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Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis

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BACKGROUND: Earlier reviews have suggested that IVF/ICSI pregnancies are associated with higher risks. However, there have been recent advances in the way IVF/ICSI is done, leading to some controversy as to whether IVF/ICSI singletons are associated with higher perinatal risks. The objective of this systematic review was to provide an up-to-date comparison of obstetric and perinatal outcomes of the singletons born after IVF/ICSI and compare them with those of spontaneous conceptions.

METHODS: Extensive searches were done by two authors. The protocol was agreed a priori. PRISMA guidance was followed. The data were extracted in 2 × 2 tables. Risk ratio and risk difference were calculated on pooled data using Rev Man 5.1. Quality assessment of studies was performed using Critical Appraisal Skills programme. Sensitivity analysis was performed when the heterogeneity was high ($I^2 > 50\%$).

RESULTS: There were 20 matched cohort studies and 10 unmatched cohort studies included in this review. IVF/ICSI singleton pregnancies were associated with a higher risk (95% confidence interval) of ante-partum haemorrhage (2.49, 2.30–2.69), congenital anomalies (1.67, 1.33–2.09), hypertensive disorders of pregnancy (1.49, 1.39–1.59), preterm rupture of membranes (1.16, 1.07–1.26), Caesarean section (1.56, 1.51–1.60), low birthweight (1.65, 1.56–1.75), perinatal mortality (1.87, 1.48–2.37), preterm delivery (1.54, 1.47–1.62), gestational diabetes (1.48, 1.33–1.66), induction of labour (1.18, 1.10–1.28) and small for gestational age (1.39, 1.27–1.53).

CONCLUSIONS: Singletons pregnancies after IVF/ICSI are associated with higher risks of obstetric and perinatal complications when compared with spontaneous conception. Further research is needed to determine which aspect of assisted reproduction technology poses most risk and how this risk can be minimized.

Key words: IVF / ICSI / obstetric outcomes / perinatal outcomes / spontaneous conception

Introduction

It has been suggested that obstetric outcomes in pregnancies after IVF/ICSI are poor when compared with those after spontaneous conception. This had been attributed to the higher proportion of multiple pregnancies; however, with an increasing push towards the practice of single embryo transfers (SETs), multiple pregnancies have reduced dramatically.

Data available by stringent systematic reviews in 2004 (Helmerhorst *et al*., 2004; Jackson *et al*., 2004) shown that there was increased risk of preterm, very preterm, low birthweight, very low birthweight and small for gestational age (SGA) in singleton pregnancies conceived after IVF/ICSI when compared with those conceived after spontaneous conception. However, newer evidence on singletons after IVF/ICSI has been conflicting with some showing similar outcomes to spontaneous conceptions (De Neubourg *et al*., 2006; Apantaku *et al*., 2008; Fujii *et al*., 2010), and others showing poorer outcomes (Henningsen *et al*., 2011; Sazonova *et al*., 2011a).

The difference between these two periods in time could be due to the fact that IVF/ICSI treatments have changed over time (more SET, higher proportion having blastocyst transfer and use of embryos in frozen cycles).

The number of women having IVF/ICSI is increasing worldwide. It is, therefore pertinent to ask the questions: Is there risk after treatment? How great is this risk? What aspect of IVF/ICSI treatment confers increase in risk, if any? The complexity of IVF/ICSI makes it a challenge to answer these questions. Currently, it is unclear if there are any increases in obstetric and perinatal risk in singletons after IVF/ICSI.

Twin pregnancies, irrespective of the mode of conception are managed as high-risk pregnancies; however, singleton pregnancies are considered as low risk. It is of note that current updated guidance from NICE does not account for IVF/ICSI pregnancies separately http://www.nice.org.uk/nicemedia/live/11947/40115/40115.pdf. They are managed as uncomplicated pregnancies and most obstetricians and midwives are unaware of the details of infertility treatment, which are often kept confidential.

There is, therefore, a need for up-to-date evidence to determine whether there is a true increase in antenatal and perinatal complications in singleton pregnancies conceived following IVF/ICSI when compared with those conceived spontaneously. This will allow appropriate guidance to be given for clinical practice.

The aim of this study was to quantify the risks of obstetric and perinatal complications in singleton pregnancies following IVF/ICSI and compare them to those of spontaneous conceptions.

The objectives were to examine whether there are genuine differences in obstetric and perinatal outcomes in singleton pregnancies between the following groups:

(i) IVF/ICSI treatment versus spontaneous conception;
(ii) frozen replacement cycles versus spontaneous conception;
(iii) SET versus spontaneous conception; and
(iv) blastocyst transfer versus spontaneous conception.

Methods

The protocol was agreed by the group, prior to commencing the review. An extensive literature search was performed (1978–2012) on Medline, EMBASE, DARE using the key words: infertility, IVF, ICSI, *in vitro* fertilization, intra-cytoplasmic sperm injection, assisted reproduction technology (ART), blastocyst, embryo transfer, frozen embryo transfer, pregnancy outcomes, pregnancy complications, neonatal outcomes, perinatal outcomes, miscarriage, Caesarean section, LSCS, singleton pregnancy, IUGR, preterm labour, antepartum haemorrhage (APH), placenta praevia, stillbirth, pre-eclampsia, induction of labour, PET, PIH and abruption. There were no language restrictions. Relevant journals in the specialty (Human Reproduction and Fertility and Sterility) were searched electronically. Cross references from the included studies were hand searched. Two review authors (A.M., S.P.) independently conducted the searches and selected the studies to be included. Differences of opinion were resolved after team discussion. Additional information was sought on missing data from the authors if the studies which appeared to meet the eligibility criteria had unclear data or data in an unsuitable form for meta-analysis, and data were extracted using pre designed forms.

Inclusion criteria

We only included published studies that compared the obstetric and perinatal outcomes in pregnancies following (IVF/ICSI) and spontaneous conception. All matched and unmatched cohort studies with categorical data were included.

Exclusion criteria

Studies were excluded (i) if there was no control group of natural conception, (ii) if there was no matched or unmatched unexposed cohort, (iii) if obstetric and perinatal outcomes were not reported, (iv) if we were unable to differentiate the outcomes for singleton and twins and (v) when two different aspect of IVF/ICSI procedures were compared such as fresh versus frozen or singletons following SET versus double embryo transfer etc. In addition, case reports and case series were excluded. Only IVF and ICSI data were included and those following Gamete intra-Fallopian transfer (GIFT) were excluded.

PRISMA guidelines for systematic reviews were followed (http://www.plosmedicine.org/article/info:doi%2F10.1371%2Fjournal.pmed.1000097), wherever appropriate.

Outcome measures

The following outcome measures were considered: SGA, delivery prior to 32 weeks, delivery prior to 37 weeks, birthweight <2500 g, birthweight <1500 g, APH, preterm premature rupture of membranes (PPROM), hypertensive disorders of pregnancy (including pregnancy induced hypertension, pre-eclampsia and eclampsia), gestational diabetes, induction of labour, Caesarean section (both emergency and elective), congenital anomalies (major and minor), perinatal mortality and neonatal admissions.

Statistical analysis

For each outcome, data were extracted in 2×2 tables. Data were pooled if there were at least two studies with similar outcomes for the comparison groups. Outcomes per pregnancy were reported wherever possible. Meta-analysis was attempted wherever appropriate. Analysis was done using Rev Man 5.1 software. For binary (or dichotomous) outcomes, results for each study were expressed as risk ratios and risk differences with 95% confidence intervals (CIs). Heterogeneity was determined. Subgroup analysis was performed on only matched cohort studies, wherever appropriate.

Quality assessment of included studies was performed independently by two authors (S.P. and A.M.). Any disagreement regarding type and quality of the study was resolved after discussion. Checklists from the Critical

Appraisal Skills programme (CASP; http://www.phru.nhs.uk/pages/phd/resources.htm) were used to assess and assign a quality score.

Assessment of heterogeneity

We assessed whether there was sufficient similarity between the eligible studies in their design and clinical characteristics to ensure that pooling was valid. Statistical heterogeneity in the results of the studies was assessed by using the χ^2 test. A low *P*-value (or a large χ^2 statistic relative to its degree of freedom) suggested evidence of heterogeneity (Higgins, 2011). I^2 statistic was used to assess the impact of the heterogeneity on the meta-analysis. $I^2 > 50\%$ was labelled as marked heterogeneity and a sensitivity analysis was performed by altering the fixed to random effect analysis if there was marked heterogeneity.

A further sensitivity analysis was performed if there were more than five studies in the subgroup, by excluding the poor-quality studies and those containing a subfertile population as the unexposed cohort.

Assessment of reporting biases

Funnel plots were constructed for the outcomes where a significant difference was obtained. This was to guide whether the difference was due to publication or reporting bias. As there was no single primary outcome measure, funnel plots were constructed for two of the most reported outcomes: delivery at <37 weeks and birthweight <2500 g.

Results

Results of the searches

The extensive literature search performed between the years (1978–2011) on Medline, EMBASE and DARE yielded 2389 citations (Supplementary data, Fig. S1). Of these 2329 were excluded based on the title and abstract. The full text of 60 articles was obtained and another 12 were identified from the hand search of cross references. Of these, 30 articles were included in the completed review (Table I). A table of excluded studies gives the reasons for excluding studies (Supplementary data, Table SI).

Included studies

A total of 30 studies were included in the review in the various comparisons.

Comparison 1: IVF/ICSI treatment versus spontaneous conceptions

There were 30 studies included in this comparison, of which 20 were matched cohort studies and 10 were unmatched cohort studies.

Methods in the included studies

Population included. There was a variation in the population used as the exposed cohort. Most studies included both IVF/ICSI conceptions. Two studies included couples only undergoing ICSI (Wennerholm *et al*., 1996; Katalinic *et al*., 2004) and one included only those having IVF (Wennerholm *et al*., 1997). Fresh and frozen transfers were added together by most whereas one included only fresh cycles (Koudstaal *et al*., 2000).

