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Contribution of Method of Conception on Pregnancy Outcome after the 11–13 Weeks Scan

Petya Chaveeva[a] Ilma F. Carbone[a] Argyro Syngelaki[a] Ranjit Akolekar[a]
Kypros H. Nicolaides[a–c]

[a]Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London,
[b]Department of Fetal Medicine, Medway Maritime Hospital, Gillingham, and
[c]Department of Fetal Medicine, University College Hospital, London, UK

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Ovulation induction · In vitro fertilization · First-trimester screening · Miscarriage · Stillbirth · Pre-eclampsia · Gestational diabetes mellitus · Preterm delivery · Birth weight · Caesarean section

Abstract
Objective: To examine the effect of method of conception on adverse pregnancy outcome after the 11–13 weeks scan. ***Methods:*** Prospective screening study for adverse obstetric outcomes in women with singleton pregnancies and live fetus with no obvious defects at 11^{+0}–13^{+6} weeks. The method of conception was recorded as spontaneous, in vitro fertilization (IVF) and assisted by ovulation induction (OI) drugs without IVF. Regression analysis was performed to examine the association between the method of conception and pregnancy outcome after adjustment for maternal characteristics. ***Results:*** In the study population of 41,577 pregnancies, conception was spontaneous in 40,261 (96.9%), by IVF in 634 (1.5%) and by OI in 682 (1.6%). In the pregnancies conceived by assisted reproductive technology, compared to spontaneous conceptions, there was a higher risk of stillbirth, pre-eclampsia, gestational hypertension, gestational diabetes mellitus, delivery of small for gestational age neonates and caesarean section. However, multiple regression analysis showed that after taking into account maternal characteristics, the only significant contributions of IVF were for pre-eclampsia and elective caesarean section and the contributions of OI were for miscarriage, spontaneous early preterm delivery and small for gestational age. ***Conclusions:*** Conception by IVF and OI is associated with increased risk for adverse pregnancy outcome.

Introduction

Effective screening for fetal aneuploidies is provided in the first trimester of pregnancy by a combination of maternal age and the findings of ultrasonographic examination of the fetus and biochemical analysis of maternal blood [1]. Recent evidence suggests that at the same hospital visit at 11–13 weeks, data from the maternal history can be combined with the results of biophysical and biochemical tests to estimate the patient-specific risk for a wide variety of pregnancy complications, including miscarriage, stillbirth, pre-eclampsia (PE), gestational hypertension (GH), gestational diabetes mellitus (GDM), preterm delivery, and birth of small (SGA) or large (LGA)

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Prof. K.H. Nicolaides
Harris Birthright Research Centre for Fetal Medicine
King's College Hospital
Denmark Hill, London SE5 9RS (UK)
Tel. +44 203 299 8256, E-Mail kypros@fetalmedicine.com

for gestational age neonates [2]. Early estimation of risks for these pregnancy complications could potentially improve pregnancy outcome by shifting antenatal care from a series of routine visits to a more individualized patient- and disease-specific approach both in terms of the schedule and content of such visits. In this respect the 11–13 weeks assessment is likely to be the basis for a new approach to antenatal care [2].

An increasing proportion of pregnancies are conceived by assisted reproductive technology (ART) and several studies have reported that the incidence of adverse outcomes in such pregnancies may be higher than in spontaneous conceptions [3–5]. However, there are contradictory or insufficient data to allow an accurate estimate of the effect of in vitro fertilization (IVF) and the use of ovulation induction (OI) drugs without IVF on a wide range of pregnancy complications which could be incorporated in the 11–13 weeks assessment of risks.

The aim of this study is to estimate the effect of the method of conception on a series of adverse pregnancy outcomes after adjustment for confounding factors in obstetric history and maternal characteristics assessed at 11–13 weeks of gestation.

Methods

Screening Study Population

This was a prospective screening study for adverse obstetric outcomes in women attending for their routine first hospital visit in pregnancy at King's College Hospital, London, UK, and Medway Maritime Hospital, Gillingham, Kent, UK. This visit, which is held at 11^{+0}–13^{+6} weeks of gestation, includes recording of maternal demographic characteristics and previous obstetric and medical history, measurement of maternal weight and height and calculation of the body mass index (BMI), and ultrasound examination for the measurement of the fetal crown-rump length (CRL) to determine gestational age [6], measurement of the fetal nuchal translucency (NT) thickness as part of screening for aneuploidies [7] and examination of the fetal anatomy for the diagnosis of major fetal defects [8]. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by the King's College Hospital Ethics Committee.

A second ultrasound examination for fetal biometry and examination of the fetal anatomy is carried out at 20–24 weeks. In the neonatal period all babies are examined by a paediatrician. Data on pregnancy outcome are collected from the hospital maternity records or the general medical practitioners of the women.

Maternal Characteristics and Obstetric History

Patients complete a questionnaire on maternal age, racial origin (Caucasian, African, South Asian, East Asian, and 'Mixed'), method of conception (spontaneous, IVF, use of OI drugs without IVF or intrauterine insemination), cigarette smoking during pregnancy (yes or no), history of chronic hypertension (yes or no), history of type 1 or 2 diabetes mellitus (yes or no) and obstetric history including the outcome of each previous pregnancy. The questionnaire was then reviewed by a doctor together with the patient.

Outcome Measures

In this study we examined the relationship between method of conception (spontaneous, IVF, OI without IVF) with (1) miscarriage, (2) stillbirth, (3) development of PE or GH, (4) development of GDM, (5) spontaneous early preterm delivery, (6) delivery of SGA or LGA neonates, and (7) delivery by elective or emergency caesarean section.

We excluded pregnancies conceived by intrauterine insemination because we did not have data whether or not they had received OI drugs, those with fetal aneuploidies or major defects diagnosed either prenatally or in the neonatal period and pregnancies ending in termination for psychosocial reasons.

Miscarriage and Stillbirth

Miscarriage included spontaneous miscarriage and fetal death before 24 weeks. Stillbirths were fetal deaths at or after 24 weeks.

Pre-Eclampsia and Gestational Hypertension

The definitions of PE and GH were those of the International Society for the Study of Hypertension in Pregnancy [9]. In GH the diastolic blood pressure should be ≥90 mm Hg on at least two occasions, at 4 h apart, developing after 20 weeks of gestation in previously normotensive women in the absence of significant proteinuria, and in PE there should be GH with proteinuria of ≥300 mg in 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available. In PE superimposed on chronic hypertension, significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks of gestation in the absence of trophoblastic disease). In the investigation of the relationship between method of conception and PE or GH, we excluded pregnancies ending in miscarriage or fetal death before 24 weeks.

