Human Reproduction Update, Vol.19, No.3 pp. 244–250, 2013
Advanced Access publication on February 28, 2013 doi:10.1093/humupd/dmt002

human reproduction update

The longer-term health outcomes for children born as a result of IVF treatment. Part II–Mental health and development outcomes

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Submitted on June 20, 2012; resubmitted on January 7, 2013; accepted on January 9, 2013

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BACKGROUND: Limited data exist with regard to longer-term mental health and psychological functioning of children born from IVF treatment. With the known adverse perinatal outcome for children born from IVF treatment, it would be expected that there is a negative impact upon their mental development.

METHODS: A search strategy restricted to studies relating to the medical condition of children of at least 1 year of age, born from IVF treatment was performed to include case series, data linkage and prospective studies published from 1 January 2000 to 1 April 2012.

RESULTS: Limited long-term follow-up data suggest that there is an increase in the incidence of cerebral palsy and neurodevelopmental delay related to the confounders of prematurity and low birthweight. Previous reports of associations with autism and attention-deficit disorder are believed to be related to maternal and obstetric factors. There exists a potential increase in the prevalence of early adulthood clinical depression and binge drinking in the offspring of IVF, with the reassuring data of no changes with respect to cognitive development,

school performance, social functioning and behaviour. Whether these potential associations are related to the IVF treatment, the adverse obstetric outcomes associated with IVF treatment, the genetic or subsequent environmental influences on the children is yet to be determined.

CONCLUSIONS: In general, the longer-term mental and emotional health outcome for children born from IVF treatment is reassuring, and is very similar to that of naturally conceived children; however, further studies are required to explore any association with depression, and its causality in more detail.

Key words: IVF / ICSI / ART / long-term outcome / mental health

Background

What is already known of the long-term mental health outcomes of children born from IVF treatment?

Previous reviews of children born from IVF treatment have frequently been limited by short-term follow-up which has raised concerns with regard to the neurological outcomes resulting from IVF treatment (Koivurova *et al*., 2003; Bonduelle *et al*., 2005). The data may be biased due to problems related to multiple gestations, prematurity and the consequences of neonatal hospitalization. However, reviews that have focused on adolescence have generally produced reassuring data, but they have highlighted a possible increased risk of depression in children born resulting from IVF treatment (Ludwig *et al*., 2006; Steel and Sutcliffe, 2009; Wilson *et al*., 2011). This review aims to provide a more detailed description of the longer-term mental health outcomes of children born from IVF than has previously been reported.

The purpose of this systematic review was to synthesize the data from the studies listed to provide a comprehensive summary of the data to date as to the longer-term mental health and development consequences of birth resulting from IVF treatment.

Methods

On 1 April 2012, an English language literature search was performed of PubMed, EMBASE, BioMed central PsycInfo, Science Direct, Cochrane Google Scholar and Cochrane Controlled Trials Register, published from 1 January 2000 until 1 April 2012 relating to children of at least 1 year of age born from IVF treatment, with a control group available for analysis, including case series, data linkage studies and prospective studies to cover the following topics: cerebral palsy and neurological and neuromotor development, cognitive function, school performance, social functioning and behaviour, attention-deficit disorder, autism, depression and anxiety and addiction, as described in Table I. The first author (R.H.) conducted a review of abstracts generated by the search. The paper was reviewed if appropriate, any uncertainty was discussed with the second author (R.J.N.), and if appropriate, the contents of the paper and the reference list were reviewed. The data were analysed according to the PRISMA checklist and a PRISMA flowchart was constructed, as described in our companion paper (Part I, Fig. 1), and the studies used in the literature review are listed and described in Supplementary data, Table SI.

Results

Developmental delay and psycho-social development

Cerebral palsy and neurodevelopmental delay

Population studies performed on younger children are influenced by the significantly increased risk of cerebral palsy in children conceived from IVF, such as that reported by the Swedish Medical Birth Registry when linked to national disability databases (Stromberg *et al*., 2002). For singletons, the risk of cerebral palsy was increased almost five times; however, after adjustment for prematurity and low birthweight, no difference in the rate of cerebral palsy, mental retardation, developmental delay and behavioural disorder was recorded, suggesting that it is the adverse obstetric outcome associated with IVF that is responsible for any increase in neurological sequelae rather than IVF *per se* (Stromberg *et al*., 2002). However, a prospective Danish study that recruited women in pregnancy and allocated them into groups according to the time to conception and requirement for fertility assistance, and linking to the Danish Cerebral Palsy Register (Zhu *et al*., 2010a), demonstrated a significant association with assisted reproduction techniques (ART), when adjusted for preterm birth and multiple pregnancies [odds ratio (OR) 2.30, 95% confidence interval (CI) 1.12–4.73] (Zhu *et al*., 2010a).

