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The longer-term health outcomes for children born as a result of IVF treatment: Part I–General health outcomes

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BACKGROUND: Several million children have been born from *in vitro* fertilization (IVF) treatment, but limited data exist regarding their health and development beyond the first year of life. It has been alleged that IVF may lead to long-term adverse consequences, in addition to the documented worse perinatal outcome and increased risk of congenital abnormalities in children born resulting from IVF treatment.

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

RESULTS: Limited long-term follow-up data suggest that there is potentially an increase in the incidence of raised blood pressure, elevated fasting glucose, increase in total body fat composition, advancement of bone age and potentially subclinical thyroid disorder in the IVF offspring. Whether these potential associations are related to the IVF treatment *per se*, the adverse obstetric outcomes associated with IVF treatment or are related to the genetic origin of the children is yet to be determined.

CONCLUSIONS: This review provides evidence to suggest that the short-term health outcome for children born from IVF treatment is positive. However, it is expected that the cardiovascular and metabolic risk factors found in childhood and tracking into adulthood could be worse in later life, and may be responsible for chronic cardiometabolic disease. These observations need to be addressed by further studies.

Key words: IVF / ICSI / ART / long-term outcome / metabolic syndrome

Introduction

According to the most recent statistics available for Australia and New Zealand, there were 70 541-assisted reproductive technology (ART) treatments [*in vitro* fertilization (IVF) intracytoplasmic sperm injection (ICSI) and frozen embryo replacement cycles] undertaken in 2009 (Wang, 2011). Of these cycles, 17.2% resulted in the birth of 12 127 live-born babies (Wang, 2011), with an estimated 1 in 25 children born in Australia currently being born as a result of IVF treatment (Norman, 2011). It is believed that in some countries the percentage of children born resulting from IVF treatment is substantially higher; for instance in Denmark it is estimated that almost 5% of children born result from IVF treatment (ESHRE, 2011). Worldwide over 4 million children have been born resulting from IVF treatment (ESHRE, 2011). It is of concern that despite the increasing number of babies born annually worldwide subsequent to IVF treatment, good data only exist on the short-term outcome of infants born as a result of IVF treatment (Kalra and Barnhart, 2011), but only very limited data as to their long-term health and development. Furthermore, there is a paucity of data regarding the follow-up of children born subsequent to the cryopreservation of embryos (Wennerholm *et al.*, 2009). Owing to the known adverse obstetric and perinatal outcomes (Halliday, 2007), and the increased risk of congenital abnormalities in children born resulting from IVF treatment (Bower and Hansen, 2005; Davies *et al.*, 2012), as well as the suspected increased risk of imprinting disorders in children resulting from IVF treatment (Oliver *et al.*, 2012), it is possible that there may be consequences to the child as a result of their mode of conception that are only identifiable beyond the first year of life.

An imprinting disorder is a congenital abnormality resulting from abnormal methylation patterns on inherited genes (Manipalviratn *et al.*, 2009). These appear to be exceedingly rare disorders; however, it is believed that it is possible that abnormal methylation patterns may arise during ART and lead to epigenetic alterations in the offspring (Winston and Hardy, 2002). Some epigenetic modifications are associated with growth; hence, alterations in the profile may have consequences for growth of offspring from ART. This assertion has been substantiated in animal studies and the effects of ovarian stimulation and the embryo culture media employed have been queried (Young *et al.*, 2001; Farin *et al.*, 2004; Ceelen *et al.*, 2008b).

The purpose of this systematic review was to synthesize the data from available studies to provide a comprehensive summary of the data to date on longer-term general health consequences of birth resulting from IVF treatment, and to provide an insight into the potential mechanisms for the differences detected while considering potential confounders within the literature.

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

The majority of previous reviews of children born from IVF treatment have been limited by short-term follow-up. However, those that have focused on adolescence have generally produced reassuring data, despite a possible increased risk of malignancy and potential differences in metabolic indices in children born resulting from IVF treatment (Ludwig *et al.*, 2006; Halliday, 2007; Steel and Sutcliffe, 2009; Wilson *et al.*, 2011). There is a need to provide a more detailed description of the longer-term general health outcomes of children born resulting from IVF than have previously been reported.

Difficulties in the interpretation of the literature

As described very few longer-term prospective studies that follow-up children born resulting from IVF exist to assist in the counselling of couples prior to embarking on an IVF treatment cycle, and there are several difficulties that lie in the interpretation of the available literature. Consequently much of the information is derived from the use of linked databases and it is unclear whether they are powered for the studied outcomes.