Gestational Diabetes

Screening for GDM in our hospitals is based on a two-step approach. In all women a random plasma glucose is measured at 24–28 weeks of gestation, and if the concentration is >6.7 mmol/l an OGTT is carried out within the subsequent 2 weeks. The diagnosis of GDM is made if the fasting plasma glucose level is at least 6 mmol/l or the plasma glucose level 2 h after the oral administration of 75 g glucose is ≥7.8 mmol/l [10]. In women with normal random blood sugar an OGTT is performed if they have persistent glucosuria, they develop polyhydramnios, or the fetus becomes macrosomic. Women with the diagnosis of GDM are given dietary and exercise advice and are encouraged to test capillary blood glucose before and 1 h after each meal. If during a period of 1–2 weeks the pre-meal or 1 h post-meal blood glucose level is higher than 5.5 and 7 mmol/l, respectively, the women are treated with insulin. In the investigation of the relationship between method of conception and GDM, we excluded pregnancies with pre-pregnancy diabetes mellitus type 1 or 2 and those ending in miscarriage or delivery before 30 weeks because they may not have had screening and diagnosis of GDM.

Spontaneous Preterm Delivery

Spontaneous preterm deliveries included those with spontaneous onset of labour and those with preterm pre-labour rupture of membranes occurring before 34 completed weeks (238 days). In the investigation of the relationship between method of conception and spontaneous preterm delivery, we excluded pregnancies ending in miscarriage or fetal death and those with iatrogenic delivery before 34 weeks.

Small and Large for Gestational Age

The definitions of SGA and LGA were delivery of neonates with birth weight below the 5th centile or above the 95th centile for gestation, respectively [11]. In the investigation of the relationship between method of conception and SGA or LGA, we excluded pregnancies ending in miscarriage or fetal death before 24 weeks.

Elective or Emergency Caesarean Section

Emergency caesarean section included all cases where such delivery was undertaken after the onset of labour, usually for failure to progress, fetal distress or intrapartum haemorrhage. This group also included cases of antepartum haemorrhage requiring caesarean section. Elective caesarean section was performed before the onset of labour for obstetrical or medical indications or at the request of the mother. In the investigation of the relationship between method of conception and elective or emergency caesarean section, we excluded pregnancies ending in miscarriage or fetal death before 24 weeks.

Statistical Analysis

First, a univariate logistic regression analysis was performed to examine the association between method of conception and each of the adverse pregnancy outcomes. Second, the risk for each of the pregnancy outcomes was calculated from the formula: odds/(1 + odds), where odds = e^Y, and Y was derived from the univariate logistic regression analysis. Third, we performed a multivariate logistic regression analysis for the prediction of each pregnancy outcome from method of conception, maternal age, racial origin, smoking, history of chronic hypertension or diabetes, and previous history of adverse pregnancy outcome or family history of PE. The statistical software package SPSS 16.0 (SPSS Inc., Chicago, Ill., USA) was used for data analyses.

Literature Search

We searched MEDLINE and EMBASE from 1978, when the first child conceived by IVF was born, to November 2010 to identify English language articles reporting on the outcome of pregnancies conceived by IVF and OI without IVF. We included all case-control and cohort studies which reported data from singleton pregnancies regarding the primary outcome measures including miscarriage, stillbirth, PE, GH, GDM, early preterm delivery, birth of SGA or LGA neonates and delivery by elective or emergency caesarean section. We only included and used the reported data in each paper. We excluded duplicate publications.

Two independent reviewers extracted the data from each article and these were then examined by a third reviewer. Odds ratio (OR) with 95% confidence intervals (CIs) were calculated for each outcome in each study. Forest plots were constructed and a random-effects model, which takes into account the random variation within studies [41], was used to calculate weighted summary ORs by taking into account the weight of each study.

Forest plots and summary ORs were generated using the MedCalc software version 9.6.2.0 (MedCalc Software, Mariakerke, Belgium).

Results

Study Population

During the study period, we carried out an ultrasound examination at 11–13 weeks in 45,191 singleton pregnancies with a live fetus and CRL of 45–84 mm. We excluded from further analysis 77 (0.2%) cases because they conceived by intrauterine insemination, 2,739 (6.1%) because there were no or incomplete data on pregnancy outcome, 682 (1.5%) because of the pre- or postnatal diagnosis of aneuploidies or major defects and 116 (0.3%) because of pregnancy termination.

The maternal and pregnancy characteristics of the 41,577 cases included in the study are shown in table 1. In the OI and IVF groups, compared to the spontaneous conception group, the maternal age was higher, more women had pre-existing diabetes mellitus and fewer were cigarette smokers. In the OI group maternal BMI was increased and in the IVF group there were more Caucasians and fewer women were parous.

Pregnancy Complications

Univariate logistic regression analysis demonstrated that use of OI drugs was associated with an increased risk of subsequent miscarriage, GDM, spontaneous delivery before 34 weeks, delivery of SGA neonate and elective caesarean section, whereas IVF was associated with an increased risk of subsequent development of PE, GH and GDM, iatrogenic delivery before 34 weeks and both emergency and elective caesarean section (table 2).

The results of multivariate logistic regression analysis for the prediction of pregnancy complications from method of conception and maternal characteristics and previous obstetric history are summarized in tables 3–7. Significant contributions, independent of maternal characteristics, were provided by IVF only for early-onset PE and elective caesarean section and by OI only for miscarriage, spontaneous delivery before 34 weeks and delivery of SGA neonates (fig. 1).

Literature Search

Forest plots of ORs from previous reports and our study for second-trimester miscarriage, stillbirth, PE, GH, GDM, early preterm delivery before 32 or 34 weeks, delivery of SGA neonate with birth weight below the 5th

Table 1. Maternal characteristics in the study population

Independent variable	Spontaneous conception (n = 40,261)	Ovulation induction drugs (n = 682)	In vitro fertilization (n= 634)
Maternal age, median (IQR), years	31.1 (26.4–35.1)	32.5 (28.1–36.8)*	36.3 (33.2–39.3)*
Body mass index, median (IQR)	24.4 (22.0–28.0)	24.6 (22.2–28.7)*	24.4 (21.9–27.4)
Racial origin, n (%)			
Caucasian	30,367 (75.4)	515 (75.5)	531 (83.3)*
African	6,526 (16.2)	110 (16.1)	46 (7.3)*
South Asian	1,638 (4.1)	31 (4.5)	25 (3.9)
East Asian	706 (1.8)	10 (1.5)	17 (2.7)
Mixed	1,024 (2.5)	16 (2.3)	15 (2.4)
Cigarette smoking, n (%)	4,498 (11.2)	46 (6.7)*	10 (1.6)*
History of chronic hypertension, n (%)	421 (1.0)	9 (1.3)	12 (1.9)
History of pre-existing diabetes, n (%)			
Type 1	177 (0.4)	6 (0.9)	9 (1.4)*
Type 2	118 (0.3)	6 (0.9)*	1 (0.2)
Parity, n (%)			
Nulliparous	19,045 (47.3)	322 (47.2)	482 (76.0)
Parous	21,216 (52.7)	360 (52.8)	152 (24.0)*

Comparison between outcome groups by Mann-Whitney U test with post-hoc Bonferroni correction. * $p < 0.025$.