To summarize the literature, Hvidtjorn *et al*. (2009) published a thorough systematic review and meta-analysis of the association of cerebral palsy, developmental delay and autism resulting from all forms of fertility treatment in 2009, which for the purposes of the current review was used as a summary of the previously published literature. The authors reviewed 41 papers that had a follow-up period beyond the first year of life (Hvidtjorn *et al*., 2009). Nine studies (eight of which were performed in Scandinavia) were stratified by multiplicity. The majority of studies identified their cohort through registries, and some of the studies classified ovulation induction in the 'naturally conceiving' cohorts (Hvidtjorn *et al*., 2009). All studies demonstrated a significant increase in the incidence of cerebral palsy in the children conceived after IVF; however, a substantial number of all the pregnancies in the studies resulting from ART were multiples. After controlling for singleton pregnancies, the OR for cerebral palsy was 1.82 (CI 1.31–2.52); however, the data were not adjusted for other obstetric factors which are more common in IVF pregnancies, such as growth restriction and prematurity (Hvidtjorn *et al*., 2009). The authors state that substantial influences on the rate of cerebral palsy in singletons are prematurity and possibly the 'vanishing twin phenomena'

Table I Search strategy.

Search date	1 April 2012
Sources searched	PubMed, EMBASE, BioMed central PsycInfo, Science Direct, Cochrane Google Scholar and Cochrane Controlled Trials Register Limited to publications dated from 1 January 2000 to 1 April 2012
	Search criteria used for the title and abstract were: Reproductive Techniques, Assisted OR Fertilization *in Vitro* OR Sperm Injections, Intracytoplasmic OR IVF (keyword) or ICSI (keyword) (include all subheadings) AND Child OR Infant OR children (keyword) OR baby (keyword) OR offspring (keyword) (include all subheadings) AND Follow-up studies OR follow-up (keyword) OR long-term (keyword) OR Child Development OR development (keyword) OR Health OR health (keyword) OR Morbidity (include all subheadings) Other MESH terms and keywords used to find articles on specific aspects of the topic: Psychological Development; Neurology; Cognitive Ability, Cognitive Development, Intelligence, Intelligence Quotient, Behaviour, Behaviour Problems, Attention Deficit Disorder with Hyperactivity; Autism, Motor Development, Motor Skills, Psychosocial Development, Emotional Adjustment, Delayed Development, Developmental Disabilities, Intellectual Development Disorder, Language Development, Language Delay, Language Disorders, Nervous System Single-embryo transfer (keyword) Cryopreservation (keyword); frozen embryos (keyword)
Other information sources checked	Reference lists of included studies were searched to identify additional relevant papers
Inclusion criteria	Published in English language peer-reviewed journal Studies limited to children conceived subsequent to the following treatments; IVF, frozen embryo transfer, gamete intrafallopian transfer, zygote intrafallopian transfer, tubal embryo transfer, minimal stimulation IVF Studies that recorded health outcomes beyond the first year of life Studies involving data collection and or comparison with a contemporary cohort of individuals from the general population or who were naturally conceived, or a systematic review of such papers
Exclusion criteria	Articles not published in English Articles where it was not possible to identify the fertility treatment employed Studies which exclusively analysed multiple pregnancies and studies where the IVF/ICSI or control group had <70 participants The following treatments were excluded; PGD/PGS, *in vitro* maturation, surrogacy and studies of fertility treatment using donor sperm, oocyte or embryo donation Studies with a follow-up period of <12 months Studies without an identifiable comparison cohort and case studies Studies where it was not possible to identify the fertility treatment employed to enable analysis of the IVF outcomes
Categories of studies	Physical health and adjustment-papers were assigned to Part I
	Psychosocial health and adjustment-papers were assigned to Part II
Method for assessing and interpreting the evidence	Abstracts were provisionally classified and full-text articles obtained for critical appraisal. Each publication was evaluated by one reviewer (R.H.) and in instances of uncertainty were reviewed by R.J.N.

after a double-embryo transfer (Pinborg *et al.*, 2005), although in Australia, where single-embryo transfer is very common, any increase in the rate of cerebral palsy appears to be related to low birthweight and prematurity (Reid *et al.*, 2010).