Adverse obstetric outcome and the 'developmental origins of health and disease'

It is well established that there are significantly greater obstetric and perinatal complications that may befall a mother and her infant as a result of her IVF treatment (Helmerhorst *et al.*, 2004; Halliday, 2007). This was originally believed to be a result of the associated risk of a multiple gestation; however, with the increasing move to single embryo/blastocyst transfer in several countries, it has become evident that the perinatal risks of a singleton pregnancy resulting from IVF treatment are greater than those that result from a spontaneous conception. Indeed there appears to be an incremental risk according to the degree of subfertility and type of fertility treatment performed, with spontaneously conceiving women with a history of subfertility having a significantly worse perinatal prognosis than those with normal fertility (Basso and Baird, 2003; Zhu *et al.*, 2007; Raatikainen *et al.*, 2012). Furthermore, women who require intrauterine insemination have a significantly worse perinatal outcome than women who spontaneously conceive (Allen *et al.*, 2006; Zhu *et al.*, 2007). Women, who conceive a singleton pregnancy as a result of IVF, have the worst perinatal outcome; there is an approximate doubling of the risk of stillbirth, growth restriction, premature delivery and neonatal nursery admission for their baby (Helmerhorst *et al.*, 2004; Jackson *et al.*, 2004; Halliday, 2007; Maheshwari *et al.*, 2012). Hence a woman with subfertility has an increased perinatal risk due to her subfertility, although whether this relates to her increased age or attendant medical condition, such as PCOS, endometriosis, fibroids and the presence of a hydrosalpinx or an endometrial defect, is impossible to determine. Furthermore, there appears to be perinatal differences that result from an embryo transferred in a fresh or cryopreserved IVF cycle, or indeed whether it was transferred singly or as part of a double embryo transfer. An infant conceived subsequent to a cryopreservation cycle is likely to be heavier than an infant conceived after a fresh IVF cycle (Henningsen *et al.*, 2010); whether this is due to the endometrial environment at the time of conception or the cryopreservation process is as yet unknown. The perinatal mortality of singletons conceived subsequent to a double embryo transfer procedure is significantly increased (Sullivan *et al.*, 2012).

Research on animals has established that the peri conception environment is crucial for an offspring's longer-term health and development (Fleming *et al.*, 2011, 2012). Hence it is important to bear in mind when interpreting the literature that with the passage of time embryo culture techniques and media used have changed dramatically [such as the rare use of gamete intra-fallopian tube transfer today], which may lead to difficulty in extrapolating data from the literature into modern day practice. Furthermore, it is important to be aware that the health of the woman at conception may have a significant influence on her child's longer-term health, which may be a particular confounder in infertility treatment where the cause of infertility may directly relate to the mother's health (Fleming *et al.*, 2011, 2012).

If an infant does not achieve its growth potential, either due to an adverse peri conception environment, the maternal environment in pregnancy, or due to the as yet unknown processes associated with IVF treatment which lead to growth restriction, it will embark on life with an increased risk of disease in later life, particularly if it has rapid 'catch-up growth' in childhood. This is the 'developmental origins of health and disease hypothesis' (DOHaD), formerly the 'Barker hypothesis' (Barker, 2006). This proposal relies on the assumption that exposure to an adverse environment at critical stages of development will lead to adaptive change, which may result in medical consequences later in life, such as the development of diabetes and cardiovascular disease. A rather dramatic expression of this in the twentieth century was the 'Dutch Winter Famine' (Roseboom *et al.*, 2011), where the development of later life disease was dependent upon the time of exposure of the fetus while *in utero*, when undergoing adaptive changes to the adverse environment of the famine. To further complicate the interpretation of the literature, intrauterine growth restriction is associated with the following medical conditions in later life; premature pubarche (Ibanez *et al.*, 1999, 2000), earlier menarche (Ibanez *et al.*, 2000; Sloboda *et al.*, 2007), an advancement of male puberty (Hui *et al.*, 2012), renal disease (Painter *et al.*, 2005; Abitbol and Rodriguez, 2012), cardiovascular disease (Barker *et al.*, 1989), the metabolic syndrome (Leunissen *et al.*, 2009), diabetes (Eriksson *et al.*, 2006) and neurological consequences (Tideman *et al.*, 2007). Hence, it is essential that any study assessing the consequences of IVF for the offspring must aim to control for intrauterine growth patterns. Furthermore, it is important to make the distinction between 'small for gestational age', which is usually due to genetic influences as opposed to 'growth restriction', which is due to placental insufficiency or maternal health, and potentially leads to growth restraint and selective perfusion of fetal vital organs and under perfusion of less vital structures. It is the latter situation that may lead to long-term consequences for the fetus, whereas the former situation is an appropriately grown fetus. Unfortunately, the literature that does aim to control for the potential increased neonatal morbidity of the fetus by controlling for growth often uses the surrogate definition 'small for gestational age' which may exclude some growth-restricted fetuses, as fetal growth restraint may still be evident in a 3.5-kg infant if it develops signs of placental insufficiency in the third trimester, manifest by 'falling-off the centiles' if it underwent serial growth scans prior to delivery. Consequently, excluding infants from follow-up purely on the basis of being small for gestational age may not exclude many infants that suffered prenatal growth restraint, and were, therefore, at risk of the later onset disease according to the DOHaD hypothesis, leading to an overestimation of the childhood risks caused by IVF treatment.