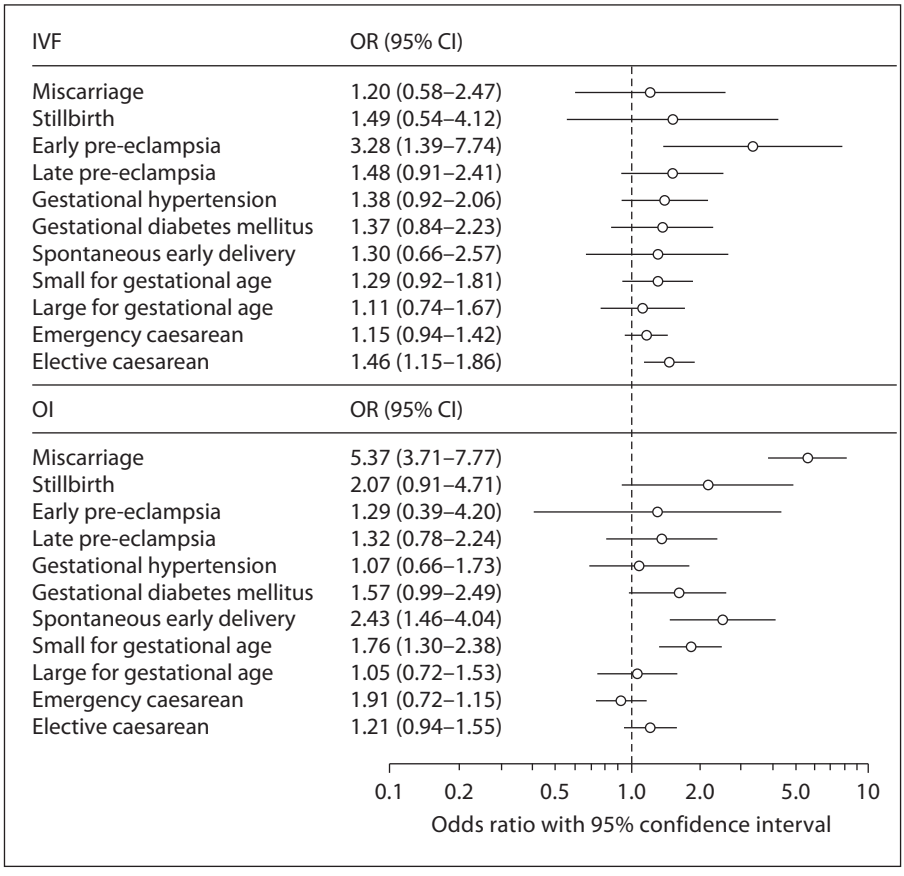

Fig. 1. Forest plot of ORs, after adjustment for maternal characteristics and obstetric history, for the risk of complications in pregnancies conceived by IVF and after OI compared to SCPs.

Table 2. Univariate regression analysis demonstrating the ORs with 95% CI for adverse pregnancy outcomes in pregnancies conceived by IVF and by use of OI drugs without IVF, compared to spontaneous conceptions

Adverse outcome	Ovulation induction drugs		In vitro fertilization	
	OR (95% CI)	p value	OR (95% CI)	p value
Miscarriage	5.20 (3.61–7.48)	<0.0001	1.30 (0.64–2.64)	0.462
Intrauterine death	2.17 (0.96–4.91)	0.064	1.49 (0.55–4.04)	0.430
Hypertensive disorders				
Early-onset pre-eclampsia	1.47 (0.47–4.63)	0.512	3.13 (1.38–7.13)	0.007
Late-onset pre-eclampsia	1.36 (0.81–2.28)	0.243	1.74 (1.08–2.80)	0.022
All pre-eclampsias	1.32 (0.82–2.12)	0.249	1.95 (1.29–2.95)	0.002
Gestational hypertension	1.17 (0.73–1.87)	0.520	1.87 (1.26–2.76)	0.002
Gestational diabetes	1.68 (1.07–2.63)	0.025	1.62 (1.01–2.61)	0.046
Preterm delivery				
Iatrogenic	1.29 (0.48–3.47)	0.619	2.99 (1.52–5.85)	0.001
Spontaneous	2.35 (1.42–3.89)	0.001	1.36 (0.70–2.65)	0.364
Growth disorders				
Large for gestation	1.19 (0.83–1.72)	0.346	1.01 (0.68–1.50)	0.960
Small for gestation	1.61 (1.20–2.16)	0.002	1.30 (0.93–1.80)	0.122
Caesarean section				
Emergency	1.02 (0.81–1.28)	0.859	1.89 (1.55–2.30)	<0.0001
Elective	1.38 (1.10–1.73)	0.005	1.96 (1.58–2.44)	<0.0001

Table 3. Logistic regression analysis for the prediction of miscarriage and stillbirth by maternal factors and obstetric history. Note that the classification of parity used for the two outcome measures was different

Independent variable	Miscarriage		Stillbirth	
	OR (95% CI)	p value	OR (95% CI)	p value
Maternal age	1.04 (1.02–1.05)	<0.0001	1.01 (0.99–1.04)	0.401
Body mass index	1.03 (1.01–1.05)	<0.0001	1.05 (1.02–1.07)	<0.0001
Racial origin		<0.0001		0.005
Caucasian	1.00	–	1.00	–
African	3.41 (2.75–4.23)	<0.0001	1.95 (1.37–2.76)	<0.0001
South Asian	1.22 (0.69–2.15)	0.488	1.52 (0.74–3.12)	0.260
East Asian	1.09 (0.45–2.65)	0.857	0.91 (0.22–3.69)	0.891
Mixed	2.59 (1.61–4.17)	<0.0001	1.36 (0.55–3.33)	0.506
Cigarette smoking	1.45 (1.06–1.98)	0.019	2.08 (1.39–3.11)	<0.0001
Conception		<0.0001		0.174
Spontaneous	1.00		1.00	–
Ovulation induction drugs	5.37 (3.71–7.77)	<0.0001	2.07 (0.91–4.71)	0.084
In vitro fertilization	1.20 (0.58–2.47)	0.620	1.49 (0.54–4.12)	0.439
History of chronic hypertension	0.94 (0.47–1.89)	0.863	2.92 (1.43–5.98)	0.003
History of pre-existing diabetes	1.57 (0.74–3.30)	0.239	2.97 (1.28–6.93)	0.012
Parity		<0.0001		0.031
Nulliparous without previous miscarriage (PM)	1.00	–		
Nulliparous with PM at <16 weeks	1.71 (1.27–2.29)	<0.0001		
Nulliparous with PM at 16–23 weeks	10.27 (5.85–18.0)	<0.0001		
Parous without PM	1.03 (0.80–1.34)	0.808		
Parous with PM at <16 weeks	1.09 (0.74–1.59)	0.663		
Parous with PM at 16–23 weeks	4.15 (2.40–7.16)	<0.0001		
Nulliparous			1.00	–
Parous without previous stillbirth			0.70 (0.51–0.95)	0.024
Parous with previous stillbirth			1.63 (0.59–4.55)	0.347

Table 4. Logistic regression analysis for the prediction of pre-eclampsia (PE) and gestational hypertension by maternal factors and obstetric history