No further studies were identified. Any increase in cerebral palsy must be accounted for in any studies analysing the neurodevelopment of children conceived after IVF and ICSI treatment.

With regard to developmental delay, the review by Hvidtjorn *et al.* (2009) found that most studies demonstrated no differences in the incidence of developmental delay or delayed behavioural development when IVF-conceived children were compared with naturally conceived children.

Cognitive function and intelligence quotient

One of the first studies with 5 years of follow-up was Leslie *et al.* (2003), which concluded that the mental development of ICSI, IVF and naturally conceived children when assessed, by blinded assessors, at 5 years of age was similar across all groups. The only significant independent predictor of below-average intelligence quotient (IQ) was lower maternal education level (Leslie *et al.*, 2003).

In general, small short-term prospective analyses of the neurological development of children conceived from IVF and ICSI are reassuring, and indeed, one study suggested that children conceived as a result of IVF treatment may have a higher IQ than naturally conceived children (Leunens *et al.*, 2006; Belva *et al.*, 2007). However, a Belgium study (Leunens *et al.*, 2006), after following their cohort for a further 2 years, commented that the IQ of the ICSI cohort approximated to the spontaneously conceived cohort, suggesting that this may represent an influence of maternal educational level on mental development in early life in the ICSI-conceived cohort (Leunens *et al.*, 2008).

A large US study demonstrated that IVF-conceived children perform better on standard testing than their matched peers for all grades