There was a wide variation in the control cohorts. Unexposed cohorts were from spontaneous conception but some only included spontaneous conception in subfertile population (Pelinck *et al*., 2010; De Geyter *et al*., 2006) whereas others excluded this group (Dhont *et al*., 1999; Koudstaal *et al*., 2000). Some authors excluded pregnancies resulting from ovulation induction (Dhont *et al*., 1999; Kapiteijn *et al*., 2006) whereas others were not able to identify them from all non-IVF/ICSI conceptions. In one study women acted as their own control (Henningsen *et al*., 2011).

There was a variation in the gestation beyond which pregnancies were included in each study: beyond 16 weeks (Koudstaal *et al*., 2000; Katalinic *et al*., 2004); 20 weeks (Howe *et al*., 1990; Verlaenen *et al*., 1995; Dhont *et al*., 1997; Healy *et al*., 2010; Wen *et al*., 2010; Koivurova *et al*., 2002); 22 weeks (Isaksson *et al*., 2002; Poikkeus *et al*., 2007; Pelkonen *et al*., 2010); 24 weeks (Perri *et al*., 2001; Ochsenkuhn *et al*., 2003; Pelinck *et al*., 2010); 25 weeks (Reubinoff *et al*., 1997); 28 weeks (Tan *et al*., 1992) and between 37 and 41 weeks (De Geyter *et al*., 2006). Some studies included only babies weighing ≥500 g (Dhont *et al*., 1997; Kapiteijn *et al*., 2006; Apantaku *et al*., 2008). The minimum gestation of an ongoing pregnancy was not mentioned in a number of studies (Olivennes *et al*., 1993; Wennerholm *et al*., 1996, 1997; Westergaard *et al*., 1999; Delgadillo *et al*., 2006; Buckett *et al*., 2007; Schieve *et al*., 2007; Pinborg *et al*., 2010; Henningsen *et al*., 2011; Sazonova *et al*., 2011b).

Data collection. The method of data collection varied as well. In most of the studies, it was collected by case notes review (Howe *et al*., 1990; Olivennes *et al*., 1993; Apantaku *et al*., 2008) or data bases (Dhont *et al*., 1999; Isaksson *et al*., 2002; Buckett *et al*., 2007); however, in some studies it was collected via a questionnaire (Dhont *et al*., 1997; Pelinck *et al*., 2000).

Methodological quality of included studies

CASP scoring for matched cohort studies ranged from 8 to 12 (out of 12) with 16 studies scoring ≥10. All matched cohort studies had cohorts matched for the main confounders, i.e. age and parity. Most studies varied in controlling for other confounders. Some matched for year of delivery, hospital where delivered, medical illness (Reubinoff *et al*., 1997; Koudstaal *et al*., 2000), smoking status, order of gestation (Dhont *et al*., 1997) or fetal sex (Dhont *et al*., 1999). Others matched for ethnicity, medical problems, DES exposure and insurance status (Howe *et al*., 1990; Koudstaal *et al*., 2000).

Scoring for unmatched cohort studies ranged from 8 to 12 (out of 12) with 8 of 10 scoring ≥ 10. Of the 10 unmatched cohort studies, 2 included a prospective cohort (Katalinic *et al*., 2004; Healy *et al*., 2010).

Results of the outcome measures

Pooled data or outcome measures were as follows and are presented in Table II.

Antepartum haemorrhage. Thirteen studies reported outcome of APH ($n = 20\,807$ IVF/ICSI pregnancies). Of these nine were matched cohort and four were unmatched cohort studies.

The definitions of APH varied amongst studies: placenta praevia and abruption (Isaksson *et al*., 2002; Schieve *et al*., 2007; Apantaku *et al*., 2008; Healy *et al*., 2010; Sazonova *et al*., 2011b); placenta praevia and uterine bleeding (Reubinoff *et al*., 1997; Katalinic *et al*., 2004; De Geyter *et al*., 2006) and only placenta praevia (Howe *et al*., 1990; Tan *et al*., 1992). Definition of vaginal bleeding varied from: women finding it important enough to warrant consultation (Verlaenen

Table I Table of included studies.

Study ID	Study design	Population	Method of data collection	Risk of bias	CASP scoring
Apantaku et al. (2008)	Matched cohort study	Exposed cohort: All singleton IVF/ICSI pregnancies weighing ≥500 g between September 1999 and March 2004 Unexposed cohort: Spontaneous conceptions matched for age and parity and year of birth (excludes infertility clinic population)	Retrospective case note review from birth registers on the maternity unit	Fresh and frozen cycles not mentioned separately Included only pregnancies resulting in babies weighing ≥500 gm	10.5/12
Buckett et al. (2007)	Matched cohort study	Exposed cohort: IVF, ICSI, IVM pregnancies between January 1998 and December 2003 Unexposed cohort: one to one age and parity matched women with spontaneous conception	Data was collected from Obstetric and neonatal database	Does not mention whether women with infertility were excluded Minimum gestation of included ongoing pregnancy was not mentioned	9.5/12
Delgadillo et al. (2006)	Matched cohort study	Exposed cohort: singleton IVF pregnancies matched by maternal age between October 1999 and November 2004 Unexposed cohort: Age and parity matched spontaneously conceived pregnancies		Not clear whether women with infertility were excluded from spontaneous conception Minimum gestation of included ongoing pregnancy was not mentioned	9/12
Dhont et al. (1997)	Matched cohort study	Exposed cohort: All singletons pregnancies beyond 20 weeks of gestation conceived after IVF/ICSI between 1991 and 1995 Unexposed cohort: spontaneous singleton pregnancies resulting in babies weighing ≥500 g. Unexposed cohort were computer selected (for each case) from a register compiled by the Study centre for perinatal epidemiology They were matched for age, parity, order of gestation	Information about obstetric and perinatal outcomes for ART pregnancies was collected through questionnaires sent to referring physicians to patients Data for spontaneous pregnancies were retrieved from the SPE register. Data was based on questionnaires completed by obstetricians	Fresh and frozen transfers were not separated Not clear whether women with infertility were excluded from spontaneous conception All singleton pregnancies beyond 20 weeks of gestation were included	10/12
Dhont et al. (1999)	Matched cohort study	Exposed cohort: all singletons pregnancies resulting in babies weighing ≥500 g conceived by means of IVF/ICSI in Dutch speaking part of Belgium between January 1992 and December 1997 Unexposed cohort: spontaneous singleton pregnancies resulting in babies weighing ≥500 g. Unexposed cohort were computer selected (for each case) from a register compiled by the Study centre for perinatal epidemiology Matched for age, parity, year of birth, fetal sex	Data was collected from obstetric and prenatal file (Study centre for perinatal epidemiology)	Pregnancies resulting from ovulation induction were excluded All singleton pregnancies resulting in babies weighing ≥500 g were included	11/12

Continued

Table I *Continued*

Study ID	Study design	Population	Method of data collection	Risk of bias	CASP scoring
Henningsen *et al.* (2011)	Matched cohort	Data collection from national population-based registry from 1994 to 2008 Comparison groups: IVF/ICSI versus spontaneous conception All women who had given birth to two singletons in above groups were included	The data was collected from Danish Medical Birth Register	Women were their own unexposed cohort IVF/ICSI conception could be first/second one Spontaneous conception could include non-ART infertility treatments as it was not possible to separate them Minimum gestation of included ongoing pregnancy was not mentioned	11/12
Howe *et al.* (1990)	Matched cohort	Exposed cohort: first 100 pregnancies conceived in an IVF programme that were singleton and continued beyond 20 weeks Unexposed cohort: spontaneous conception but no history of infertility, matched by year of delivery, age, race, parity, medical problems, DES exposure and insurance status	Data were collected from IVF record, labour and delivery record	Only ongoing pregnancies beyond 20 weeks of gestation were included	10.5/12
Isaksson *et al.* (2002)	Matched cohort	Exposed cohort: women with unexplained infertility who underwent IVF/ICSI and proceeded to delivery between 1993 and 1999 Unexposed cohort: women with spontaneous conception. Unexposed cohort matched for age, parity, year of birth	Finnish Medical birth registry records were used to identify information on all pregnancies	Fresh/frozen cycles were not separately mentioned Only couples with unexplained infertility were taken as Exposed cohort Only deliveries after 22 completed weeks of gestation were included (or a birthweight $\geq$500 g)	10.5/12
Koudstaal *et al.* (2000)	Matched cohorts	Exposed cohort: IVF pregnancies established before 1992 and if antenatal care was provided by hospital that performed IVF procedure Unexposed cohort: Selected from registry of the same hospitals matched for age, parity, ethnicity, date of delivery, obstetric and medical history, height, weight, smoking status, obstetric department, date of delivery, DES exposure Blinding for outcomes at matching	Data collected from Registry	Excluded frozen transfers and fetal reductions. Unexposed cohort pregnancies were from non infertile population Only ongoing pregnancies beyond 16 week of gestation were included	11/12
Ochsenkuhn *et al.* (2003)	Matched cohort	Exposed cohort: IVF singleton pregnancy Unexposed cohort: spontaneous singleton pregnancy. Matched for age parity and date of conception	Data collected from computerized perinatal database and standardized forms from 1991 to 1996	Unexposed cohort had higher incidence of diabetes as this was tertiary diabetes referral centre Only included pregnancies that delivered after 24 completed weeks or had babies with weight >499 g.	10.5/12