Independent variable	Early-onset PE		Late-onset PE		Gestational hypertension	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Maternal age	1.00 (0.97–1.03)	0.970	1.02 (1.01–1.04)	0.002	1.03 (1.02–1.04)	<0.0001
Body mass index	1.06 (1.03–1.09)	<0.0001	1.08 (1.06–1.09)	<0.0001	1.07 (1.06–1.08)	<0.0001
Racial origin		<0.0001		<0.0001		<0.0001
Caucasian	1.00	–	1.00	–	1.00	–
African	3.50 (2.40–5.10)	<0.0001	2.59 (2.19–3.08)	<0.0001	1.47 (1.25–1.73)	<0.0001
South Asian	2.52 (1.20–5.30)	0.015	1.95 (1.38–2.77)	<0.0001	1.09 (0.77–1.53)	0.627
East Asian	0.70 (0.10–5.05)	0.719	1.73 (1.00–2.98)	0.049	1.13 (0.68–1.88)	0.629
Mixed	1.88 (0.68–5.20)	0.222	1.32 (0.80–2.16)	0.274	1.06 (0.70–1.61)	0.778
Cigarette smoking	0.68 (0.33–1.42)	0.301	0.83 (0.62–1.11)	0.211	0.56 (0.43–0.74)	<0.0001
Conception		0.024		0.179		0.284
Spontaneous	1.00	–	1.00	–	1.00	–
Ovulation induction drugs	1.29 (0.39–4.20)	0.678	1.32 (0.78–2.24)	0.303	1.07 (0.66–1.73)	0.780
In vitro fertilization	3.28 (1.39–7.74)	0.007	1.48 (0.91–2.41)	0.116	1.38 (0.92–2.06)	0.117
History of chronic hypertension	6.95 (3.87–12.50)	<0.0001	3.32 (2.36–4.66)	<0.0001	0.76 (0.45–1.27)	0.288
History of pre-existing diabetes mellitus	1.27 (0.37–4.34)	0.706	1.15 (0.62–2.17)	0.655	1.20 (0.67–2.14)	0.538
Parity		<0.0001		<0.0001		<0.0001
Nulliparous	1.00	–	1.00	–	1.00	–
Parous without previous PE	0.35 (0.23–0.54)	<0.0001	0.30 (0.25–0.36)	<0.0001	0.34 (0.29–0.40)	<0.0001
Parous with previous PE	2.06 (1.18–3.62)	0.012	1.95 (1.51–2.52)	<0.0001	1.87 (1.48–2.36)	<0.0001
Family history of PE in mother	1.95 (1.09–3.50)	0.025	1.64 (1.24–2.19)	0.001	2.00 (1.59–2.51)	<0.0001

Table 5. Logistic regression analysis for the prediction of SGA and LGA neonates and gestational diabetes by maternal factors and obstetric history

Independent variable	SGA neonates		LGA neonates	
	OR (95% CI)	p value	OR (95% CI)	p value
Maternal age	1.01 (1.00–1.02)	0.033	1.01 (1.00–1.02)	0.068
Body mass index	0.97 (0.96–0.98)	<0.0001	1.08 (1.07–1.08)	<0.0001
Racial origin		<0.0001		<0.0001
Caucasian	1.00	–	1.00	–
African	2.21 (1.97–2.48)	<0.0001	0.64 (0.56–0.75)	<0.0001
South Asian	3.08 (2.60–3.64)	<0.0001	0.49 (0.35–0.70)	<0.0001
East Asian	2.04 (1.54–2.70)	<0.0001	0.69 (0.43–1.11)	0.124
Mixed	1.64 (1.27–2.12)	<0.0001	0.73 (0.51–1.04)	0.079
Cigarette smoking	2.76 (2.44–3.11)	<0.0001	0.61 (0.50–0.74)	<0.0001
Conception		<0.0001		0.858
Spontaneous	1.00	–	1.00	–
Ovulation induction drugs	1.76 (1.30–2.38)	<0.0001	1.05 (0.72–1.53)	0.805
In vitro fertilization	1.29 (0.92–1.81)	0.134	1.11 (0.74–1.67)	0.617
History of chronic hypertension	2.04 (1.44–2.89)	<0.0001	0.94 (0.62–1.42)	0.764
History of pre-existing diabetes mellitus	0.99 (0.53–1.83)	0.968	4.88 (3.66–6.50)	<0.0001
Parity		<0.0001		
Nulliparous	1.00	–	1.00	–
Parous without previous SGA	0.44 (0.40–0.49)	<0.0001		
Parous with previous SGA	1.82 (1.56–2.13)	<0.0001		
Parous without previous LGA			1.25 (1.11–1.40)	<0.0001
Parous with previous LGA			5.01 (4.32–5.82)	<0.0001

Table 6. Logistic regression analysis for the prediction of gestational diabetes and spontaneous preterm delivery by maternal factors and obstetric history

Independent variable	Gestational diabetes		Preterm delivery	
	OR (95% CI)	p value	OR (95% CI)	p value
Maternal age	1.06 (1.05–1.08)	<0.0001	1.01 (1.00–1.03)	0.109
Body mass index	1.11 (1.10–1.12)	<0.0001	1.00 (0.98–1.02)	0.756
Racial origin		<0.0001		0.006
Caucasian	1.00	–	1.00	–
African	1.43 (1.19–1.72)	<0.0001	1.54 (1.21–1.95)	<0.0001
South Asian	2.88 (2.16–3.83)	<0.0001	1.45 (0.93–2.25)	0.098
East Asian	3.58 (2.43–5.29)	<0.0001	1.06 (0.50–2.25)	0.888
Mixed	1.19 (0.74–1.92)	0.480	0.95 (0.50–1.79)	0.863
Cigarette smoking	1.02 (0.78–1.33)	0.904	1.89 (1.46–2.45)	<0.0001
Conception		0.077		0.002
Spontaneous	1.00	–	1.00	–
Ovulation induction drugs	1.57 (0.99–2.49)	0.055	2.43 (1.46–4.04)	0.001
In vitro fertilization	1.37 (0.84–2.23)	0.206	1.30 (0.66–2.57)	0.443
History of chronic hypertension	1.00 (0.61–1.66)	0.989	1.03 (0.47–2.24)	0.941
History of pre-existing diabetes mellitus	–	–	2.09 (1.05–4.16)	0.036
Parity		<0.0001		<0.0001
Nulliparous	1.00	–	1.00	–
Parous without previous LGA	0.80 (0.68–0.94)	0.006		
Parous with previous LGA	1.68 (1.31–2.14)	<0.0001		
Nulliparous, miscarriage <16 weeks			1.30 (0.97–1.73)	0.083
Nulliparous, miscarriage 16–23 weeks			5.87 (3.78–9.12)	<0.0001
Parous, delivery 24–30 weeks			5.78 (3.52–9.50)	<0.0001
Parous, delivery 31–36 weeks			3.32 (2.29–4.82)	<0.0001
Parous, iatrogenic preterm delivery			1.77 (0.71–4.37)	0.219
Parous, delivery >37 weeks			0.79 (0.62–1.01)	0.058

and 10th centiles, and delivery by caesarean section are shown in figures 2–9 [12–40]. In the case of early delivery in our study, we selected spontaneous delivery before 34 weeks, but in most previous studies the outcome measure was total delivery before 32 weeks. In our study we had data on both elective and emergency caesarean section but most previous studies provided data only for total caesarean section.

