singletons and multiples combined found a statistically significant increase in the risk of CP in children born as the result of IVF (IVF children) compared with NC children.[27,32-34,36] However, a disproportionate number of the IVF children were multiples. Odds ratios (OR) ranged from 1.6 to 3.7 in analyses adjusting for various factors other than PTD. The strongest association between IVF and CP (OR, 3.7; 95% confidence interval [CI], 2.0-6.6) was reported by Strömberg et al.[36] A meta-analysis (without overlapping study cohorts) included 19 462 IVF children and demonstrated an increased risk of CP in IVF children (OR, 2.18; 95% CI, 1.71-2.77) (**Figure**).

Some studies also presented results from analysis including PTD. Although Strömberg et al found a decrease in the magnitude of the association after adjusting for PTD, it remained strong and statistically significant (OR, 2.9; 95% CI, 1.4-6.0). Hvidtjørn et al[32] found no association between IVF and CP after adjusting for PTD. In the study by Källen et al,[33] the OR in a stratum of children carried to term was 0.88 (95% CI, 0.46-1.70), and Klemetti et al[27] found that 88% of IVF children with CP were born preterm. Dissimilarities in analytic approach complicate an immediate comparison of these findings; however, it seems clear that the risk of CP in IVF children at least partially operates through PTD.

Only Källen et al[33] had information on time to pregnancy (TTP) and reported no association between IVF and CP after adjusting for TTP.

Singleton Findings

There was a tendency toward an increased risk for CP in singletons born as a result of IVF (IVF singletons) compared with non-IVF singletons,[27,32,35,36] but not all studies

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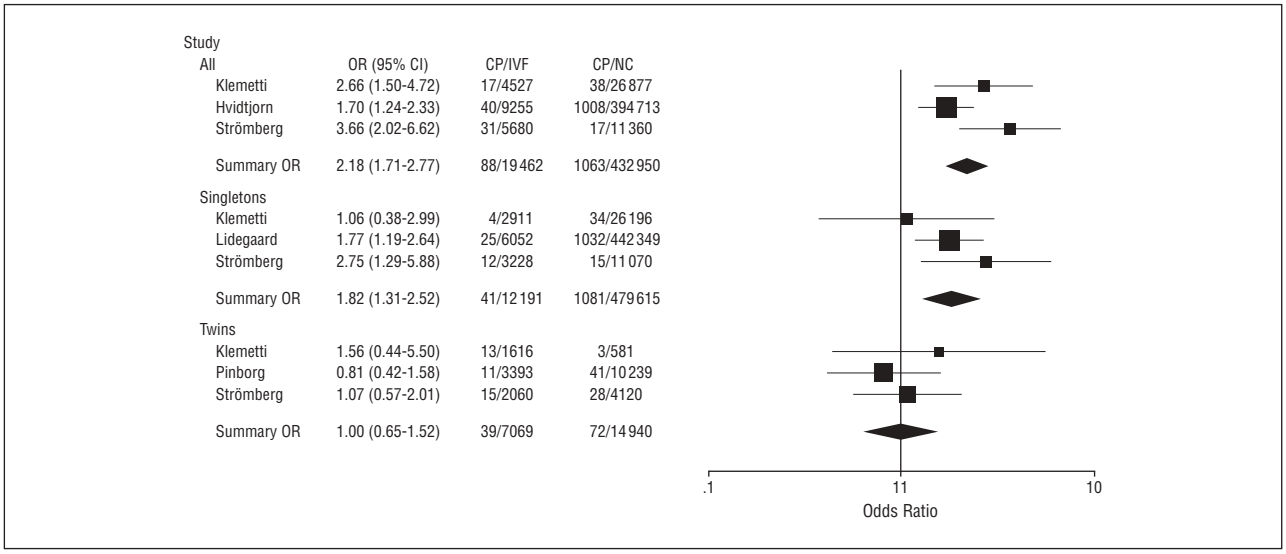

Figure. Meta-analyses of studies assessing the risk of cerebral palsy (CP) in children born as a result of in vitro fertilization (IVF). OR indicates odds ratio; CI, confidence interval; NC, naturally conceived.

reached statistical significance.[27,32] The 2 Danish studies used overlapping cohorts but had different analytical approaches; Lidegaard et al[35] reported a crude rate ratio of 1.8 ($P<.01$) in contrast to the non–statistically significant finding by Hvidtjørn et al[32] who found a hazard rate ratio of 1.28 (95% CI, 0.80-2.03) in an analysis adjusting for sex, parity, maternal age, and educational level. Strömberg et al[36] reported an OR of 2.8 (95% CI, 1.3-5.8) after adjusting for sex, year of birth, and birth hospital. A meta-analysis (without overlapping study cohorts) comprised 12 191 IVF singletons and showed an increased risk of CP in IVF singletons (OR, 1.82; 95% CI, 1.31-2.52) (Figure).