Continued

Table I *Continued*

Study ID	Study design	Population	Method of data collection	Risk of bias	CASP scoring
Pelinck *et al.* (2010)	Matched cohort	Exposed cohort: Singleton pregnancy after conventional IVF Unexposed cohort: spontaneous conception among subfertile women in the same period 2001–2006; Matched for social and biological confounders: parity, pregnancy duration, infant gender, smoking, ethnicity, height weight similar age range	Chart review and patient questionnaire	Unexposed cohort from subfertile population Only pregnancies with duration ≥24 weeks were included	10/12
Perri *et al.* (2001)	Matched cohort	Exposed cohort: singleton (IVF/ICSI) pregnancies in 1996 Unexposed cohort: spontaneously conceived singleton pregnancy in 1996, matched for maternal age, gravidity, parity, ethnic origin 1:2 matching	ART computerized database and labour and delivery note book	The analysis included only pregnancies that led to live births (>23 completed gestational weeks)	10/12
Tan *et al.* (1992)	Matched cohort	Exposed cohort: IVF conceptions Data obtained from Medical research council IVF register of all births resulting from IVF to British citizens Only deliveries after 28 weeks were included Unexposed cohort: spontaneous conceptions having antenatal care at large teaching hospital. Unexposed cohort were matched for age	Data collected from Euroking computer system. Infertility history was taken from infertility medical records and obstetric histories were obtained by questionnaire obstetricians attending deliveries	No ICSI included All women were primiparous Only included ongoing pregnancies beyond 28 weeks	8/12
Reubinoff *et al.* (1997)	Matched cohort	Exposed cohort: Consecutive IVF pregnancies at a single centre between 1983 and 1993, beyond 25 weeks of gestation leading to live births Unexposed cohort: spontaneous singleton pregnancies treated by the same obstetric service as exposed cohort matched for age, parity, ethnicity, obstetric dept, date of delivery	Data were obtained from IVF unit files, antenatal care records, maternal neonatal delivery and hospitalization charts	Includes 14% frozen replacement cycles No ICSI included Analysis included only pregnancies beyond 25 weeks of gestation	9.5/12
Verlaenen *et al.* (1995)	Matched cohort	Exposed cohort: women who conceived for the first time after IVF and who delivered a singleton fetus of more than 20 weeks gestation between January 1988 and June 1994. Only those who attended author's antenatal clinics were included Unexposed cohort: those with spontaneous conception with no history of infertility and a singleton pregnancy of >20 weeks duration, matched for age, parity, height, weight, obstetric department and year of delivery	Data were collected from records	Women with early pregnancy loss and those with embryo reduction were excluded Only included women who delivered fetus of >20 weeks gestation	10.5/12

Continued

Table I *Continued*

Study ID	Study design	Population	Method of data collection	Risk of bias	CASP scoring
Wennerholm *et al.* (1996)	Matched cohorts	Exposed cohort: all deliveries after 28 weeks of gestation conceived by ICSI during 1993–1995 Unexposed cohort: all singletons from Swedish Medical birth register (1992) with same distribution for age and parity	Details of treatment and complication was collected by medical records	ICSI alone (fresh + frozen) 90% of treatments were fresh Minimum gestation of included ongoing pregnancy was not mentioned	10.5/12
Wennerholm *et al.* (1997)	Matched cohort	Exposed cohort IVF conception with fresh embryos between 1990 and 1995. All births over 28 weeks of gestation were included Exposed cohort 2: Births between 1990 and 1995 with frozen embryos. All births over 28 weeks of gestation were included Unexposed cohort: Spontaneous conceptions The groups were matched according to maternal age, parity and date of delivery	Data were collected after medical records review	IVF conception and spontaneous pregnancies, both were cohort groups for pregnancies after frozen embryo transfer during that time period Minimum gestation of included ongoing pregnancy was not mentioned	10.5/12
Westergaard *et al.* (1999)	Matched cohort	Exposed cohort: IVF/ICSI conceptions (1994–1997) Unexposed cohort: non-ART conceptions matched for year of birth, age and parity	Data from Danish IVF registry was linked with various other registries to get the obstetric data	Only perinatal mortality data for singleton was available Minimum gestation of included ongoing pregnancy was not mentioned	10/12
Koivurova *et al.* (2002)	Matched cohort study	Exposed cohort: IVF children born in 1990–1995 Unexposed cohort: spontaneous conception matched for age, parity, social class, year of delivery, race and area of residence	Data extracted from Finnish Medical Birth Register Data for complication was extracted from medical records	Only ongoing pregnancies beyond 20 weeks of gestation were included	12/12
Schieve *et al.* (2007)	Matched cohort study	Exposed cohort IVF/ICSI conceptions Unexposed cohort: matched spontaneous singleton pregnancies	Exposed and unexposed cohort were obtained by linking the US ART surveillance system with Massachusetts birth–infant death file for births between 1997 and 1998	Data restricted to singletons with maternal age >20, high school of education, married women, adjusted for race, parity, age, birth year, hospital Infertility population excluded from spontaneous conception group Both fresh and frozen treatment were included Minimum gestation of included ongoing pregnancy was not included	12/12
De Geyter *et al.* (2006)	Unmatched prospective cohort	Prospective cohort study of infertile women between August 1996 and March 2004 Unexposed Cohort Spontaneous conception ($n = 443$) Exposed cohort IVF/ICSI ($n = 203$) all having singleton births	Information about obstetric and perinatal outcomes was collected through questionnaires sent to referring physicians of patients and repeat screening of delivery list of university hospital	Spontaneous conception group is from subfertile population Only pregnancies between 37 and 41 weeks considered	8/12

Continued

Table I *Continued*

Study ID	Study design	Population	Method of data collection	Risk of bias	CASP scoring
Healy et al. (2010)	Unmatched Retrospective Cohort study	Retrospective cohort study Exposed cohort IVF/ICSI Unexposed cohorts: general population excluding infertility population Excluded oocyte and embryo donation	Data were collected using record linkage	Includes first singleton birth Data for fresh and frozen cycles separate Only ongoing pregnancies beyond 20 weeks of gestation were included	12/12
Kapiteijn et al. (2006)	Unmatched cohort	Dutch population-based historical cohort data used from OMEGA study January 1980–January 1995 Exposed cohort: IVF/ICSI conceptions Unexposed cohort; subfertile with spont conceptions Exclusion criteria: abortion <24 weeks; intrauterine mortality >23 weeks; pregnant at the time of questionnaire	Data were obtained from nationwide historical cohort study (OMEGA) Questionnaire was completed by study participants, providing details of information on maternal characteristics as well as method of conception, duration of gestation, birth data, gender and birthweight Missing data	Unexposed cohort were from sub fertile population excluding pregnancies as a result of ovulation induction Minimum gestation of included ongoing pregnancy was not mentioned	10/12
Katalinic et al. (2004)	Unmatched prospective cohort study	Exposed cohort: ICSI singleton pregnancy for women recruited between August 1998 and August 2000 Unexposed cohort were newborns between January 1993 and December 2001 (Saxony Anhalt cohort) singleton pregnancy	Data were collected after direct contact with the patient	Only ICSI conception were included Ongoing pregnancies beyond 16 weeks were included	12/12
Olivennes et al. (1993)	Unmatched cohort	Exposed cohort: Singleton pregnancies after IVF Unexposed cohort: spontaneous conception from non-infertility population Both exposed cohort and unexposed cohort delivered in same institution during the same period (1987–1989)	Details of perinatal and obstetric complications obtained from obstetric records	Not adjusted for age and parity Women in spontaneous conception group were younger Minimum gestation of included ongoing pregnancy was not mentioned	8/12
Sazonova et al. (2011b)	Unmatched cohort study	Exposed cohort: all IVF children born in Sweden after IVF treatment during 2002–2006 Unexposed cohort: all non-IVF children born during the same period. Authors were able to exclude those who conceived after donor oocytes	Data from the IVF clinics were cross-linked with Swedish medical registry	Minimum gestation of included ongoing pregnancy was not mentioned Matched for age parity BMI smoking status duration of infertility in analysis	12/12

Continued

Table I *Continued*

Study ID	Study design	Population	Method of data collection	Risk of bias	CASP scoring
Wen *et al.* (2010)	Unmatched cohort study	Exposed cohort: IVF/ICSI pregnancies treated in one centre 1996–2005. All deliveries after 20 weeks of gestation have been included Unexposed cohort: spontaneous conceptions	Data collected by structured chart review	Fresh, frozen: all cycles included Selective fetal reduction were excluded Only pregnancies beyond 20 weeks of gestation were included Adjusted for age, medical and obstetric history, year of delivery, parity, catchment area, weight gain age, parity and year of delivery in analysis	10/12
Pelkonen *et al.* (2010)	Unmatched cohort study	Exposed cohort: FET resulting in singleton pregnancy Unexposed cohort: Spontaneous conception Random sample of 10% of mothers with spontaneous pregnancies were taken; which was matched for year of delivery and area of residence	Data taken from Finnish Medical Birth Register	Mothers in spontaneous conception group were much younger than frozen transfer group. Adjusted for age and parity in analysis All live births and stillbirths after 22 weeks of gestation and birthweight of 500 g or more were included	11.5/12
Pinborg *et al.* (2010)	Unmatched and matched cohorts	Exposed cohort: Singletons born after FET (January 1995–December 2006) Control 2 = Random sample of Non-ART singletons within the same time frame five times the size of cryo-group	Danish IVF and Danish Birth Register	Non-ART singletons might include Ovulation induction, IUI but this was <2% Age and parity showed statistically significant difference in the groups But data were adjusted for age, parity child gender and year of birth Minimum gestation of included ongoing pregnancy was not mentioned	11/12
Poikkeus *et al.* (2007)	Unmatched cohort study	Exposed cohort: singletons following fresh embryo transfers resulting in viable pregnancies, delivering in the same country (1997–2003) Unexposed cohort: spontaneously conceived randomly taken from birth register. The comparison cohort represents a 10% population-based random sample of all singleton pregnancies and births matched for year of delivery and mother's place of residence	Pregnancies were linked to Finnish medical birth register, hospital register and register of congenital malformation	SET mothers were older than mothers who had spontaneous conception All live births and stillbirths after 22 weeks of gestation and birthweight of 500 g or more were included	11.5/12

et al., 1995) to heavy menstrual period like bleeding (Oschsenkuhn *et al.*, 2003). Koudstaal *et al.* (2000) included any bleeding in the second and third trimesters. For the purpose of this review, placenta praevia, abruption and third trimester vaginal bleeding were combined as APH.