Multiple gestations

In many countries, single embryo transfer for younger women is still not the norm, and indeed when the literature is analysed the reader must accept that the IVF procedures practiced at the commencement of the study are likely to be different today. Indeed it is estimated that 37% of the ART pregnancies conceived in 2001 in the USA had more than one fetal heart detected on early ultrasound examination (Schieve *et al.*, 2004). Fortunately, infertility practice is slowly changing as in the most recent figures from Australia and New Zealand the twin pregnancy delivery rate was 8.0% (Wang, 2011). Although these recent figures are encouraging the practice of single embryo transfer has to be further embraced. Indeed, the incidence of monozygotic twinning is believed to be significantly increased from 1 to 5% by the practice of ART (Schachter *et al.*, 2001), particularly by the procedures of assisted hatching (Das *et al.*, 2009) and blastocyst transfer (Chang *et al.*, 2009). Hence any study that does not control for the presence of a multiple gestation will lead to erroneous findings. Furthermore, the situation is clouded by the fact that 10–20% of twin gestational sacs will spontaneously resolve to a singleton pregnancy (Pinborg *et al.*, 2006). It has been established that a pregnancy where there is a spontaneous fetal reduction leads to an increase in obstetric and neonatal risks, with a significantly greater risk of ante partum haemorrhage, premature delivery and growth restriction (Pinborg *et al.*, 2005, 2006), again leading to a potential overestimation of risk in the offspring of the IVF treatment group of children. Consequently, an ideal study would be a prospective study that only included patients who underwent single embryo transfer.

Congenital abnormalities

It is now well established that children born as a result of ART have an excess of congenital abnormalities when compared with spontaneously conceived children. Indeed even children spontaneously conceived by subfertile women and children born as a result of mild ovarian stimulation and intrauterine insemination treatment have a slightly increased risk of having a congenital abnormality (Hansen *et al.*, 2005). There are two potential reasons for the increased risk of conceiving a child with a congenital abnormality as a result of IVF treatment: either it is the genetic make-up of couples that need the IVF treatment or it is the treatment that they undergo (either controlled ovarian hyperstimulation or the culture media that the embryo is exposed to) that leads to this increased risk. The recent study by Davies *et al.* would tend to suggest that the risk of congenital abnormality may be more related to the couples that need fertility treatment or the micro-manipulation the gametes undergo, rather than the treatment *per se,* as children conceived as a result of IVF treatment did not have an increased risk of congenital abnormality, whereas those conceived by ICSI treatment did (Davies *et al.*, 2012). The relevance of the finding of an increased risk of congenital abnormalities in children conceived as a result of IVF treatment is that the abnormality may lead to an excess risk of long-term health issues that are related to the congenital abnormality and not the IVF treatment *per se.* For example, a man whose sperm requires ICSI treatment for poor semen parameters may have a son with an undescended testicle at birth, and subsequently poor semen parameters, reduced testicular size and excess of risk of testicular cancer. This situation may be related to his genetic origin rather than the IVF cycle he was conceived in.

Further challenges in the interpretation of the literature

Other factors that must be taken into consideration in the interpretation of the data derived from prospective cohort studies of IVF children are; that the motivation of parents to enrol their children in the studies may be different to those parents who do not enrol their child in the study; and the difficulties in deriving a representative control group (Ludwig, 2004) which is often generated from children from local schools or nurseries, introducing the bias that they are undertaking normal schooling. Furthermore, the parents of IVF conceived children may have a lower threshold for seeking medical attention. Interestingly, it has been demonstrated in a prospective blinded follow-up study of children born after ICSI treatment that study examiners were able to successfully identify the mode of conception in 75% of children, demonstrating that is very difficult to completely blind examiners when performing prospective cohort studies (Ludwig *et al*., 2009a).

It is almost universal across the literature that the children conceived as a result of assisted reproduction are born to older parents and to smaller families and are more likely to be the first born, and to mothers with a lower incidence of smoking and generally of a higher BMI; all factors known to significantly impact on the pregnancy outcome. Hence, it is very difficult to perform a study to control for all potential confounders when trying to determine whether ART has an adverse influence on the offspring. In addition the women undergoing IVF treatment generally tend to be of a higher socioeconomic group than women who do not undergo IVF treatment. Attempts to control for this confounder by matching couples by postcode have their limitations. When interpreting data derived from database studies, it is important to take all these factors into consideration.

Methods

On the 1 April 2012 an English language literature search was performed of PubMed, EMBASE, Science Direct, Cochrane Google Scholar and Cochrane Controlled Trials Register, published from 1 January 2000 to 1 April 2012 relating to children of at least 1 year of age born resulting from IVF treatment, with a control group available for analysis, including case series, data linkage studies and prospective studies to cover the following topics: the possible mechanisms of long-term developmental changes (epigenetic modifications), IVF vs. ICSI, the origin of sperm (ejaculated or testicular), multiple embryo transfer, embryo cryopreservation, controlled ovarian hyperstimulation and the endometrial environment. The following topics were covered: endocrine alterations, cardiovascular and metabolic disorder, pubertal development, respiratory disorder, allergy, ophthalmological disorder and cancer. Further methods to limit consequences to the offspring were sought; single embryo transfer, frozen embryo replacement vs. fresh replacement, the embryo culture media and minimal stimulation IVF. The search strategy is listed in Table I; the studies used in the literature review are detailed in Supplementary data Table SI. 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 (Fig. 1).