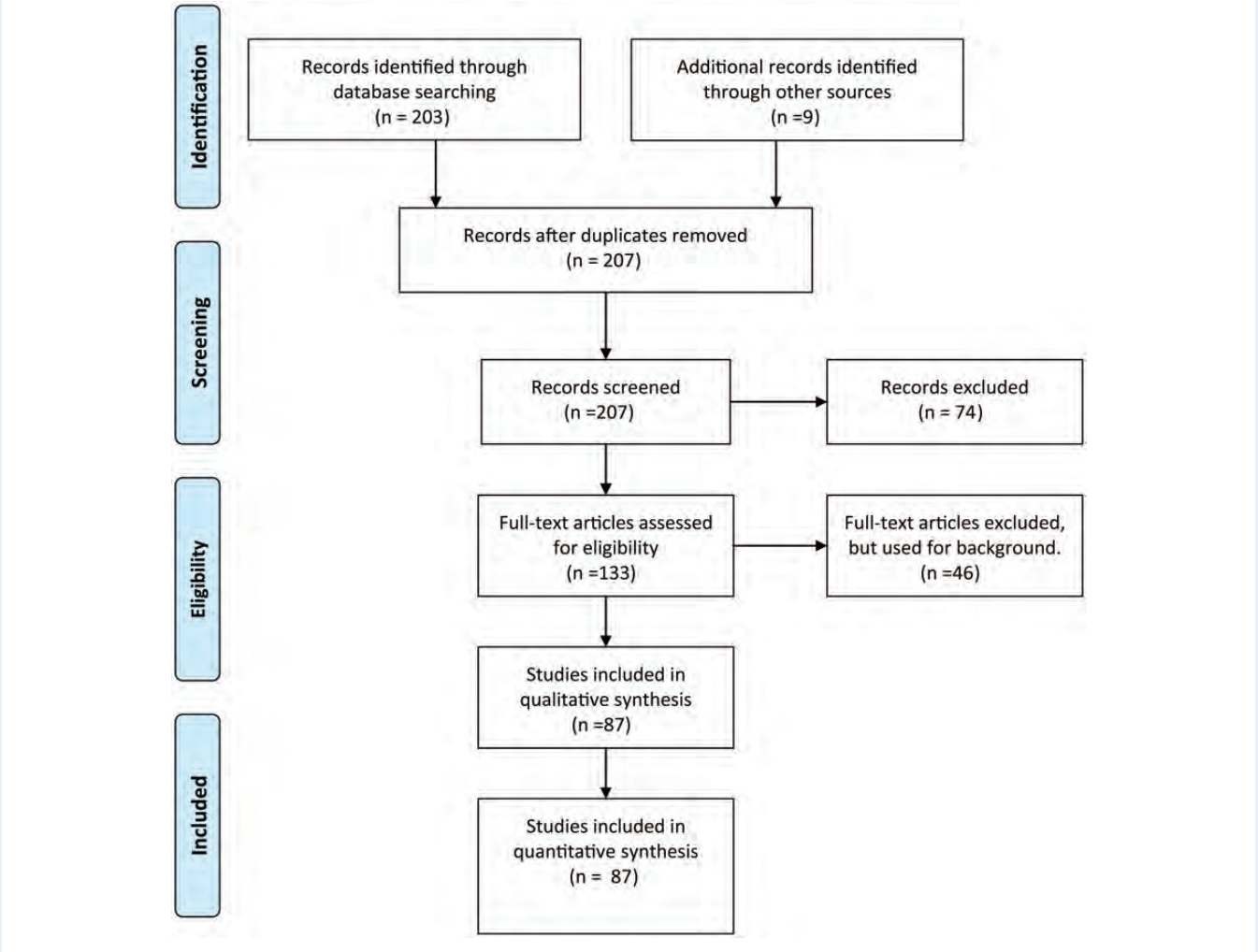

Figure 1 PRISMA decision flowchart for identified studies.

3–11, and a potential explanation that this was due to the higher socioeconomic background of the IVF-conceived children, parental age or educational level was proposed, as these factors were not analysed (Mains *et al.*, 2010). In contrast, a similar, but smaller, Dutch study suggested that ICSI-conceived children had significantly lower scores with regard to verbal learning and perceptual reasoning than spontaneously conceived control children (Knoester *et al.*, 2008).

Dutch IVF-conceived children aged 8–18 years of age who were part of a follow-up study of cardiometabolic function (Ceelen *et al.*, 2008) demonstrated no differences in cognitive function as assessed by national test scores of cognitive ability, when compared with spontaneously conceived singleton children in tests of visual-motor function, perception, coordination and information processing and attention (Wagenaar *et al.*, 2009b).

Hvidtjorn's review (Hvidtjorn *et al.*, 2009) assessed nine studies of cognitive development and reported that apart from the studies by Leunens *et al.* (2008) and Knoester *et al.* (2008), most reported no differences between the cognitive development of IVF and spontaneously conceived children.

School performance

As a follow-up to the Dutch OMEGA study (Ceelen *et al.*, 2008), the school performance of singletons conceived after IVF was compared with spontaneously conceived children, by means of the child's requirement for educational support, the results of national testing of educational achievement and the educational level grouping of the child in the Dutch educational system; no evidence of educational limitations during either primary or secondary education was obtained (Wagenaar *et al.*, 2009a).

Neuromotor development

As many studies that addressed potential neurodevelopment risk for children conceived with IVF have methodological shortcomings, a thorough systematic review of the literature was performed (Middelburg *et al.*, 2008). Many studies included children born preterm, and most studies found no differences between infants born following ART and natural conception, apart from a study of school-age children aged 5–8 years born from ICSI treatment (Knoester *et al.*, 2008).

Subsequent to the systematic review of Middelburg *et al.* (2008), three further studies have been performed that address the neuromotor development of children born from ART treatment, and demonstrated no significant differences between outcomes of children born from IVF treatment and spontaneous conceived children with regard to their motor skills up to 7 years of age (Ludwig *et al.*, 2009; Zhu *et al.*, 2010b; Jongbloed-Pereboom *et al.*, 2011). The Danish National Birth Cohort Study assessed clumsiness, believed to occur in ~5% of school age children, and demonstrated an association with an increased time to conceive in women who spontaneously conceived, but clumsiness was not related to ART treatment (Zhu *et al.*, 2010b), using a parental questionnaire to assess developmental milestones. The Zhu *et al.* (2010b) study reinforced their previous reports that a longer time to conceive may be associated with delay achieving developmental milestones and that infertility treatment, especially ICSI, may be associated with a slight delay for some of these early milestones (Zhu *et al.*, 2009).

Social functioning and behaviour

A few studies have been performed that address the psychological outcomes of children born as a result of ART. One aspect of such outcome studies that is difficult to quantify and to control for is the parental attitudes and expectations of their children. The families of children born from IVF treatment may differ in factors such as family size, parental expectations, socioeconomic factors and parental age. After reviewing the literature prior to 2006, Wagenaar *et al.* (2008b) reported that there was no difference in the incidence of behavioural and socio-emotional problems in children <8 years of age, when IVF children were compared with their spontaneously conceived peers. Subsequently, in a three country study of cognitive, motor and emotional–behaviour psychological testing at 5 years of age, minimal differences were noted between ICSI-conceived children and naturally conceived children (Ponjaert-Kristoffersen *et al.*, 2004); interestingly, the parental distress and parent–child dysfunctional interaction scores were significantly higher for the parents of the spontaneously conceived children.