The relative risk (95% CI) of having APH was 2.49 (2.30–2.69) in IVF/ICSI conceptions, when compared with spontaneous conception with an absolute increased risk (95% CI) of 2% (2–3%). There was marked heterogeneity ($I^2 = 82\%$) amongst the studies (Fig. 1). However, sensitivity analysis (Table II) did not alter the results.

Congenital anomalies. Of the seven studies ($n = 4382$ IVF/ICSI pregnancies) reporting congenital anomalies, six were matched cohort studies and one was an unmatched cohort study. All studies had a

Table II Overall table for effect and sensitivity analysis for singletons after IVF/ICSI versus singletons after spontaneous conception.

Outcome	IVF/ICSI conceptions, *n*	Overall effect (RR, 95% CI), fixed effect	Heterogeneity (I^2) (%)	Subgroup analysis (Matched cohorts)	Sensitivity analysis, good-quality studies (CASP > 10)	Sensitivity analysis, studies with infertility in unexposed cohort removed	Risk difference	Overall effect (RR, 95% CI), random effect
APH	20 807	2.49 (2.30–2.69)	82	1.98 (1.61–2.43)	2.70 (2.48–2.93)	2.53 (2.34–2.74)	0.02 (0.02–0.03)	2.44 (1.85–3.20)
Congenital anomalies	4382	1.67 (1.33–2.09)	0	1.82 (1.36–2.45)	na	na	0.02 (0.01–0.02)	Na
Hypertensive disorders of pregnancy	16 923	1.49 (1.39–1.59)	63	1.33 (1.12,1.58)	1.49 (1.39–1.60)	1.52 (1.42–1.63)	0.02 (0.01–0.02)	1.28 (1.06–1.54)
PPROM	14 141	1.16 (1.07–1.26)	86	1.52 (1.35–1.71)	1.16 (1.07–1.26)	1.16 (1.07–1.26)	0.01 (0.00–0.01)	1.17 (0.79–1.73)
Caesarean Section	12 950	1.56 (1.51–1.60)	80	1.47 (1.38–1.56)	1.54 (1.50–1.59)	1.57 (1.53–1.62)	0.09 (0.09–0.10)	1.50 (1.34–1.68)
Birthweight < 2500 g	28 352	1.65 (1.56–1.75)	45	1.72 (1.54–1.92)	1.65 (1.55–1.75)	1.66 (1.56–1.77)	0.02 (0.02–0.03)	na
Birthweight < 1500 g	27 105	1.93 (1.72–2.17)	46	1.72 (1.45–2.05)	1.96 (1.74–2.20)	1.85 (1.64–2.09)	0.01 (0.01–0.01)	na
Perinatal mortality	14 054	1.87 (1.48–2.37)	73	2.46 (1.35–4.46)	1.44 (1.06–1.95)	1.89 (1.49–2.39)	0.00 (0.00–0.00)	1.82 (0.98–3.35)
Delivery at <37 weeks	27 819	1.54 (1.47–1.62)	75	1.58 (1.43–1.75)	1.51 (1.44- 1.59)	1.55 (1.48–1.64)	0.03 (0.02–0.03)	1.62 (1.40–1.86)
Delivery at <32 weeks	24 170	1.68 (1.48–1.91)	45	1.22 (0.88,1.70)	1.68 (1.47–1.90)	1.65 (1.44–1.90)	0.01 (0.00–0.01)	na
Transfer to NICU	3530	1.58 (1.42–1.77)	0	1.58 (1.42–1.77)	na	na	0.07 (0.05–0.09)	na
Gestational diabetes	13 399	1.48 (1.33–1.66)	43	1.53 (1.36–1.72)	1.51 (1.35–1.69)	1.52 (1.35–1.70)	0.01 (0.01–0.01)	na
Induction of labour	3557	1.18 (1.10–1.28)	0	1.19 (1.10–1.28)	na	na	0.05 (0.03–0.07)	na
Small for gestation age	13 207	1.39 (1.27–1.53)	0	1.49 (1.10–2.01)	1.39 (1.26–1.53)	1.39 (1.27–1.53)	0.01 (0.01–0.01)	na

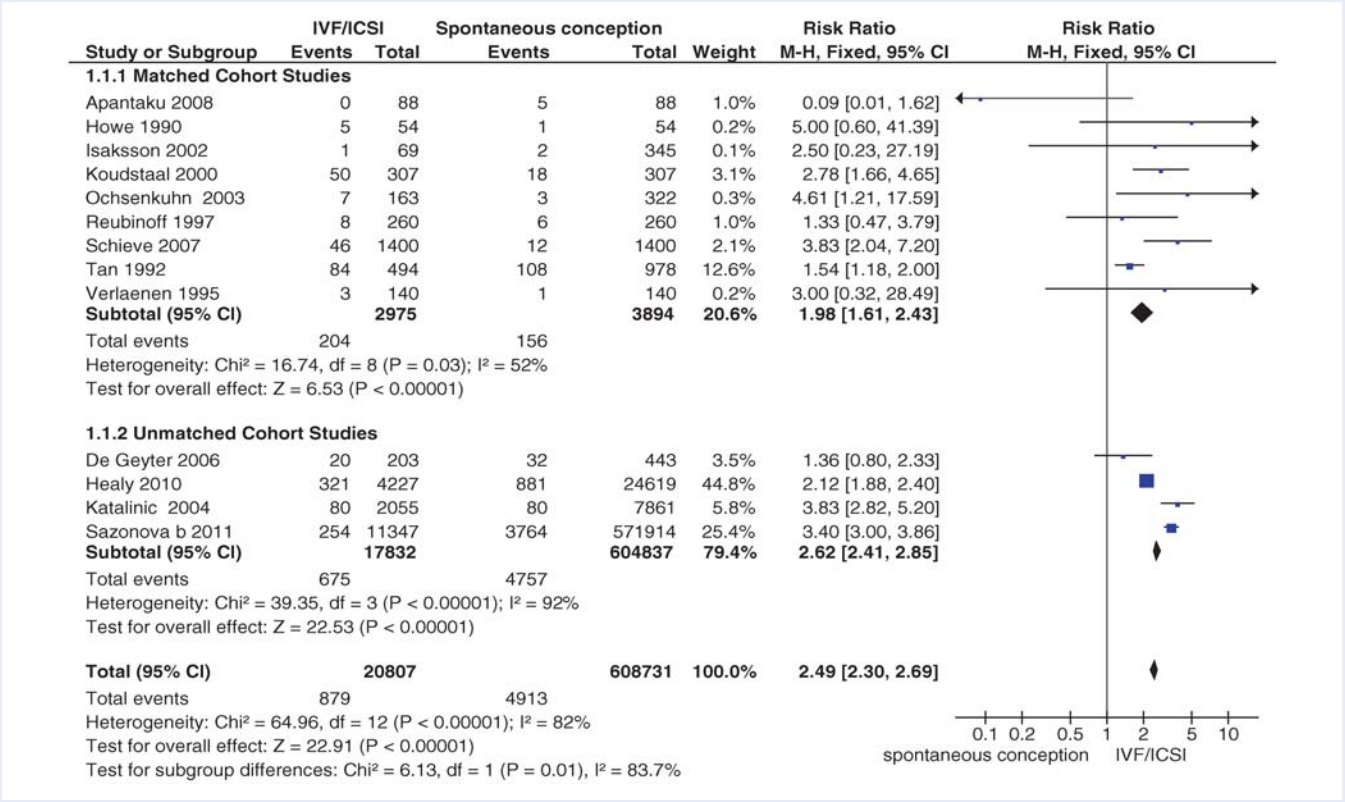

Figure 1 Outcome APH (IVF/ICSI versus spontaneous conception).

CASP score of ≥10 and none included spontaneous conceptions exclusively from a subfertile population as unexposed cohort.

Reporting of congenital anomalies varied amongst studies: both major and minor anomalies (Dhont *et al.*, 1999; Koudstaal *et al.*, 2000; Koivurova *et al.*, 2002; Apantaku *et al.*, 2008; Wen *et al.*, 2010), major anomalies (Isaksson *et al.*, 2002) and minor anomalies only (Verlaenen *et al.*, 1995). All major and minor anomalies were combined in this review.

The relative risk (95% CI) of having a congenital anomaly was 1.67 (1.33–2.09) in IVF/ICSI conceptions (Fig. 2), when compared with spontaneous conceptions with an absolute increased risk (95% CI) of 2% (1–2%). There was no heterogeneity ($I^2 = 0\%$) amongst the studies.

Hypertensive disorders of pregnancy. Of 15 studies ($n = 16\,923$ IVF/ICSI pregnancies) reporting hypertensive disorders of pregnancy, 11 were matched cohort studies. Three matched cohort and two unmatched cohort studies had low scores on CASP scoring. Only three studies had spontaneous conception exclusively from a subfertile population as the unexposed cohort.

Hypertensive disorders of pregnancy included: all cases of PIH, i.e. systolic BP > 140 and >90 diastolic after 20 weeks of pregnancy (Tan *et al.*, 1992; Olivennes *et al.*, 1993; Verlaenen *et al.*, 1995; Reubinoff *et al.*, 1997; Koudstaal *et al.*, 2000; Isaksson *et al.*, 2002; Ochsenkuhn *et al.*, 2003; De Geyter *et al.*, 2006 Delgadillo *et al.*, 2006; Schieve *et al.*, 2007; Pelinck *et al.*, 2010), only pre-eclampsia (Apantaku *et al.*, 2008; Sazonova *et al.*, 2011b); PIH or eclampsia (Katalinic *et al.*, 2004); or mild and severe PIH (Howe *et al.*, 1990). For the purpose of this review, all cases of pregnancy induced hypertension, pre-eclampsia and eclampsia were combined together.