Discussion

The combined data from this study and previous reports indicate that in ART pregnancies there is an increase in the rate of subsequent stillbirth, PE, GH, GDM, early preterm delivery, birth of SGA neonates and caesarean section. There was also a non-significant increase in risk of second-trimester miscarriage. The results demonstrated that essentially there were no qualitative differences between the women undergoing IVF and those receiving OI drugs but only small differences in the magnitude of risk for the same pregnancy complications. These findings raise the possibility that the risk may be the consequence of subfertility itself rather than the interventions involved in ART. Unfortunately we did not have the necessary data to examine the various pregnancy complications in relation to the causes of subfertility or the different regimes for OI.

Our study has shown that there were significant differences in maternal characteristics between the ART and spontaneously conceived pregnancies (SCPs). We therefore performed multivariate logistic regression analysis and demonstrated that after taking into account certain maternal characteristics and obstetric history, firstly, ART did not contribute to increased risk for most pregnancy complications and, secondly, there were clear qualitative differences between IVF and OI in their effects on complications. In the IVF group, compared to

Table 7. Logistic regression analysis for the prediction of elective and emergency caesarean section by maternal factors and obstetric history

Independent variable	Emergency caesarean section		Elective caesarean section	
	OR (95% CI)	p value	OR (95% CI)	p value
Maternal age	1.05 (1.05–1.06)	<0.0001	1.07 (1.07–1.08)	<0.0001
Body mass index	1.06 (1.06–1.07)	<0.0001	1.05 (1.04–1.06)	<0.0001
Racial origin		<0.0001		0.005
Caucasian	1.00	–	1.00	–
African	1.23 (1.14–1.34)	<0.0001	0.93 (0.84–1.03)	0.161
South Asian	1.33 (1.15–1.54)	<0.0001	1.29 (1.09–1.53)	0.003
East Asian	1.12 (0.89–1.40)	0.325	1.32 (1.03–1.68)	0.028
Mixed	0.93 (0.77–1.13)	0.445	0.90 (0.72–1.14)	0.384
Cigarette smoking	1.18 (1.07–1.30)	0.001	0.92 (0.82–1.05)	0.213
Conception		0.290		0.003
Spontaneous	1.00	–	1.00	–
Ovulation induction drugs	0.91 (0.72–1.15)	0.433	1.21 (0.94–1.55)	0.141
In vitro fertilization	1.15 (0.94–1.42)	0.179	1.46 (1.15–1.86)	0.002
History of chronic hypertension	1.32 (1.01–1.72)	0.045	1.71 (1.31–2.24)	<0.0001
History of pre-existing diabetes mellitus	3.67 (2.76–4.89)	<0.0001	3.41 (2.47–4.70)	<0.0001
Parity		<0.0001		<0.0001
Nulliparous	1.00	–	1.00	–
Parous with one or more vaginal deliveries (VDs) only	0.26 (0.24–0.28)	<0.0001	0.96 (0.88–1.03)	0.258
Parous with one caesarean section (CS) only	2.77 (2.46–3.11)	<0.0001	9.89 (8.78–11.15)	<0.0001
Parous with one CS plus one or more VDs	0.51 (0.38–0.69)	<0.0001	3.75 (3.00–4.69)	<0.0001
Parous with two or more CSs only	2.48 (1.48–4.17)	0.001	72.28 (49.22–106.13)	<0.0001
Parous with two or more CSs plus one or more VDs	1.04 (0.38–2.80)	0.946	20.47 (10.82–38.72)	<0.0001

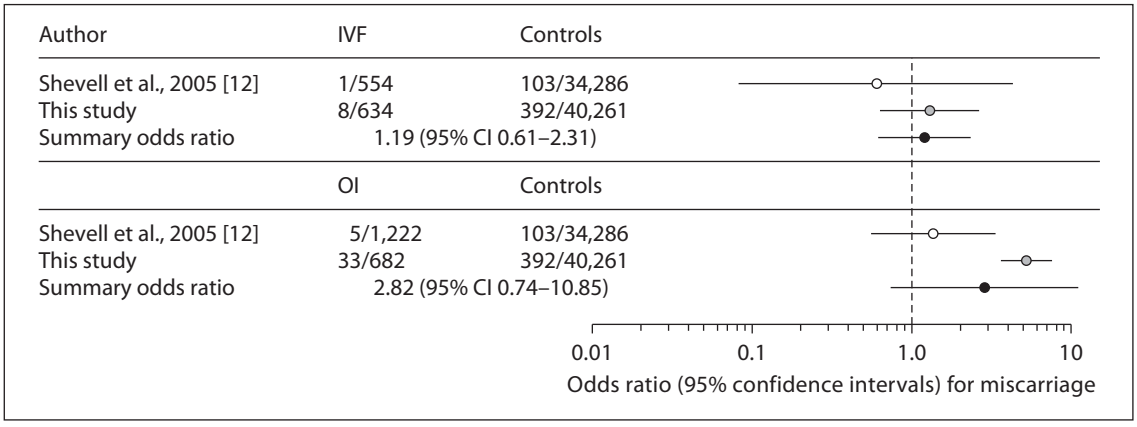

Fig. 2. Forest plot of ORs from previous reports and current study for the risk of second-trimester miscarriage in pregnancies conceived by IVF and after OI compared to SCPs.

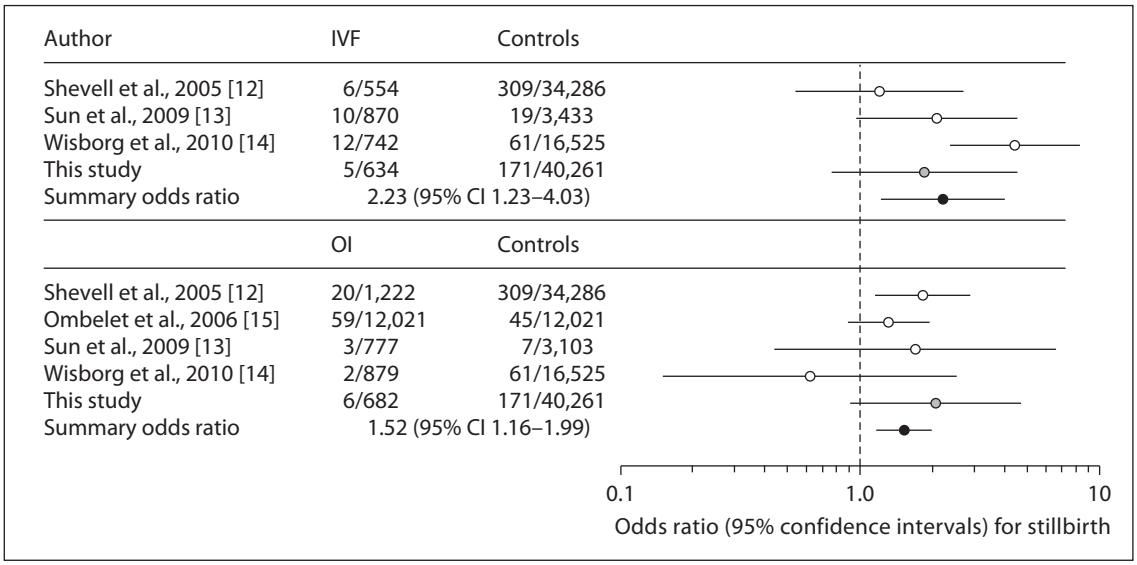

Fig. 3. Forest plot of ORs from previous reports and current study for the risk of stillbirth in pregnancies conceived by IVF and after OI compared to SCPs.