Results

Metabolic and cardiovascular effects

One of the earliest cohort studies of children born as a result of IVF treatment into adulthood did not describe an increase in the prevalence of being overweight or obese in a US IVF population in comparison with a representative normal population (Beydoun *et al*., 2010). However, if adjustment is made for antenatal, maternal and parental factors it appears that IVF children, when assessed in late childhood and adolescence, have significantly more peripheral body fat deposits, despite minimal differences in BMI (Ceelen *et al*., 2007). Further work from this group suggests that despite early life catch-up growth, early childhood gain in height, weight and BMI were similar and appeared in general not to lead to an increase in blood pressure in late childhood; however, those children that did have rapid weight gain in early childhood, but not late infancy, were at risk of developing high blood pressure recordings in late childhood (Ceelen *et al*., 2009). At a mean age of 12.3 years IVF children had higher systolic and diastolic blood pressures than the control group (109 vs. 105 and 61 vs. 59 mmHg, respectively), and IVF children had a higher sum of skin folds and higher fasting serum glucose concentrations (Ceelen *et al*., 2008a).

These blood pressure differences were also noted in a small case-controlled series of IVF-conceived children from Greece (Sakka *et al*., 2010), at a mean age of 8.8 years, but there were no differences in any of the extensive metabolic parameters studied between the two groups (Sakka *et al*., 2010).

A Belgium cohort of ICSI-conceived children found a tendency towards a higher percentage of body fat in boys (Belva *et al*., 2012a). After adjustment girls had significantly higher BMI, percentage body fat mass, peripheral, central and total sum of skin folds, mean upper arm circumference and waist circumference in comparison with their spontaneously conceived peers (Belva *et al*., 2012a). This study would suggest that the more unfavourable fat deposition develops during adolescence, and with the later pubertal development of boys this was potentially missed in this study, due to the relative early age at the assessment.

Other groups have analysed serum insulin-like growth factor-1 (*IGF-1*) levels in early childhood, and demonstrated no difference in levels at 5 years of age despite significantly lower levels in the first year of life (Kai *et al*., 2006). In contrast, a New Zealand study of young children found that IVF children were taller, and had a trend towards a higher serum *IGF-1* and a significantly elevated serum *IGF-II* than the control group, with a more favourable lipid profile and no differences in the percent fat mass as assessed by DEXA scanning (Miles *et al*., 2007).

Therefore, the literature suggests that the offspring of IVF treatment may be at an increased risk of developing an unfavourable fat distribution, the potential for an adverse metabolic profile and an increased blood pressure in adolescence.

Cancer

Early reports of children born as a result of IVF treatment raised the suspicion that there appeared to be an excess of cancer risk in children, with a particular association with retinoblastoma (Moll *et al*., 2003). Subsequent analysis of all the cases of retinoblastoma in the Netherlands over a 12-year period by questionnaire did not confirm the earlier assertion (Marees *et al*., 2009), and cohort studies from Australia, Holland and Israel appeared to refute this initial assertion as they did not demonstrate an increase in cancer risk using data linkage (Bruinsma *et al*., 2000; Lerner-Geva *et al*., 2000; Klip *et al*., 2001;). In ~13% of cases of unilateral non-hereditary retinoblastoma cases, it is believed that hypermethylation of the CpG island in the *RB1* promoter region within the tumour is responsible for the cancer, leading to the concern that epigenetic phenomena may be responsible

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 were 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: Puberty; Puberty, Precocious; Puberty, Delayed Development Endocrine System Nervous System Motor Development Metabolism; Metabolic Diseases; Cardiovascular Diseases; Heart Diseases; Ophthalmology; Eye Diseases; Visual Acuity; ocular (keyword); vision (keyword) Hearing Disorders Asthma; Drug Allergies; Food Allergies; allergies (keyword) Neoplasms; cancer (keyword) 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, FET, 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, IVM, surrogacy and studies of fertility treatment using donor sperm, oocyte or embryo donation Studies with 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 manuscript 1. Psychosocial health and adjustment papers were assigned to manuscript 2
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 was reviewed by R.J.N.

FET, frozen embryo transfer; PGD, pre-implantation genetic diagnosis; PGS, pre-implantation genetic screening; IVM, *in vitro* maturation.

for the initiation of the cancer (Dommering *et al*., 2012). When this group analysed the tumours of seven children conceived by IVF or ICSI with retinoblastoma they did not find any evidence of hypermethylation of the CpG island in this region (Dommering *et al*., 2012).

A meta-analysis of 11 cohort studies derived an adjusted standardized incidence ratio for cancer of 1.33 (CI: 0.62–2.85) for children born from IVF treatment (Raimondi *et al*., 2005). This group has subsequently established a collaboration of 10 cohorts to retrospectively pool and analyse the data derived from several nations so that the small number of cancers that may arise in the IVF children and trends in cancer type may be prospectively determined, although no data are available to date (Felix *et al*., 2009).