A multi-site study of the socio-emotional development of children conceived as a result of ICSI treatment, performed at 5 years of age, provided very reassuring data with respect to parental stress, parent–child dysfunction, marital discord and child behaviour problems and temperament (Barnes *et al.*, 2004). Both Knoester *et al.* (2007) and Wagenaar *et al.* (2009a) also reported reassuring data for children born from IVF and ICSI treatment with regard to behaviour when compared with spontaneously conceived children.

Zhu *et al.* (2011) used three Danish birth cohorts of singleton children between 7 and 21 years of age to study the emotional, behavioural and social functioning of the children born with and without fertility assistance. For children born after fertility treatment, the parent and self-reported emotional, hyperactivity, peer problems and prosocial behaviour scores were similar to children born of fertile couples.

Attention deficit disorder

Studies of school-age children did not find any increase in the prevalence of attention-deficit hyperactivity disorder (ADHD) (Wagenaar *et al.*, 2009b; Mains *et al.*, 2010). However, subsequent to these studies, a report appeared to suggest an association with attention-deficit disorder amongst IVF-conceived children using a self-reported diagnosis (Beydoun *et al.*, 2010), although a data linkage study of prescriptions for ADHD did not find an association of ADHD with IVF *per se* (Kallen *et al.*, 2011). However, ADHD is found to be more common in children of women who are younger, who smoke, have a period of unwanted childlessness, high BMI, pre-eclampsia, undergo a Caesarean section and who deliver a child pre-term, of low birthweight and with growth restriction, suggesting that any reported association with IVF may be entirely due to these confounders (Kallen *et al.*, 2011).

Autism

A systematic review of the neurological development of children born as a result of IVF (Hvidtjorn *et al.*, 2009) concluded that the data were inconsistent and inconclusive for several reasons: the incidence of autism, or at least the tendency to make a diagnosis, appears to have increased over the last three decades making an association with IVF treatment difficult to derive. Furthermore, the author states that a study would require a sample size in excess of 5000 exposed children with an unexposed cohort size of 15 000 to detect a doubling of the prevalence of autism with 80% power. Additionally, the diagnosis of autism in the studies is variably derived from registries, rehabilitation centres or questionnaires and all but one of the studies was performed in Scandinavia (Hvidtjorn *et al.*, 2009). These authors performed a large registry-based review of a potential association of autism spectrum disorder with IVF controlling for multiple demographic factors, and reported the risk of infantile autism and autism spectrum disorder was not increased in children born as a result of IVF treatment (Hvidtjorn *et al.*, 2011). Mothers of children with autism spectrum disorder were more likely to be older, primiparous, smokers and to deliver a pre-term infant of a low birthweight, again suggesting confounders may explain previous associations with IVF-conceived children (Hvidtjorn *et al.*, 2011).

Depression/anxiety disorder

There have been concerns that psychological disorders may be more prevalent in children conceived from IVF treatment (Beydoun *et al.*, 2010). Indeed, a study by Wagenaar *et al.* (2009a) of parental and teacher observations reported that more IVF children scored in the borderline/clinical range on the syndrome scale withdrawn/depressed behaviour compared with their spontaneously conceived counterparts. The discrepancy between this study, and the subsequent follow-up of children who completed a self-reported questionnaire, reporting no difference in these conditions, may be due to the fact that only a subset was reassessed (70%, potentially introducing a bias), or there may be a difference in reporting between the adults and the children.

Smoking, drinking and addiction

As described in our companion paper, Beydoun *et al.* (2010) reported a questionnaire follow-up of children conceived from IVF at a mean age of 21.2 years. The findings suggest that rates of smoking were within the expected range; however, there was a significantly increased prevalence of female binge drinking in the IVF population and a slightly increased risk of depression, with one in four respondents reporting a diagnosis of attention-deficit or hyperactivity disorder (Beydoun *et al.*, 2010).

Discussion

What do we know about the longer-term mental health outcomes for IVF offspring?