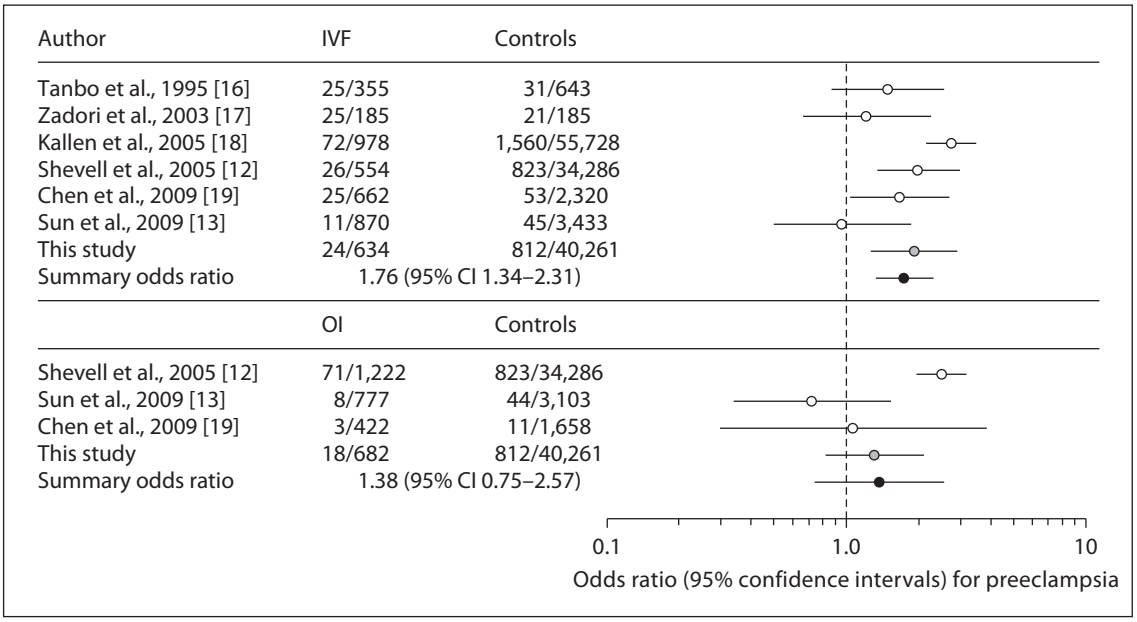

Fig. 4. Forest plot of ORs from previous reports and current study for the risk of PE in pregnancies conceived by IVF and after OI compared to SCPs.

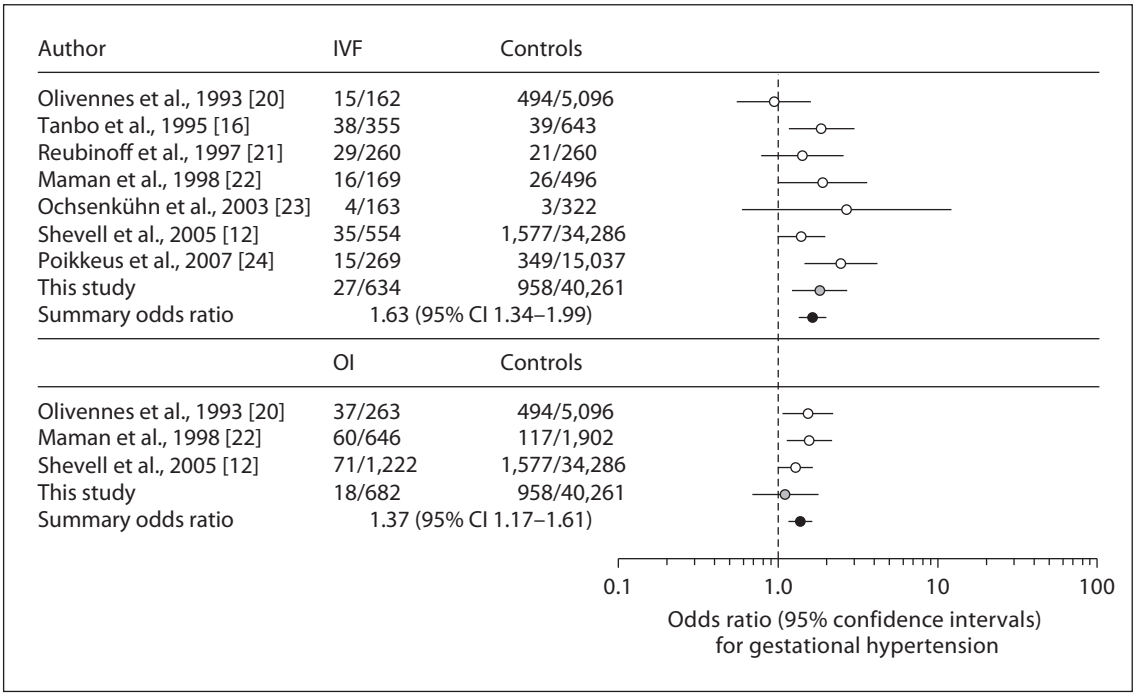

Fig. 5. Forest plot of ORs from previous reports and current study for the risk of GH in pregnancies conceived by IVF and after OI compared to SCPs.