A subsequent Swedish cohort study (Kallen *et al*., 2005; Kallen *et al*., 2010), controlling for all potential factors that may be expected to lead to an increased risk of childhood cancer, derived the odds ratio for the development of childhood cancer for children born as a result of IVF of 1.42 (CI: 1.09–1.87 $P = 0.01$), with an excess of haematological malignancies and particularly histiocytosis. Other factors that were significantly associated with a risk of cancer that may potentially provide an insight to potential mechanisms of the development of

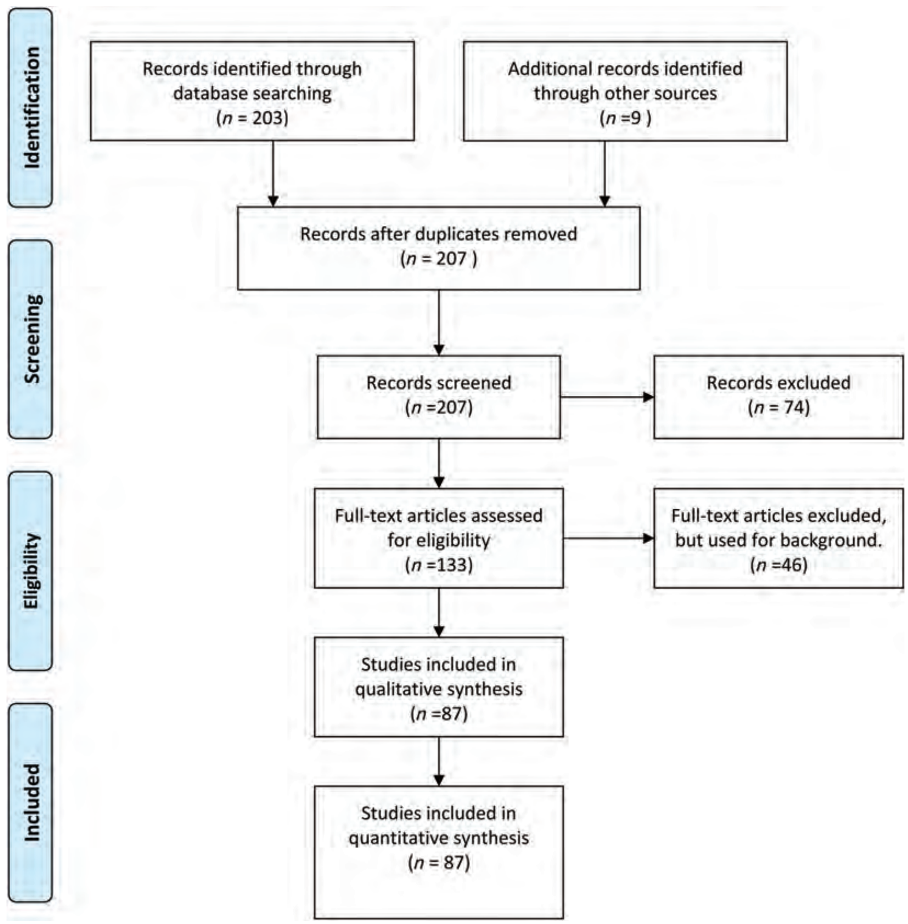

Figure 1 PRISMA decision flowchart for identified studies.

early malignancy were pre-term birth, birthweight in an excess of 4.5 kg and a low Apgar score. The association of excess birthweight (Milne *et al*., 2008) and neonatal asphyxia and oxygen treatment (Spector *et al*., 2005) with the subsequent development of childhood cancer has previously been reported in several non-IVF studies.

Despite the relevant data from Kallen *et al*., the data suggest that the offspring of IVF treatment are not at an increased risk of developing cancer, although it is believed that to perform a study adequately powered to detect a significant increase in childhood cancer as a result of IVF treatment that a population group would be required of ~20 000 children (Lerner-Geva *et al*., 2000).

Respiratory and allergic disorder: asthma, allergy and atopy

Preterm delivery and low birthweight have been identified as risk factors for asthma (Jaakkola *et al*., 2006), and consequently due to the increased perinatal risks associated with an IVF conception it would be expected that asthma would be more prevalent in an IVF population. Data derived from the Swedish Hospital Discharge Register using data linkage demonstrated an increased hospital admission rate for asthma beyond the first year of life (OR: 1.37 CI: 1.2–1.56); however, this was not controlled for prematurity or growth restriction (Ericson *et al*., 2002). A small observational study of the prevalence of asthma among adults conceived by IVF demonstrated a similar rate to a standard reference population (Sicignano *et al*., 2010).

In a further case-controlled study of 158 IVF-conceived children in Turkey, the prevalence of asthma, atopy and allergic rhinitis at a mean age of 4 years was not noted to be increased (Cetinkaya *et al*., 2009), and in one study was reportedly less in ICSI-conceived children compared with spontaneously conceived children (Ludwig *et al*., 2009b).

It would, therefore, appear that the prevalence of asthma is not increased in a group of IVF-conceived children, and from the limited data available, the rate of atopy and allergy is not increased.

Endocrine disorders

Other than modulations in IGF secretion as previously described, studies of the influence of IVF on subsequent endocrine disturbances in the offspring are limited to one uncontrolled study addressing the prevalence of thyroid hormone disturbance. This demonstrated a significantly higher prevalence of subclinical hypothyroidism than in the control group, and no children had detectable thyroid antibodies (Sakka *et al*., 2009). This finding is significant, as subclinical hypothyroidism has been associated with the metabolic syndrome (Uzunlulu et al., 2007), and hence, this is an area that should be studied in greater depth in the future.