The relative risk (95% CI) of having hypertensive disorder of pregnancy was 1.49 (1.39–1.59) in IVF/ICSI conceptions, when compared with spontaneous conception with an absolute increased risk (95% CI) of 2% (1–2%). There was marked heterogeneity ($I^2 = 63\%$) amongst the studies (Fig. 3). However, sensitivity analysis (Table II) showed a persistent increased risk in IVF/ICSI conceptions.

Preterm premature rupture of membranes. Of seven studies ($n = 14\,141$) reporting PPROM, four were matched cohort studies. Two matched cohort and two unmatched cohort studies had low CASP scores. Only one study had a subfertile population exclusively as the unexposed cohort.

PPROM was defined as leakage of amniotic fluid in absence of uterine activity before 37 completed weeks. An explicit definition was only given by two studies (Delgadillo *et al.*, 2006; Apantaku *et al.*, 2008).

The relative risk (95% CI) of having PPROM was 1.16 (1.07–1.26) in IVF/ICSI conceptions, when compared with spontaneous conception (Supplementary data, Fig. S2). There was marked heterogeneity ($I^2 = 86\%$) amongst the studies. Sensitivity analysis (Table II) did not show an increased risk of PPROM in IVF/ICSI conceptions.

Caesarean section. Of 17 studies ($n = 12\,950$ IVF/ICSI conceptions) reporting Caesarean section (both elective and emergency), 14 were matched cohort studies. Three matched cohort and two

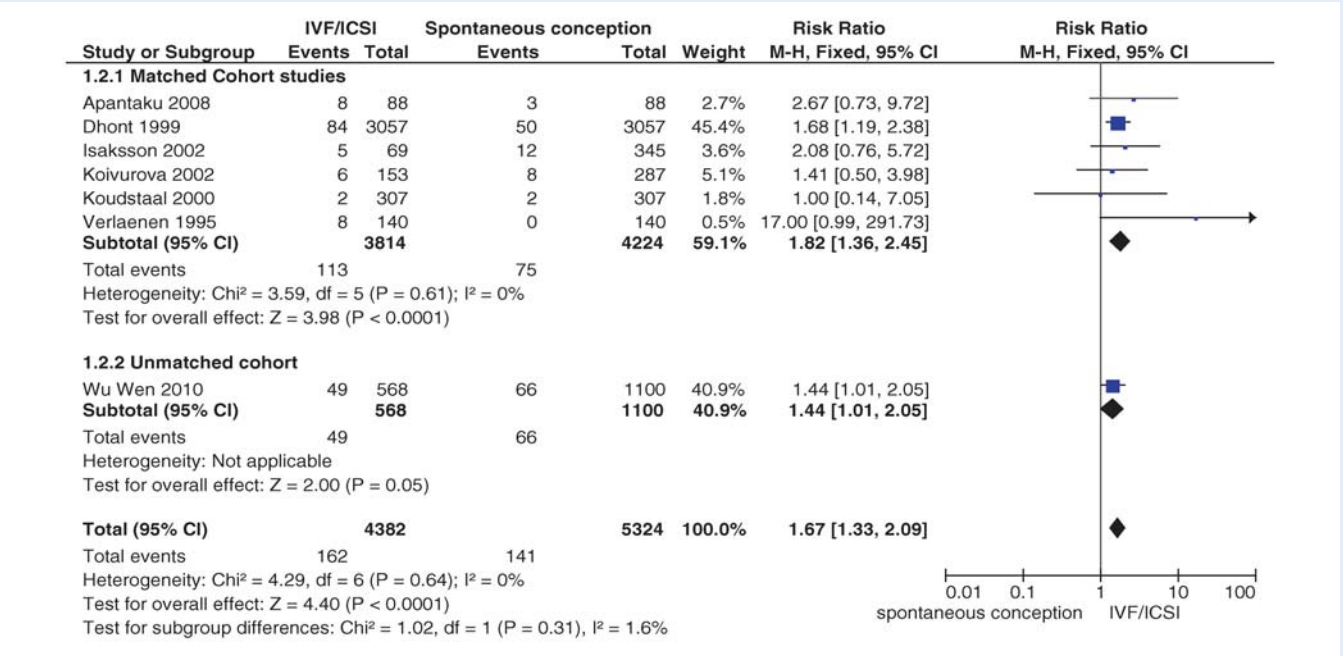

Figure 2 Congenital anomalies: IVF/ICSI versus spontaneous conception.

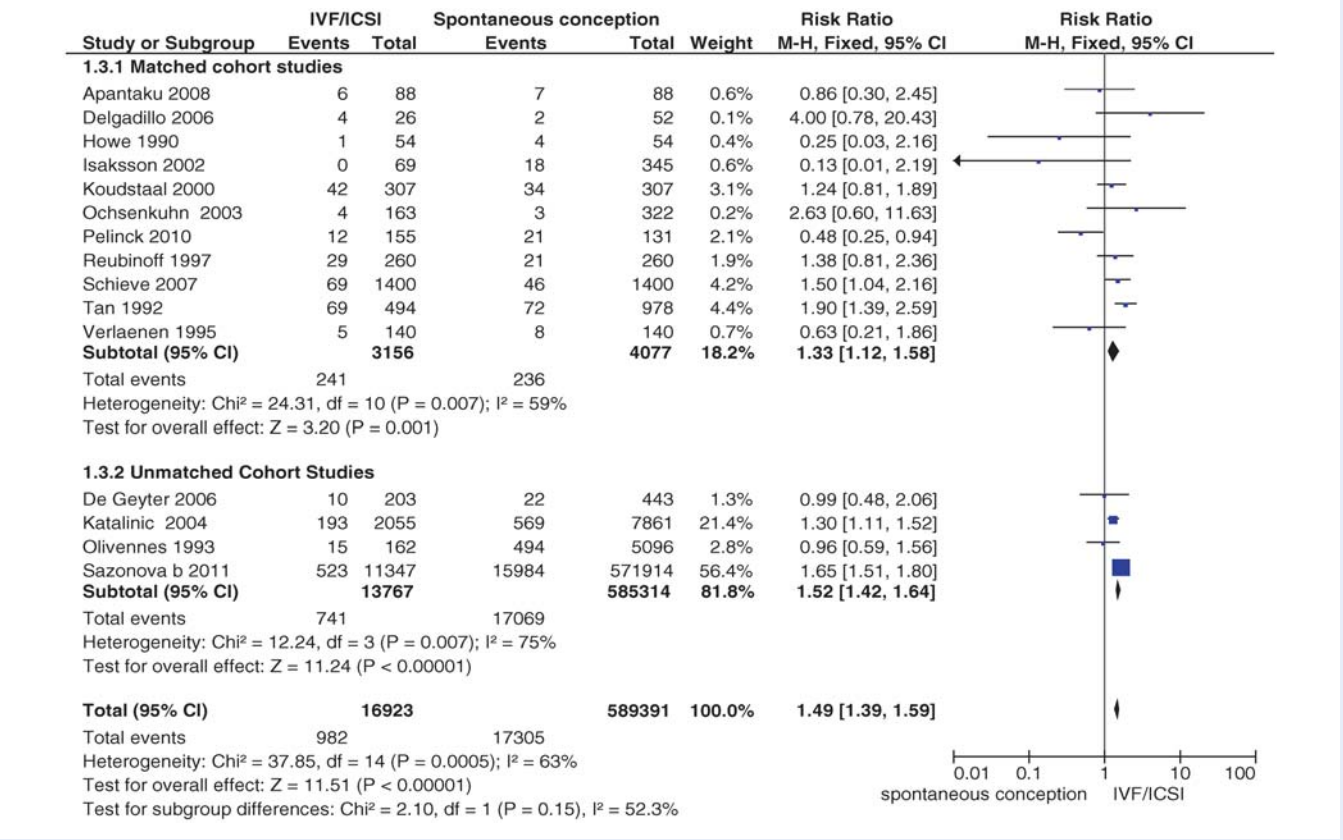

Figure 3 Hypertensive disorders of pregnancy (IVF/ICSI versus spontaneous conception).

unmatched cohort studies had low scores on CASP scoring. Only three studies had spontaneous conceptions exclusively from subfertile population as the unexposed cohort.

Of 17 studies, 4 gave separate data on elective and emergency Caesarean section (Reubinoff *et al.*, 1997; Wennerholm *et al.*, 1997; Koudstaal *et al.*, 2000; Perri *et al.*, 2001) and 2 (Howe *et al.*, 1990; Verlaenen *et al.*, 1995) enumerated the indications of Caesarean section. For the purpose of this review elective and emergency sections were pooled together.

The relative risk (95% CI) of having a Caesarean section (both elective and emergency) was 1.56 (1.51–1.60) in IVF/ICSI conceptions, when compared with spontaneous conception with an absolute increased risk (95% CI) of 9% (9–10%). There was marked heterogeneity ($I^2 = 80\%$) amongst the studies (Supplementary data, Fig. S3). However, sensitivity analysis (Table II) did not alter the results.

Birthweight <2500 g

Of 19 studies ($n = 28\,352$ IVF/ICSI pregnancies) reporting proportion of deliveries with birthweight <2500 g, 16 were matched cohorts. Four matched cohort studies had low scores on CASP scoring. Only three studies had spontaneous conceptions exclusively from a subfertile population as the unexposed cohort.

The relative risk (95% CI) of having a baby with birthweight <2500 g was 1.65 (1.56–1.75) in IVF/ICSI conceptions, when compared with spontaneous conception with an absolute increased risk (95% CI) of 3% (2–5%). There was moderate heterogeneity ($I^2 = 45\%$) amongst the studies (Supplementary data, Fig. S4). However, sensitivity analysis (Table II) did not alter the results.

A Funnel plot did not reveal any publication bias (Supplementary data, Fig. S5).

Birthweight <1500 g

Of 14 studies ($n = 27\,105$ IVF/ICSI pregnancies) reporting proportion of deliveries with birthweight <1500 g, 11 were matched cohorts. Two studies had low scores on CASP scoring. Only three studies had spontaneous conception exclusively from a subfertile population as the unexposed cohort.