Multiples Findings

While the effect estimates varied (OR range, 0.6-1.5) of the 5 studies examining CP in twins born as a result of IVF (IVF twins) vs non-IVF twins, confidence limits were wide and overlapping (1.0) in all studies.[27,30-32,36] In contrast, in the study on the risk of CP in triplets, assisted conception had a statistically significant protective effect.[26]

AUTISM SPECTRUM DISORDERS

Generalizability

Data regarding ASD can be found in Table 4. All but 1 of the ASD studies (an Israeli case-control study)[26] originated in Scandinavian countries; consequently, they have the same limitations regarding external validity as the CP studies.

Methodological Quality of Included Studies

Sample Size and Precision. The identified ASD studies covered the period from 1970 to 2001. During this period the prevalence of ASD apparently changed considerably from 4 to 5 per 10 000 children to 6 to 7 per 1000 children.[38] It has been questioned whether this increase reflects a true rise in the prevalence of ASD or at least partly reflects changes in diagnostic criteria and increased medical and/or public awareness of these disabilities.[39,40] Given that active monitoring of ASD was not in operation in most areas, the expected prevalence at a particular time and area is not known. If we apply a conservative estimate of about 3/1000 children for the time period of these ASD studies, it would require sample sizes of 5268 exposed and 15 804 unexposed to detect a risk of 2.0 in cohort studies with 80% power and 95% CI (estimations in Calculations in Epi Info; Centers for Disease Control, Atlanta, Georgia). Only 2 studies on multiples and singletons combined and 1 on singletons alone achieved this size.[34,35]

Exposure Data. For the cohort studies from Scandinavia, nondifferential misclassification of OI in the unexposed group was likely, as described above for the CP studies.

In the 1 case-control study, information on exposure was retrieved differently, namely from birth records. However, a validation study on information about infertility treatment in birth records indicated low sensitivity overall for fertility treatment reporting and potentially differential reporting. Higher-risk infants such as multiples were more likely than singletons to be correctly reported as conceived after infertility treatment (personal communication, L.S.; February 1, 2008).

Outcome Data. Most studies obtained information on outcome from hospital discharge registers[27,31,34,35,41] and others used records from rehabilitation centers[36,42] or questionnaires confirmed by discharge registers.[30] Autism spectrum disorder was defined as a diagnosis of *ICD-10* code F84.0, F84.1, F84.5, or F84.9 or *ICD-8* and *Diagnostic and Statistical Manual of Mental Disorders* (Third or Fourth Edition) *(DSM III-IV)*. Three of the studies used only infantile autism as the study outcome, 3 used ASD, and 2 used an even broader range of psychiatric diagnoses including ASD, complicating the comparison between the studies. Diagnosis was retrieved from Hospital Discharge Registers, from The Danish Psychiatric

Central Research Register, and in 1 case from an autism treatment organization.[42]

Findings. Two studies evaluated children born after assisted conception in general,[41,42] while the remaining 6 evaluated IVF using information from all of the fertility clinics in each country. Findings were inconsistent overall and when considering singletons and multiples separately. Only the study by Klemetti et al[27] reported a statistically significant increased risk for a broad range of psychiatric disorders (F80-F98) including ASD in children born after IVF (OR, 1.68; 95% CI, 1.11-2.58); however, they did not provide results for ASD alone.

In contrast, Maimburg and Væth[41] reported a protective effect between assisted conception and infantile autism in their case-control study, including 473 children with infantile autism and 473 matched control children (OR, 0.37; 95% CI, 0.14-0.98) adjusting for several factors including gestational age.