Therefore, the limited endocrine data available suggest that IVF conception may confer a susceptibility to thyroid disorder on the offspring.

Ophthalmological and auditory disorders

Ludwig's prospective study of ICSI-conceived children demonstrated no differences in hearing or visual test results between an ICSI cohort and a recruited spontaneously conceived cohort, although, interestingly, significantly more of the control group were wearing glasses (16 vs. 10%) (Ludwig et al., 2009b). Compared with published data regarding visual impairment in children, these results appear high which may relate to the age of the children at assessment or it may represent selection bias.

Other studies of the vision and hearing ability of children aged 2–8 years, born from IVF treatment, when compared with spontaneously conceived children, or by linkage to databases of visual impairment, suggest that there are no differences after adjustment for potential confounders (Sutcliffe et al., 2001; Bonduelle et al., 2005; Belva et al., 2007; Knoester et al., 2008; Tornqvist et al., 2010).

From the small studies performed to date, with a limited duration of the follow-up, there does not appear to be a difference in the hearing or visual acuity in children born as a result of ART when compared with spontaneously conceived children.

Growth and pubertal development

Growth

Several cohort studies from Denmark, the Netherlands, the UK and the US have studied the long-term growth and development of children born as a result of IVF treatment (Kai et al., 2006; Ceelen et al., 2008c; Basatemur et al., 2010; Beydoun et al., 2011). The Danish cohort study consisted of IVF and ICSI-conceived children along with 1530 naturally conceived children, that were followed up to 3 years of age, and a further cohort of Danish children that were part of a wider international cohort study (Bonduelle et al., 2005), that were examined, along with 70 naturally conceived children, at 5 years of age. The unadjusted data demonstrated that at 3 years of age ICSI children were significantly smaller than their target weight, but not at 5 years of age and there were no differences across the modes of conception in the serum levels of IGF-1(Kai et al., 2006). These findings are similar to those reported from Finland and a large European study (Koivurova et al., 2003; Bonduelle et al., 2005).

Interestingly, a small New Zealand study reported that IVF children were taller than controls at 7 years of age when corrected for parental height (Miles et al., 2007). A UK cohort of IVF children (Sutcliffe et al., 2001) underwent questionnaire follow-up at 7–9 and 10–12 years of age (Basatemur et al., 2010). Despite being born at an earlier gestation to the naturally conceived children, in line with all other studies, other than the New Zealand study, the growth of the IVF-conceived children did not differ to spontaneously conceived children through childhood (Basatemur et al., 2010).

Pubertal timing

Despite previously raised concerns in a case-series of the risk of precocious puberty in ART-conceived children (Rojas-Marcos et al., 2005), no differences were found in the timing of pubic hair development in the IVF boys and girls when compared with the control group in the Dutch OMEGA study. This was despite IVF conceived girls having higher serum luteinizing hormone and dihydroepiandrostenedione (DHEAS) concentrations compared with the control group (Ceelen et al., 2008c). Sakka et al. (Sakka et al., 2010) reported no difference in the serum DHEAS concentrations, the incidence of precocious adrenarche or the Tanner staging between IVF-conceived children and spontaneously conceived children. However, when small for gestational age children conceived via IVF were compared with small for gestational age children conceived spontaneously, as expected, there was a significantly increased incidence of precocious puberty and higher serum DHEAS levels, with no difference in Tanner staging (Sakka et al., 2010).

The Dutch OMEGA study demonstrated that IVF-conceived children are similar in height, weight and BMI, with no evidence of an advancement of male or female puberty, when compared with matched control children, when assessed between 8 and 18 years, despite being smaller at birth and born at an earlier gestational age (Ceelen et al., 2008c). However, the bone age in the IVF cohort of girls did appear to be advanced in comparison with the control group (Ceelen et al., 2008c). Further the follow-up of the Belgium cohort of ICSI-conceived children at 14 years of age demonstrated that pubertal development in boys and girls was comparable after controlling for confounders. Of note ICSI-conceived girls had similar age at pubarche and menarche but breast development was less advanced than in their spontaneously conceived peers (Belva et al., 2012b). In a US questionnaire-based study, no cases of delayed or precocious puberty or pubarche were recorded and all pubertal milestones were at the appropriate age. Unfortunately no control group was used as a comparator in this study (Beydoun et al., 2011).

Potentially these studies may suggest that IVF-conceived children may be at an increased risk of premature activation of the adrenal gland, despite apparent normal pubertal timing. There may also be advancement in female bone age in addition to an elevated LH and DHEAS in the IVF-conceived girls. Whether this is due to a degree of growth restriction in the IVF cohort (Ibanez et al., 2000) or whether it is due to the IVF *per se* is unclear.