The relative risk (95% CI) of having a baby with birthweight <1500 g was 1.93 (1.72–2.17) in IVF/ICSI conceptions, when compared with spontaneous conception with an absolute increased risk (95% CI) of 1% (1–1%). There was moderate heterogeneity ($I^2 = 46\%$) amongst the studies (Supplementary data, Fig. S6). However, sensitivity analysis (Table II) did not alter the results.

Of 14 studies ($n = 19\,431$ IVF/ICSI pregnancies) reporting mean birthweights, 11 were matched cohort and 3 were unmatched cohort studies. All except two were good quality. The mean difference in birthweight was −149.33 g (95% CI; −161.91, −136.74; Fig. 4). There was moderate heterogeneity ($I^2 = 42\%$) amongst the studies and sensitivity analysis did not alter the results.

Perinatal mortality. Of eight studies ($n = 14\,054$ IVF/ICSI pregnancies) reporting perinatal mortality, five were matched cohort studies. All except one was good quality and one had a subfertile population exclusively as the unexposed cohort.

Most studies included stillbirth and early neonatal death. Definitions varied slightly: intrauterine death after 27 completed weeks of gestation (Westergaard *et al.*, 1999); intrauterine death at gestation >20 weeks or birthweight >500 g (Wen *et al.*, 2010); or stillbirth/early neonatal death of a child weighing >500 g (Dhont *et al.*, 1999; Koudstaal *et al.*, 2000; Ochsenkuhn *et al.*, 2003)]. No specific definition of perinatal mortality was given in other studies (Olivennes *et al.*, 1993; Verlaenen *et al.*, 1995; Isaksson *et al.*, 2002; Sazonova *et al.*, 2011a). For the purpose of this review intrauterine death, stillbirth (as

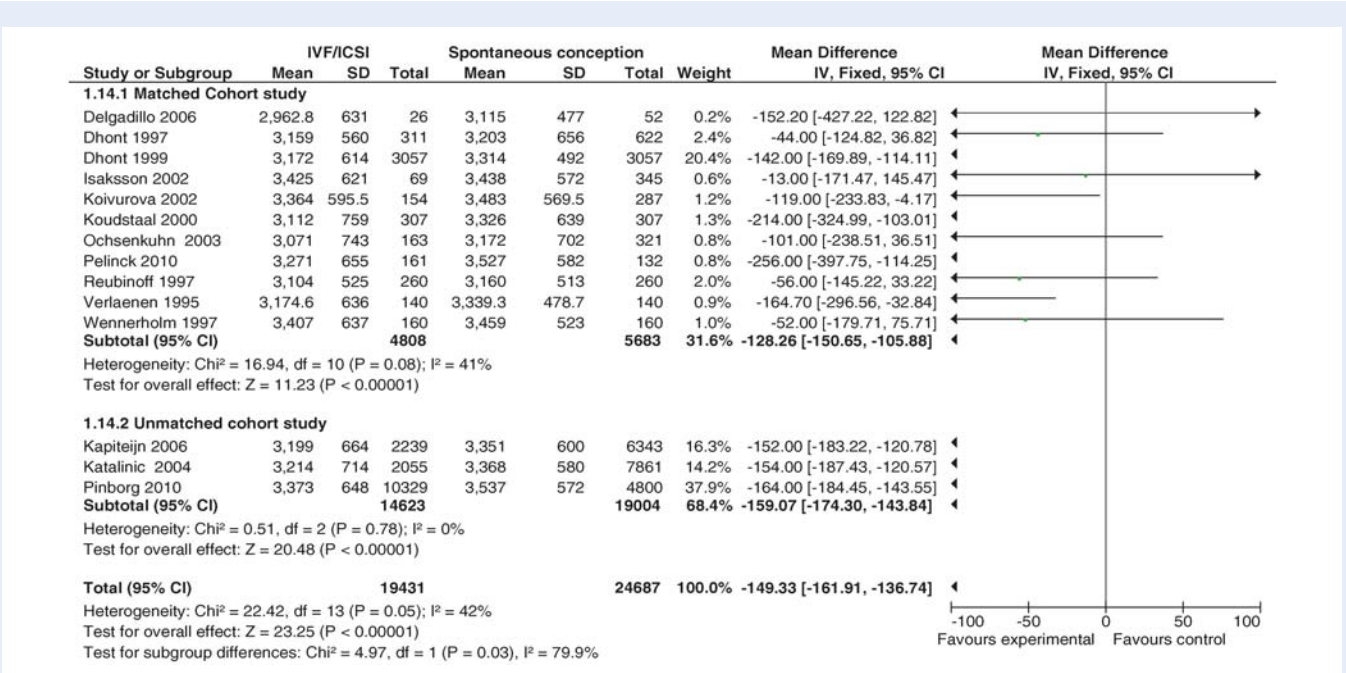

Figure 4 Mean difference in birthweights (IVF/ICSI versus spontaneous conception).

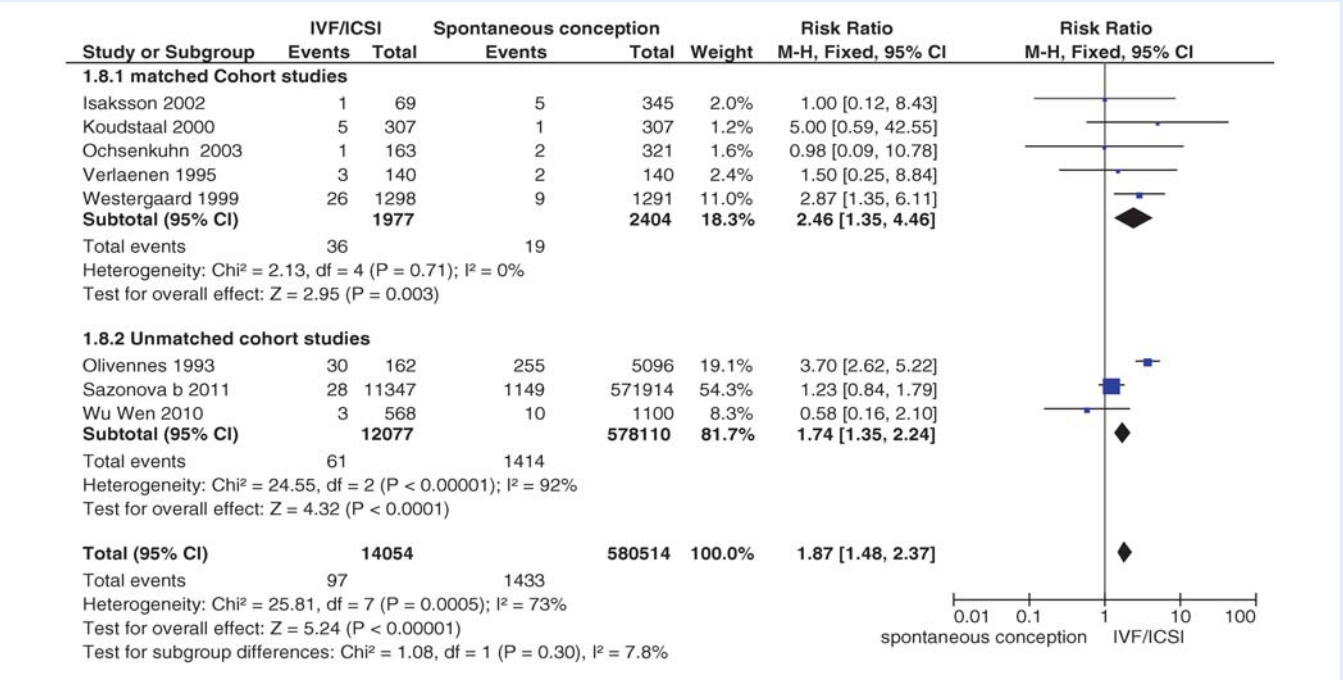

Figure 5 Perinatal mortality (IVF/ICSI versus spontaneous conception).

reported by individual studies) and neonatal death within 7 days were pooled together to determine perinatal mortality.

The relative risk (95% CI) of perinatal mortality was 1.87 (1.48–2.37) in IVF/ICSI conceptions, when compared with spontaneous conception. The increased risk of perinatal mortality persisted in the subgroup analysis of matched cohort studies and only good-quality studies. However, the increase did not persist when analysis was done with random effects in view of the marked heterogeneity ($I^2 = 73\%$) amongst the studies (Fig. 5).

Delivery at <37 weeks. Of 22 studies ($n = 27\,819$ IVF/ICSI pregnancies) reporting proportion of deliveries/labour at <37 weeks, 18 were matched cohort studies. Four matched cohort studies had low scores on CASP scoring. Only three studies had spontaneous conceptions exclusively from a subfertile population in the unexposed cohort.

The definition of preterm labour/delivery was delivery prior to 37 weeks in all studies except Dhont *et al.* 1997 where preterm labour was defined as regular uterine contractions before 37 completed weeks that required administration of tocolytics or lead to preterm birth.

The relative risk (95% CI) of having delivery at <37 weeks was 1.54 (1.47–1.62) in IVF/ICSI conceptions, when compared with spontaneous conception with an absolute increased risk (95% CI) of 3% (2–3%). There was marked heterogeneity ($I^2 = 75\%$) amongst the studies (Fig. 6). However, sensitivity analysis (Table II) did not alter the results.

A funnel plot did not reveal any publication bias (Supplementary data, Fig. S7).

Delivery at <32 weeks. Of 11 studies ($n = 24\,170$ IVF/ICSI pregnancies) reporting proportion of deliveries at <32 weeks, 7 were matched cohorts. Only two studies had spontaneous conceptions exclusively from a subfertile population in the unexposed cohort.