DEVELOPMENTAL DELAY

Generalizability

Developmental delay associations can be seen in Table 4. Most studies on developmental delay limited their study participants to children exposed to assisted conception at 1 or 2 fertility clinics, introducing the possibility of selection bias if these clinics were not representative of the entire population. Furthermore, bias might have resulted from differential participation because of substantial nonparticipation in some studies requiring individual examination of the included children. For example, in one of the largest international studies,[43] participation rates varied across countries, with rates from 25% to 96% and differences of participation rates of exposed and nonexposed children up to 50%.

Perhaps the foremost problem with these studies was that 21 of them excluded children with risk factors such as multiplicity, PTD, and neonatal complications a priori to test the possible influence of IVF or ICSI on development apart from these complications. While this was certainly a reasonable method for the stated objective, it severely compromised the value of the studies to inform an increase in general developmental delay in the total population of children born after assisted conception, as one could argue that delivery of multiples and PTD are key factors in the causal pathway.

However, studies on developmental delay were conducted on several continents, ensuring representation of diverse populations.

Methodological Quality of Included Studies

Sample Size and Precision. Except for 1 population-based register study,[33] the studies on developmental delay individually included between 43 and 999 children, with each study sample of insufficient size to identify relatively rare events such as CP or ASD. Many sample sizes were also insufficient to detect moderate differences in the broader child development measures.

Exposure and Outcome Data. Exposed children were identified at fertility clinics. Nearly all studies used parental questionnaires and/or some type of individual standardized examination of the child to assess development, but they used different measurement scales. The population-based study used hospital discharge registers and ICD codes.[33] While ascertainment of both exposure and outcome were based on reliable sources and standardized measures, these strengths did not overcome the limitations of possible selection bias due to low participation rates in some studies and selection of specific low-risk children only.

Findings. We identified 30 studies assessing developmental delay in children born after assisted conception. Seventeen studies evaluated children born after ICSI solely, 13 also evaluated IVF, and 2 evaluated children born after assisted conception in general. Eight studies reported the number of children with CP in their cohorts and 2 stated the number of children with ASD. The numbers were too small for statistical estimation regarding these conditions, as would be expected in cohorts of fewer than 1000 children. In one study the children identified with CP or other adverse outcomes were excluded before further examination.[44]

Fourteen studies assessed motor development,[43-56] and 2 reported that children born as a result of ICSI (ICSI children) had a statistically significant higher risk of delayed motor development at 1 to 2 or 5 years of age, respectively.[44,57] Eleven studies assessed behavioral development[33,44,46,56,58-64]; 2 reported a statistically significant higher risk of delayed behavioral development in ICSI children aged 1 to 2 years [44] and IVF children aged 9 to 10 years,[58] respectively. The large population-based register study found an increased risk of behavioral problems in children born after IVF (OR, 1.74; 95% CI, 1.11-2.74).[33] Nine studies assessed delay in cognitive development[43,45,51,54,56-58,65,66] and 1 study reported that ICSI children had a statistically significant lower risk of delayed cognitive development at 8 years of age, while another study reported that ICSI children had a statistically significant higher risk of delayed cognitive development at 5 to 8 years of age.[65] Eleven studies assessed delay in mental development,[44,46-50,52,67-71] and 1 found less adverse outcomes in twins born as a result of assisted conception[71] while all other studies on developmental delay described non–statistically significant findings.

COMMENT

This systematic review included studies assessing the risks of CP, ASD, and developmental delay in children born after assisted conception. Owing to the size of the study cohorts and the concordant results, the CP studies offer persuasive evidence of an increased risk of CP in children born after IVF that is explained in part by an increased risk of PTD. Cerebral palsy is a lifelong condition and a heavy burden on the child, family, and health care system in terms of both personal and economic costs.[72]

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In contrast, studies assessing the risk of ASD were inconsistent. This might have been owing to the aforementioned methodological problems in these studies or simply might have reflected a lack of association between assisted conception and ASD. As ASD seems to have a heterogenic etiology, the effect of weak associations will only be apparent in larger samples.[40] Moreover, a possible association between assisted conception and ASD needs examination in studies covering recent time periods with more complete ASD reporting.

Studies on developmental delay following assisted conception mainly included small select groups of low-risk children, and they presented generally non–statistically significant results. Thus, data on larger samples of the full range of children conceived via assisted conception are needed.