Testicular function

It would be expected that the testicular function of boys conceived as a result of ICSI treatment for poor semen parameters is of particular concern to parents. As part of the Belgium longitudinal cohort study of ICSI-conceived children (Belva et al., 2007), De Schepper provided reassuring information on early testicular development as measured by serum inhibin B, anti-Mullerian hormone and testicular size (De Schepper et al., 2009). Further the assessment of 50 boys in this cohort at 14 years of age demonstrated that their serum inhibin B levels were within the normal ranges for their stage of adolescence (Belva et al., 2010).

General health and wellbeing

Ludwig et al. (2009b) in their review of the health and development of children conceived as a result of ART reported that although most studies did not find an increased risk of childhood illnesses up to the age of 5 years, others (Koivurova et al. and Bonduelle et al.)

suggest an increased risk of childhood illnesses at up to 3 and 5 years of age, respectively (Koivurova *et al*., 2003; Bonduelle *et al*., 2005), which mainly relate to problems in the neonatal period. The Koivurova study was continued by extended follow-up of those recruited earlier as a result of double or triple embryo replacement, and they confirmed their earlier data that IVF-conceived children have more hospital admissions, and for a longer duration, than spontaneously conceived children; however, no corrections were made for prematurity (Koivurova *et al*., 2007).

In contrast, the Leuven group studied the quality of life of ICSI-conceived children and detected no differences in their scores (Knoester *et al*., 2007), use of medical care (apart from an increase use of physiotherapy due to coordination problems in the IVF-conceived children) or the incidence of common and chronic disease of childhood, in an adjusted comparison with spontaneously conceived children (Knoester *et al*., 2008). Similar data have been reported by Ludwig *et al*. (2009b) and Belva *et al.* (2007).

Beydoun *et al.* reported on the longest follow-up of children conceived from IVF, at a mean age of 21.2 years, using a questionnaire (Beydoun *et al*., 2010). While there is a substantial risk of bias in such a follow-up study, the findings suggest that there was a significantly increased prevalence of female binge drinking in the IVF population and a slightly increased risk of depression; one in four respondents reported a diagnosis of attention deficit or hyperactivity disorder, although it appeared that there was no increased susceptibility to life-long chronic diseases of the cardiometabolic, respiratory, neurological, gastrointestinal, haematological, urogenital, musculoskeletal or reproductive systems (Beydoun *et al*., 2010).

Frozen embryo replacement

In Australia 37% of the 70 000 ART cycles use a thawed-frozen embryo (Wang, 2011). As pregnancy rates with frozen embryos are approaching those of a fresh embryo replacement cycle, it is just as important that children born resulting from a frozen ART cycle are followed up to ensure that no long-term sequelae are missed. Wennerholm *et al.* reviewed this topic in 2009 and concluded that data concerning an infant outcome after the slow freezing of embryos was reassuring, and the authors suggested that properly controlled long-term follow-up studies for the embryos, blastocysts and oocytes frozen using both slow and vitrification processes are required (Wennerholm *et al*., 2009). The authors report that two studies reported on infant growth up to 18 months [225 children with a matched control group (Wennerholm *et al*., 1998)] and 24 months of age (81 children) compared with ICSI and IVF children by questionnaire (Nakajo *et al*., 2004). They concluded that with this limited follow-up, the early childhood growth was similar for children conceived subsequent to cryopreservation when compared with children that were spontaneously conceived, and similar to children conceived as a result of the transfer of an embryo in a fresh IVF cycle (Wennerholm *et al*., 2009). With regard to childhood morbidity and mental development, few differences have been recorded between children conceived after cryopreservation and those resulting from the transfer of fresh embryos and spontaneously conceived children; however, the data were too limited to draw any conclusions (Wennerholm *et al*., 2009).

It appears that the early health of children born resulting from a frozen embryo is similar to that of a child conceived from a fresh embryo replacement, although the follow-up studies are limited and freezing protocols may differ significantly.

Discussion

What do we know about longer-term general 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. As is understandable with long-term follow-up studies, none of the reports are large, with most involving <250 participants, other than those using database linkage, and many use a subfertile population who did not require ART as the control group. Literature reviews of children born as a result of IVF technology by Williams and Sutcliffe and Wilson *et al.* (Williams and Sutcliffe, 2009; Wilson *et al*., 2011) conclude that there are minimal differences between the physical health of 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. This review of the literature suggests that potentially there is emerging evidence for raised diastolic and systolic blood pressure (Ceelen *et al*., 2008a; Sakka *et al*., 2010), an elevated fasting glucose (Ceelen *et al*., 2008a), an increase in total body fat composition (Ceelen *et al*., 2007), potentially an advancement of bone age (Ceelen *et al*., 2008c) and growth velocity in early life (Ceelen *et al*., 2009), possibly an increase in visual impairment (Tornqvist *et al*., 2010) and potentially an increase in the incidence of thyroid disorder (Sakka *et al*., 2009) in the offspring of IVF, see Table II. However, it is difficult to determine whether these potential associations are related to the IVF treatment *per se,* or are related to the adverse obstetric outcomes associated with IVF treatment or if they relate to the genetic origin of the children.