The relative risk (95% CI) of having delivery at <32 weeks was 1.68 (1.48–1.91) in IVF/ICSI conceptions. There was moderate heterogeneity ($I^2 = 45\%$) amongst the studies (Supplementary data, Fig. S8). However, sensitivity analysis (Table II) did not alter the results.

Admission to Neonatal Intensive Care Unit. Of five studies ($n = 3530$ IVF/ICSI pregnancies) reporting admission to Neonatal Intensive Care Unit (NICU), all were matched cohorts. All five studies had CASP score of ≥10 and one had a subfertile population exclusively as the unexposed cohort. There is no data on the duration of admission and kind of treatment in NICU, in any of the included studies.

The relative risk (95% CI) of admission to NICU was 1.58 (1.42–1.77) in IVF/ICSI conceptions, when compared with spontaneous conception with an absolute increased risk (95% CI) of 7% (5–9%). There was no heterogeneity ($I^2 = 0\%$) amongst the studies (Supplementary data, Fig. S9).

Gestational diabetes. Of six studies ($n = 13\,399$ IVF/ICSI pregnancies) reporting gestational diabetes, four were matched cohort and two were unmatched cohort studies. Two matched cohorts and one unmatched cohort study had CASP scores of <10. There are no details on how gestational diabetes was diagnosed in an individual set up, except in Delgadillo *et al.* (2006) where diagnosis was on the basis of impaired glucose tolerance test.

The relative risk (95% CI) of having gestational diabetes was 1.48 (1.33–1.66) in IVF/ICSI conceptions, when compared with spontaneous conception with an absolute increased risk (95% CI) of 1% (1–1%). There was moderate heterogeneity ($I^2 = 43\%$) amongst the studies (Supplementary data, Fig. S10). The increased risk persisted

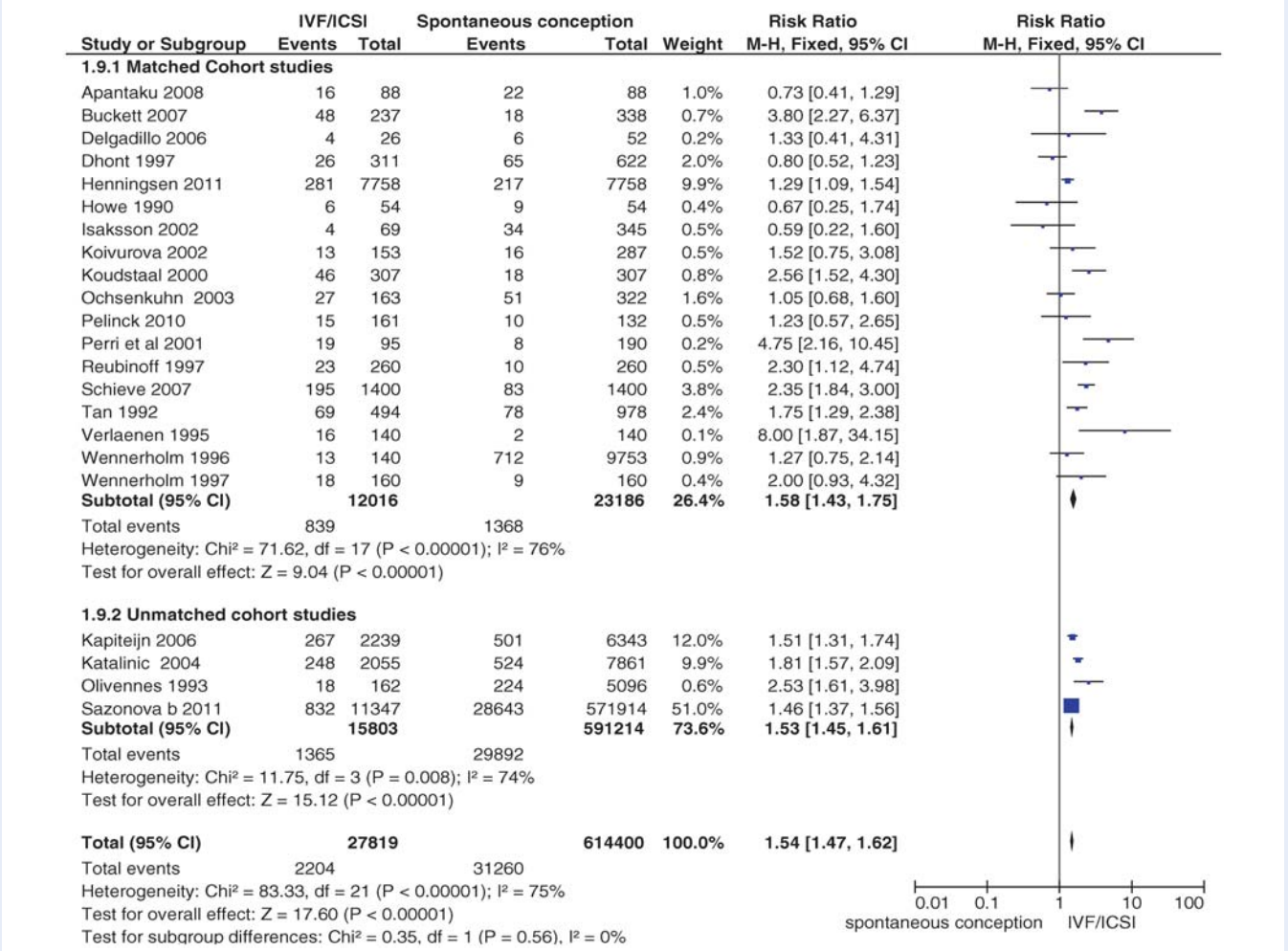

Figure 6 Delivery at <37 weeks (IVF/ICSI versus spontaneous conception).

in subgroup of matched cohort studies and when sensitivity analysis was done using only good-quality studies (Table II).

Induction of labour. Of five studies ($n = 3557$ IVF/ICSI pregnancies) reporting induction of labour, four were matched cohort studies. All matched cohorts had good scores on CASP scoring. There were no details in any of the studies for the reasons of induction of labour.

The relative risk (95% CI) of induction of labour was 1.18 (1.10–1.28) in IVF/ICSI conceptions, when compared with spontaneous conception with an absolute increased risk (95% CI) of 5% (3–7%). There was no heterogeneity ($I^2 = 0\%$) amongst the studies (Supplementary data, Fig. S11).

Small for gestational age. Of seven studies ($n = 13\,207$ IVF/ICSI pregnancies) reporting proportion of babies born SGA, four were matched cohort and three were unmatched cohort studies. One study had an unexposed cohort exclusively from a subfertile population. Three studies had CASP scores <10.

The definitions used for SGA were: birthweight <10th percentile for the appropriate gestation week determined by standardized growth charts (Tan *et al.*, 1992; Olivennes *et al.*, 1993; Reubinoff *et al.*, 1997; Koudstaal *et al.*, 2000); birthweight <3rd percentile (Wen *et al.*, 2010); or birthweight <2 SD of the population for that gestation (Isaksson *et al.*, 2002; Sazonova *et al.*, 2011b).

The relative risk (95% CI) of having a baby which is SGA was 1.39 (1.27–1.52) in IVF/ICSI conceptions (Fig. 7) with an absolute increased risk (95% CI) of 1% (1–1%). There was no heterogeneity amongst the studies ($I^2 = 0\%$). Sensitivity analysis, by removing studies with low scores, did not alter the results (Table II).

Comparison 2: Frozen embryo transfer versus spontaneous conception

Four studies were included in this comparison, of which Healy *et al.* (2010) only reported APH, which was not reported by any other study.

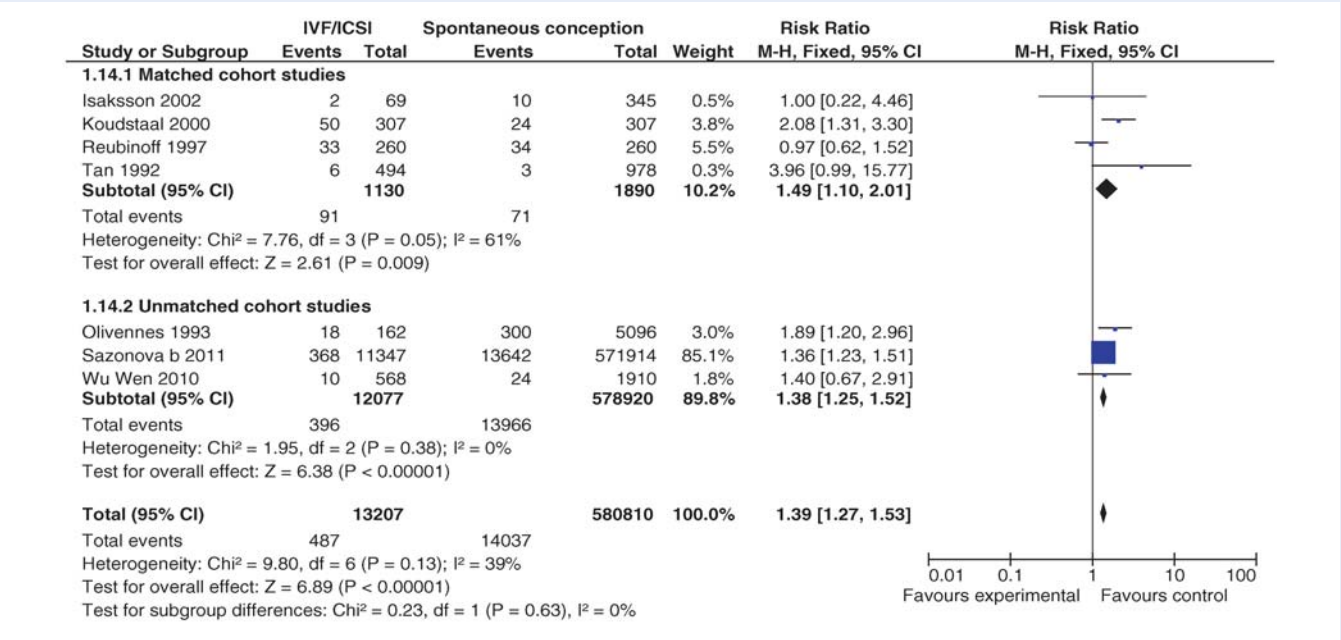

Figure 7 SGA (IVF/ICSI versus spontaneous conception).