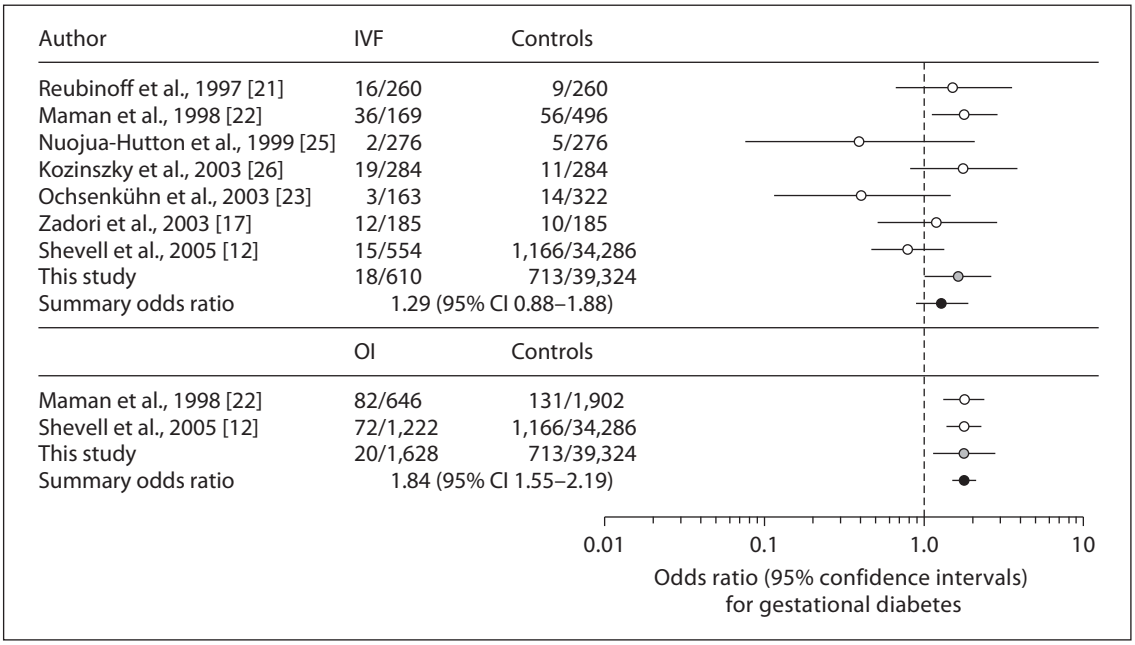

Fig. 6. Forest plot of ORs from previous reports and current study for the risk of GDM in pregnancies conceived by IVF and after OI compared to SCPs.

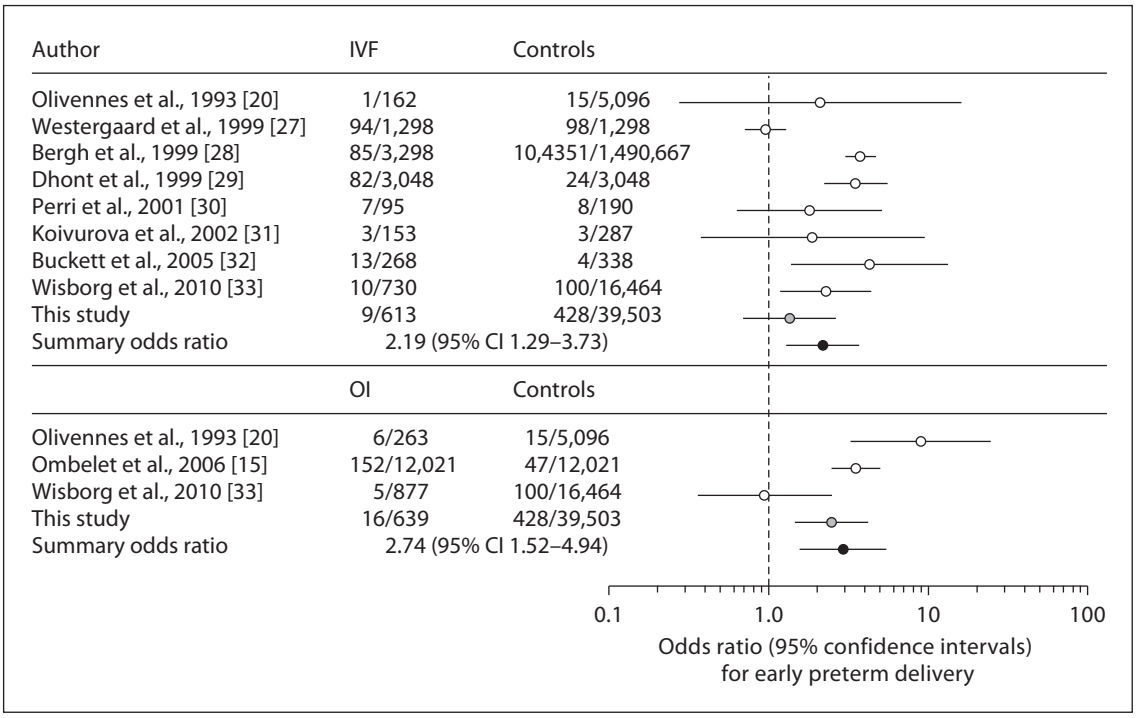

Fig. 7. Forest plot of ORs from previous reports and current study for the risk of delivery before 34 weeks' gestation in pregnancies conceived by IVF and after OI compared to SCPs.

spontaneous conceptions, there was a higher risk of early-onset PE and elective caesarean section. In the OI group, compared to spontaneous conceptions, there was a higher risk of miscarriage, spontaneous delivery before 34 weeks and delivery of SGA neonates. We did not record detailed data on the possible causes of subfertility requiring ART and it is therefore not possible to conclude that the observed effects are the consequence of the ART rather than maternal characteristics.

The inability to distinguish between ART and maternal factors that predated such therapy as the cause of the observed association with pregnancy complications is further reinforced by the pattern of such complications which cannot be explained by a single pathophysiological mechanism. In normal pregnancy the spiral arteries in the placental bed are invaded by trophoblast, which becomes incorporated into the vessel wall and replaces the endothelium, muscular layer and neural tissue [42–45]. These physiological changes convert the spiral arteries from narrow muscular vessels to wide non-muscular channels independent of maternal vasomotor control. In early-onset PE this process is impaired. In IVF there was a threefold increase in risk for early PE, independent of maternal characteristics, suggesting that the procedure could somehow result in impaired placentation. However, had this been the case it would be expected that in this group in addition to the increased risk of PE there would have been a higher incidence of miscarriage, stillbirth and delivery of SGA neonates. Similarly, if in a high proportion of the OI group there was underlying polycystic ovarian syndrome it would be expected that in this group there would have been a higher incidence of GDM. Previous studies examining the outcome of pregnancies in women with polycystic ovarian disease reported increased incidence of GDM, PE, GH and preterm delivery together with a paradoxical decrease in LGA [46]. In this respect it was suggested that in polycystic ovarian syndrome the presence of placental insufficiency mitigates against the development of fetal macrosomia due to the increased glucose load associated with GDM.

The finding of increased rate of elective caesarean section in the IVF group is likely to be the consequence of parental and medical anxiety rather than the result of any specific pregnancy complication, which would in any case be reflected in increased rate of emergency rather than elective caesarean section.