There is reassuring evidence that there does not appear to be an increased risk of childhood cancer (Bruinsma *et al*., 2000; Klip *et al*., 2001; Kallen *et al*., 2010), insulin resistance (Sakka *et al*., 2010), an increased prevalence of asthma and allergic disorders (Cetinkaya *et al*., 2009), poor quality of life (Beydoun *et al*., 2010), an advancement in pubertal staging (Ceelen *et al*., 2008c), or alterations in growth patterns (Basatemur *et al*., 2010), in children born as a result of ART.

How might IVF status affect child development?

The reason for the increased risk in obstetric and neonatal complications noted in children born from IVF is not entirely clear; however, there has been speculation that the cause can be explained in part by the spontaneous reduction in a twin pregnancy down to a singleton pregnancy early in fetal life (Pinborg *et al*., 2005), as a twin pregnancy is associated with an adverse fetal outcome. However, twins born as a result of ART are also more likely to have an adverse outcome; therefore, this cannot be the sole explanation (Hansen *et al*., 2009). It has been postulated that the elevated estrogen levels encountered within the endometrial cavity during a fresh IVF cycle, in comparison with the more physiological environment generated with a frozen embryo replacement cycle, may be the cause of the finding that the children conceived during a fresh IVF cycle are smaller at birth than those conceived during a frozen embryo replacement cycle (Henningsen

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

General health outcome in adolescence	Summary of effect
Cardiovascular and metabolic	↑ ↔ Fat deposition ↑ Diastolic and systolic blood pressure ↑ ↔ Fasting glucose ↔ Fasting insulin, lipids,
Cancer	↔ All cancers
Asthma, allergy and atopy	↔
Hearing and visual acuity	↔
Growth and pubertal development	↔ Height ↔ BMI ↑ ↔ Bone age ↑ ↔ ♀ Premature activation of the adrenal gland ↔ Menarche and thelarche ↔ ♂ Markers of testicular function
Endocrine abnormalities	↑ Subclinical hypothyroidism
Quality of life	↔ General wellbeing

↑Increased.
↔ No effect.
↑ ↔ Potentially increased.
♀ Female.
♂ Male.

et al., 2010). Evidence derived from studying the altered expression of endometrial genes and their secretions in stimulated cycles in comparison with spontaneous cycles provides evidence to support this clinical finding (Macklon *et al.*, 2008; van der Gaast *et al.*, 2008). A further factor which could have a potentially negative impact upon the developing embryo is the use of exogenous gonadotrophins, as there is evidence from both human observations and mouse models that FSH may have a direct or indirect effect on oocyte aneuploidy. It is believed that increased endogenous or exogenous FSH (supplied during an IVF cycle) could induce meiotic disruption, leading to short- and longer-term consequences for the offspring (Vialard *et al.*, 2011). This has led to the interest in minimal stimulation IVF protocols as a treatment to avoid the potential for a negative influence of FSH upon the oocyte and the endometrium (Hohmann *et al.*, 2003; Kato *et al.*, 2012a).

How does ICSI compare?

This review did not set out to make a distinction between the longer-term health outcomes of children born from IVF and those born from ICSI treatment. There is a concern that children born as a result of ICSI are at a greater risk of congenital abnormalities than children conceived through IVF (Davies *et al.*, 2012), and, furthermore, there is a concern that children born using different origins of sperm for ICSI treatment may have different outcomes, as the use of cryoprotectants for the practice of sperm, testicular tissue and embryo cryopreservation may add a further potential insult to the developing embryo, and represent a potential mechanism for a long-term influence on fetal development. This should be the focus of further review.

Feng *et al.* reported that Y*q* de novo chromosomal microdeletions occurred in 0% of spontaneously conceived children, 5.3% of IVF-conceived children and were present in 26.7% of ICSI-conceived children, despite none being present in their fathers (Feng *et al.*, 2008), although these findings are not supported by other investigators (Cram *et al.*, 2000)

How to limit the potential long-term consequences of IVF for the offspring

It is apparent that the long-term implications for an infant that results from a multiple gestation are significantly worse than if it were a singleton gestation; hence, efforts to further encourage the use of a single embryo replacement strategy have to be fully endorsed (Wang *et al.*, 2009). Furthermore, further research is required to determine the optimal environment for IVF; does the 'minimal stimulation' approach lead to an improved obstetric, neonatal and long-term child health outcome (Kato *et al.*, 2012b), or does the routine use of a frozen embryo transfer policy, rather than a fresh embryo transfer policy, confer benefits to the offspring due to an improved endometrial environment (Shih *et al.*, 2008)? Furthermore, does one embryo culture medium confer a greater benefit or less harm to the offspring than another embryo culture medium?

Conclusions

This systematic review of the literature provides some reassuring evidence with regard to the longer-term general health outcome for children born as a result of IVF treatment. However, it is expected that the cardiovascular and metabolic risk factors found in childhood and tracking into adulthood could be worse in later life, and may ultimately be responsible for chronic cardiometabolic disease. The described observations reported suggest that there is an urgent need for longer follow studies of IVF-conceived children. As it is too difficult to determine whether the several observed associations demonstrated are related to the IVF treatment *per se*, or are related to the adverse obstetric outcomes associated with IVF treatment and/or are related to the genetic origin of the children, there is an imperative for future studies to investigate the causality of these outcomes in more detail.

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.

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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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