This review was devised to provide an overview of the literature that assessed the longer-term follow-up of children born from IVF from a mental health aspect. In line with the reviews of IVF technology (Williams and Sutcliffe, 2009; Wilson *et al.*, 2011), we conclude that there are minimal differences in the early neurodevelopment and neurological outcome between IVF-conceived children and spontaneously conceived children, if allowance is made for the confounders of multiple gestation and prematurity. All authors suggest that there is a great need for longer-term data. Further, this review pertaining to the mental health, cognitive function and behaviour of children conceived by IVF potentially suggests that there is an increase in the prevalence in early adulthood of clinical depression, attention-deficit disorder (ADD/ADHD) and binge drinking (Beydoun *et al.*, 2010).

There is reassuring evidence that there appears to be no increased risk of neurocognitive impairment (Middelburg *et al.*, 2008), adolescent behavioural problems (Wagenaar *et al.*, 2010), functioning at school (Wagenaar *et al.*, 2008a) or of a poor quality of life (Beydoun *et al.*, 2010) in children born from IVF (Table II). Furthermore, there is some evidence to suggest that these children may well perform at a higher level in academic testing at school (Mains *et al.*, 2010), although this may be a function of the education level of parents.

Confounding factors for the mental health development of IVF-conceived children

As described in our companion paper [Part I. General Health Outcomes (Hart and Norman)], there are many potential confounders that must be taken into consideration in analysing the literature pertaining to the children conceived from IVF treatment. Children conceived from IVF treatment in the majority of the studies analysed are born to older parents, are born at an earlier gestation, at a lower birthweight and into a smaller family of a higher economic status than spontaneously conceived children (Hvidtjorn *et al.*, 2011). All these factors, with the addition of smoking, are obstetric and maternal risk factors for the development of autism spectrum disorder in a child (Hvidtjorn *et al.*, 2011) and, additionally, a period of unwanted childlessness, pre-eclampsia, prematurity, low birthweight and growth restraint are also features associated with the subsequent development of ADHD.

Many of the authors of studies of the mental health, development and behaviour of children born as a result of IVF treatment believed that to have adjusted for obstetric and neonatal demographic factors in the subsequent data analysis would have been flawed. As it is known that there is an increased chance of an adverse obstetric and neonatal outcome in IVF pregnancies, a woman embarking on IVF treatment needs to be informed of the potential consequences of an IVF conception, pregnancy and their influences into childhood and adolescence.

The literature suggests that the incidence of cerebral palsy is increased in children born as a result of IVF treatment. The risk has been explained by prematurity and growth restraint. Any association with a slight delay in neuromotor development appears to be associated with an increased time to conceive, rather than the fertility treatment itself. The subsequent achievement of their developmental milestones, their cognitive development, school performance, social functioning and the behaviour of children conceived by IVF treatment is no different to naturally conceived children.

Table II Summary table of potential effects of IVF treatment on various mental health outcomes for the offspring.

Mental health outcomes in adolescence	Summary of effect
Cognitive function	↑ ↔ cognitive scores
School performance	↔ educational achievement
Neuromotor development	↔
Social functioning and behaviour	↔ both at home and at school
Attention-deficit disorder	↔
Autism	↔
Depression	↑ ↔
Binge drinking	↑ ♀ more than ♂
Smoking	↔

↑, increased; ↔, no effect; ♀, female; ♂, male.

Conclusion

This systematic review of the literature provides some reassuring evidence with regard to the longer-term mental health outcome for children born as a result of IVF treatment. However, there are potential associations with an increase in the risk of cerebral palsy and slight developmental delay, which appears to be explained by obstetric factors rather than IVF *per se*. Any potential association with autism or ADHD needs to be explored by further study as many of the associations with these conditions are more common in a child born to a couple with subfertility.

Whilst there may be some preliminary evidence for an increase in the incidence of adolescent depression and female binge drinking, the majority of evidence provides a reassuring outlook for the longer-term mental health of children born from IVF treatment.

Supplementary data

Supplementary data are available at http://humupd.oxfordjournals.org/.

Authors' roles

R.H. initiated the review and screened the publications for inclusion and was principally responsible for writing the manuscript. R.J.N. assisted with manuscript preparation and with data interpretation.

Funding

No funding sources were used in the preparation of this manuscript.

Conflict of interest

R.H. is part owner of an IVF company and shareholder; he has received travel grants and honoraria from pharmaceutical manufacturers of gonadotrophins and is on the medical advisory board of pharmaceutical companies that manufacture gonadotrophins. R.J.N. is part owner of an IVF company and shareholder; he has received travel grants and honoraria from pharmaceutical manufacturers of gonadotrophins and is on the medical advisory board of pharmaceutical companies that manufacture gonadotrophins.

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