We did not identify any studies assessing the risk of CP, ASD, or developmental delay in children born after OI specifically. The lack of evidence on the long-term risks of OI is of concern given associations shown in previous studies between OI and PTD, LBW, and delivery of multiples.[1,4-8]

While the studies offer persuasive evidence of an association between IVF and CP, gaps remain in understanding this relationship. Because the increased risk of CP in children born after IVF seems to operate partly through the causal pathway of IVF, delivery of multiples, and PTD, the extent of the CP risk associated with IVF in a population will likely depend on the rate of IVF multiples. This rate is lower in Scandinavian countries that regulate the number of embryos transferred; eg, in Denmark in 2005 only 1.5% of IVF children were triplets and 32.6% were twins.[73] In contrast, the rate of multiples born after IVF in the United States in 2004 was 50%, with a larger proportion of triplets and longer gestations.[2]

The etiology behind the risk of CP in IVF singletons remains unclear, but 2 Danish studies suggest that the phenomenon of vanishing embryos in early pregnancy might be part of the etiology. Hvidtjørn et al[74] found that 3.9 of 1000 (95% CI, 2.2-5.5/1000) singletons born after transfer of more than 1 embryo had CP, similar to the proportion among twins born after the transfer of 2 embryos (4.4 of 1000 children; 95% CI, 1.9-6.9). Pinborg et al[75] showed that the group of IVF singletons in which a coembryo had vanished before 22 weeks of gestational age had nearly twice the risk of CP (OR, 1.9; 95% CI, 0.7-5.2) compared with IVF singletons originating from pregnancies with only 1 fetus at 8 weeks of gestational age. These findings need further exploration.

We also still need to determine whether the increased risk of CP after IVF is associated with subfertility, type of subfertility, or any specific subtype of IVF. Subfertility has been associated with adverse pregnancy outcomes such as PTD and neonatal death,[76,77] though not by Kapitejn et al.[9] Ericson et al[34] found an increased risk of hospitalization with increasing time to pregnancy. We found only 1 study that adjusted for time to pregnancy[33] and, in doing so, the risk of CP disappeared. The type of subfertility was taken into account in 1 study only, revealing similar risks of CP within the different types, though this was based on small numbers.[32]

While animal studies report long-term adverse effects of urinary gonadotrophins compared with other treatment regimens used in controlled ovarian stimulation,[78,79] only a few studies in this review compared different treatment types. Three studies evaluated possible differences between conventional IVF and ICSI[31-33] and found comparable risks in the 2 groups. One study compared the risk of CP in children born after use of fresh vs frozen embryos and reported a hazard rate ratio of 2.32 (95% CI, 0.80-6.76) in the latter group,[32] but this was based on small numbers.

A comprehensive search in PubMed and EMBASE revealed 130 articles, of which 41 were eligible for review. The main reasons for exclusion of articles were (1) commentary and/or review, (2) different exposure or outcome, and (3) no NC comparison group. Excluded articles are shown in an online appendix. We consider the possible selection bias minimal, as none of the studies excluded fulfilled the a priori criteria.

In summary, this systematic review revealed important gaps in the evidence of long-term outcomes in children born after assisted conception. Possible associations between assisted conception and ASD need assessment in larger studies with well-defined outcomes. Studies on assisted conception and CP from countries outside of Scandinavia are needed as well as studies with detailed information on TTP, underlying causes of infertility, and types of IVF treatment. The long-term outcomes of OI must be addressed. Given the continually increased use of fertility treatments worldwide, studies addressing these very large gaps in the knowledge of the long-term health and development of children born after assisted conception are an important public health objective.

Accepted for Publication: May 29, 2008.
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Schendel, and Thorsen. *Study supervision:* Schieve, Schendel, Jacobsson, and Thorsen.

Financial Disclosure: None reported.

Funding/Support: The study was funded by the Danish Agency for Science, Technology, and Innovation; the University of Aarhus; the Elsass Foundation; the Health Insurance Foundation; the Augustinus Foundation; the Julie von Müllens Foundation; Direktør Jacob Madsen & Hustru Olga Madsens Fond; and the Aase and Ejnar Danielsen Foundation.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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(REPRINTED WITH CORRECTIONS)