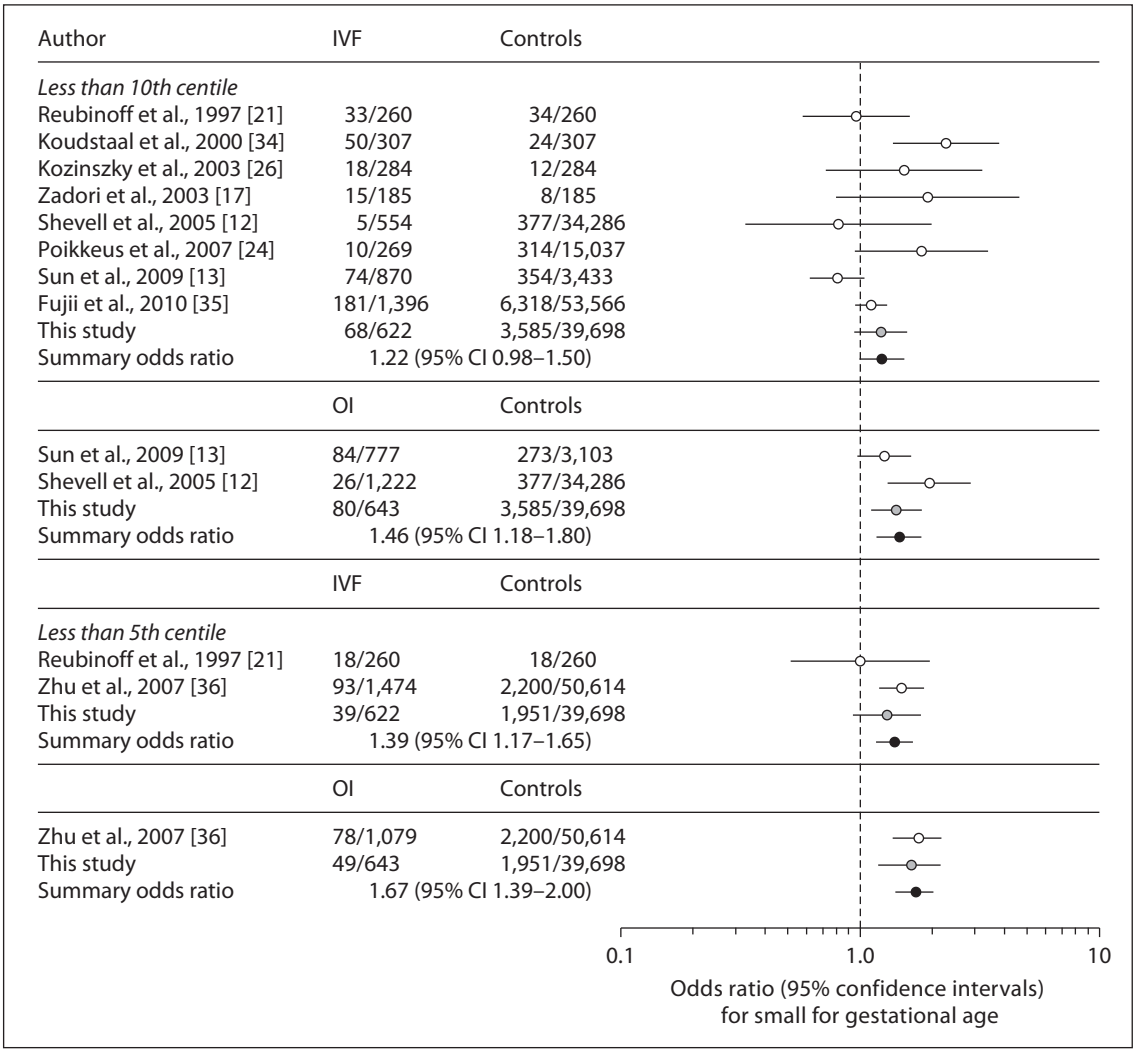

Fig. 8. Forest plot of ORs from previous reports and current study for the risk of delivery of SGA neonate in pregnancies conceived by IVF and after OI compared to SCPs.

In conclusion, ART pregnancies are at increased risk of several pregnancy complications, including fetal death, hypertensive disorders, GDM, preterm delivery, birth of SGA neonates, and caesarean section. However, most of these complications are the consequence of the characteristics of the subfertile women undergoing IVF or OI which predate the interventions involved in ART. Further focused investigations of specific complications, including early-onset PE in IVF pregnancies and second-trimester miscarriage, spontaneous early delivery and birth of SGA neonates in OI pregnancies, will determine whether these are truly the consequence of ART or the type of women undergoing such therapy.

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Disclosure Statement

There are no conflicts of interest to declare.

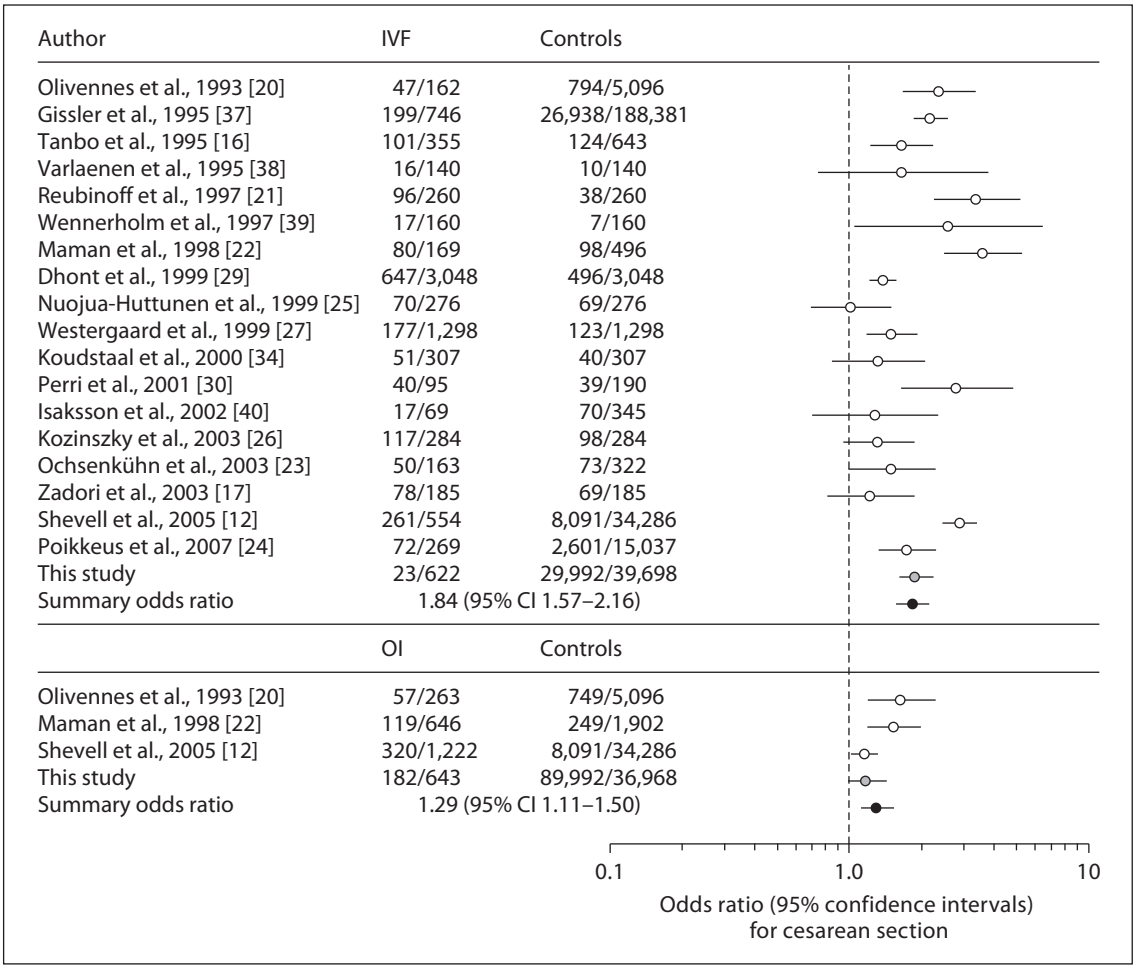

Fig. 9. Forest plot of ORs from previous reports and current study for the risk of delivery by caesarean section in pregnancies conceived by IVF and after OI compared to SCPs.

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