Table III Singleton after frozen embryo transfer versus singleton after spontaneous conception.

Outcome	FET pregnancies, *n*	Overall effect (RR, 95% CI), fixed effect	Heterogeneity (I^2) (%)
Caesarean section	2947	1.76 (1.65–1.87)	0
Birthweight <2500 g	2947	1.27 (1.05–1.52)	0
Birthweight <1500 g	2787	1.51 (1.01–2.27)	0
Delivery at <37 weeks	2947	1.39 (1.20–1.61)	0
Delivery at <32 weeks	2947	1.45 (0.98–2.13)	0

Methods in the included studies

Three studies were included in the meta-analysis in this comparison group. Two were matched cohort studies (Wennerholm *et al.*, 1997; Pinborg *et al.*, 2010) and one was a register-based cohort study (Pelkonen *et al.*, 2010). All the studies adjusted for maternal age and parity. Data were collected by reviewing the medical records or using record linkage or from the birth registers in all three of the studies. All three studies had high scores on CASP scoring (Table I). The spontaneous conception group may have included ovarian stimulation and IUI (2%) in study by Pinborg *et al.* (2010). In the other studies, it is not clear whether these could have been part of unexposed cohort.

Results of outcome measures

Table III represents the pooled risk ratio of various outcomes (Supplementary data, Fig. S13), reported for frozen embryo transfer versus spontaneous conception. There is a statistically significant increased risk of the need for Caesarean section, a baby with a birthweight of <2500 g, a baby with a birthweight of <1500 g and delivery prior to 37 weeks in pregnancies as a result of a frozen replacement cycle when compared with those after spontaneous conception.

Comparison 3: SET versus spontaneous conception

Two studies were included in this comparison (Poikkeus *et al.*, 2007; Sazonova *et al.*, 2011b).

Methods in the included studies

Both included studies were population-based unmatched cohort studies. Data were obtained by data linkage through various established registries. Poikkeus *et al.* (2007) adjusted for year of birth and place of residence in the design stage and maternal age, parity and socioeconomic status in the analysis stage. Sazonova *et al.* (2011b) adjusted for age, parity, smoking status, duration of infertility in the analysis. Both studies included all elective and non-elective SETs. The proportions of elective SET were 83.3% (Poikkeus *et al.*, 2007) and 55.2% (Sazonova *et al.*, 2011b). Both studies included only fresh transfers.

Table IV Singleton after SET versus singleton after spontaneous conception.

Outcome	SET pregnancies, *n*	Overall effect (RR, 95% CI), fixed effect	Heterogeneity (I^2) (%)
APH	6316	4.05 (3.48–4.71)	0
Caesarean section	6316	1.49 (1.43–1.56)	0
Hypertensive disorders of pregnancy	6316	1.58 (1.40–1.77)	0
PPROM	6316	1.53 (1.30–1.80)	0
Birthweight <1500 g	6316	1.94 (1.54–2.45)	0
Birthweight <2500 g	6316	1.70 (1.53–1.89)	0
Perinatal mortality	6316	1.23 (0.38–4.04)	70
Delivery at <37 weeks	6316	1.53 (1.40–1.67)[a]	92
Delivery at <32 weeks	6316	1.80 (1.45–2.24)	0

[a]Random effect 1.98 (1.07–3.67).

Results of the outcome measures

The pooled risk ratio for outcome measures is shown in Table IV and Supplementary data, Fig. S13. There was a statistically increased risk of APH, Caesarean section, hypertensive disorders of pregnancy, PPROM, birthweight <2500 g, birthweight <1500 g and preterm delivery (<32 weeks and <37 weeks) in singleton IVF/ICSI pregnancies (even when only single embryo is transferred) when compared with singletons from spontaneous conception. There was no significant difference in perinatal mortality, however, the numbers are insufficient for this outcome measure.

Comparison 4: Blastocyst transfer versus spontaneous conception

No studies could be found for this comparison.

Discussion

Main findings

There is an increased risk of obstetric and perinatal complications in singleton pregnancies conceived through IVF/ICSI when compared with spontaneous conception. The increased risk is seen in all the outcome measures.

The increased risk is persistent even when (i) the effect of stimulation is removed (in frozen embryo transfers) and (ii) SETs are performed (removing the effect of vanishing twins that could be present after double embryo transfer).

Strengths

This is the most up-to-date review on this subject. We included studies which had matched unexposed cohort or unmatched cohort studies which adjusted for potential confounders. Sensitivity analysis was performed to evaluate the robustness of the existing data. In addition, comparisons to determine the impact on outcomes if we remove the effect of stimulation (frozen embryo transfer) and vanishing twin (SET) were also performed. Absolute risk differences in addition to risk ratios were calculated in two groups to give a clearer idea to clinicians managing these women.

Weaknesses

We have not managed to report on any early pregnancy outcomes as all studies have reported on ongoing pregnancies beyond first trimester. Individual methodological differences, variation in design, inclusion exclusion criteria, definition and ascertainment of outcomes are inherent in systematic reviews of observational studies. However, we have taken care to (i) exclude the studies where there was no unexposed cohort, (ii) perform subgroup analysis on matched cohorts, (iii) perform sensitivity analysis and (iv) use funnel plots to report publication bias.

Although we have shown that there is increased risk of complications in IVF/ICSI pregnancies with this systematic review, we cannot determine whether this increased risk is due to the inherent infertility itself or the process of ovarian stimulation and/or embryo culture.

Moreover, we might have missed some of the early poor outcomes especially in the studies where pregnancies were included only after 26 weeks. These shortcomings can only be overcome by individual patient data meta-analysis.

Comparison with existing reviews

There are two existing reviews (Helmerhorst *et al*., 2004; McGovern *et al*., 2004) of outcomes for singletons after IVF/ICSI. Our findings are consistent with Helmerhorst *et al*. for the outcomes they have measured (preterm delivery <37 weeks or <32 weeks; low birthweight <2500 g or <1500 g; Caesarean section; NICU admission and perinatal mortality), and with McGovern *et al*. which only explored the risk of preterm delivery. We have explored other complications as well (APH; congenital anomalies; gestational diabetes and induction of labour). Our findings for risk of birth defects are consistent with a separate review (Hansen *et al*., 2005). This confirms that despite advances in IVF/ICSI technologies, culture media and more SETs, singleton pregnancies resulting as a result of these technologies remain at a higher risk of obstetric and perinatal complications when compared with spontaneous conceptions.

There is increased incidence of low birthweight as well as prematurity. As birthweight is affected by gestation, one could argue that low birthweight is secondary to the prematurity. Some studies have actually explored the proportion of babies delivered SGA, taking into consideration the gestational age and population, which confirms that

despite adjustment of gestational age, birthweight is low in IVF/ICSI conceptions.

Quality of evidence

There are 30 studies included in the comparison of IVF/ICSI versus spontaneous conception. The datasets are large and the CIs are very narrow. The quality of most of the studies was high and they have adjusted for most important confounders of age and parity. Hence, we can conclude (despite limitations of observational studies and their systematic review) that these pregnancies are associated with higher risk of obstetric and perinatal complications compared with spontaneous conceptions. Matched cohort studies are the best way to answer this question and there were 20 of them in this review.

Interpretation of the study

There could be an ascertainment bias with the findings of increased complications with IVF/ICSI; i.e. women may be more anxious following fertility treatment and therefore more likely to report problems. However, there were standardized definitions used for most outcome measures in most of the studies included in this review. Also, higher rates in objective outcomes such as preterm delivery, low birthweight, perinatal mortality etc., are unlikely to be secondary to ascertainment bias. Outcomes such as increased Caesarean section and induction of labour are more likely to represent patient and/or clinician's anxiety.

It must be acknowledged though that while obstetric complications may be higher with IVF/ICSI pregnancies, the absolute increase in number of pregnancies with increased risk will be small, considering that the background overall risk of these complications is small.

Implications for practice

Based on the findings of this study and previous other studies, awareness of the increased obstetric risks with IVF/ICSI might suggest that these pregnancies be managed as 'high risk'. This would involve more contact with caregivers through the pregnancy and tailoring of care to deal with any complications that may be picked up. This has implications for resources and confidentiality. Currently in the UK women are not obliged to disclose to the professionals providing antenatal care if their pregnancy was as a result of IVF/ICSI. Most often details of fertility treatments are not in antenatal records. This calls for more co-ordinated thinking between reproductive medicine specialists and obstetricians.

Implication for research

After establishing that IVF/ICSI pregnancies are associated with higher obstetric and perinatal risks, the next step will be to determine how we can minimize the risks. In order to determine what poses minimum obstetric and perinatal risks to these pregnancies further comparisons are needed between (i) fresh versus frozen transfers, (ii) blastocyst versus cleavage stage transfers, (iii) singletons after SET versus singleton after DET, (iv) slow freezing versus vitrification, (v) IVF versus ICSI and (vi) IVM versus IVF/ICSI.

Conclusions

Singletons pregnancies after IVF/ICSI are associated with higher risks of obstetric and perinatal complications when compared with those from spontaneous conceptions, and should be managed as high-risk pregnancies. This will have resource implications for antenatal care. Further research is needed to determine which aspect of ART causes most risk and how this risk can be minimized.

Supplementary data

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

Authors' roles

A.M. conceived the idea and wrote the protocol. S.P. and A.M. did the searches, data entry and analysis. A.S., M.H. and S.B. contributed to the protocol. They were also involved in editing the manuscript. A.S., M.H. and S.P. did the quality assessment of the studies. All authors contributed to the final draft.

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Conflict of interest

None to declare.

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