

Assisted reproductive technology and the risk of pregnancy-related complications and adverse pregnancy outcomes in singleton pregnancies: a meta-analysis of cohort studies

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Objective: To determine whether there are any increases in pregnancy-related complications and adverse pregnancy outcomes in singleton pregnancies after assisted reproductive technology (ART) compared with those conceived naturally.

Design: Meta-analysis.

Setting: University-affiliated teaching hospital.

Patient(s): Singleton pregnancies conceived with ART and naturally.

Intervention(s): PubMed, Google Scholar, Cochrane Libraries and Chinese database were searched through March 2015 to identify studies that met pre-stated inclusion criteria. Either a fixed- or a random-effects model was used to calculate the overall combined risk estimates. Subgroup analysis was performed to explore potential heterogeneity moderators.

Main Outcome Measure(s): Pregnancy-related complications and adverse pregnancy outcomes.

Result(s): Fifty cohort studies comprising 161,370 ART and 2,280,241 spontaneously conceived singleton pregnancies were identified. The ART singleton pregnancies had a significantly increased risk of pregnancy-induced hypertension (relative risk [RR] 1.30, 95% confidence interval [CI] 1.04–1.62; $I^2 = 79\%$), gestational diabetes mellitus (RR 1.31, 95% CI 1.13–1.53; $I^2 = 6\%$), placenta previa (RR 3.71, 95% CI 2.67–5.16; $I^2 = 72\%$), placental abruption (RR 1.83, 95% CI 1.49–2.24; $I^2 = 22\%$), antepartum hemorrhage (RR 2.11, 95% CI 1.86–2.38; $I^2 = 47\%$), postpartum hemorrhage (RR 1.29, 95% CI 1.06–1.57; $I^2 = 65\%$), polyhydramnios (RR 1.74, 95% CI 1.24–2.45; $I^2 = 0\%$), oligohydramnios (RR 2.14, 95% CI 1.53–3.01; $I^2 = 0\%$), cesarean sections (RR 1.58, 95% CI 1.48–1.70; $I^2 = 92\%$), preterm birth (RR 1.71, 95% CI 1.59–1.83; $I^2 = 80\%$), very preterm birth (RR 2.12, 95% CI 1.73–2.59; $I^2 = 90\%$), low birth weight (RR 1.61, 95% CI 1.49–1.75; $I^2 = 80\%$), very low birth weight (RR 2.12, 95% CI 1.84–2.43; $I^2 = 67\%$), small for gestational age (RR 1.35, 95% CI 1.20–1.52; $I^2 = 82\%$), perinatal mortality (RR 1.64, 95% CI 1.41–1.90; $I^2 = 45\%$), and congenital malformation (RR 1.37, 95% CI 1.29–1.45; $I^2 = 41\%$). Relevant heterogeneity moderators have been identified by subgroup analysis. Sensitivity analysis yielded consistent results. No evidence of publication bias was observed.

Conclusion(s): The ART singleton pregnancies are associated with higher risks of adverse obstetric outcomes. Obstetricians should manage these pregnancies as high risk. (Fertil Steril® 2016;105:73–85. ©2016 by American Society for Reproductive Medicine.)

Key Words: Adverse pregnancy outcomes, assisted reproductive technology, pregnancy-related complications, singleton pregnancies, meta-analysis

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Today, in the context of high incidence of infertility (1), an increasing number of couples require assisted reproductive technology (ART), such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), to build their family (2). More than 200,000 babies are born worldwide each year by ART (3, 4), and to date, approximately 5 million in all (5). Children conceived with ART currently constitute as much as 3.3% of all births in Australia (6), 4.2% in Israel (7), 1.5% in Japan (8), 1% in the United States (9), 5.9% in Denmark (10), and 1.7%–2.2% in the largest European countries (Germany, France, United Kingdom, and Italy) (11). It is well documented that pregnancies resulting from ART are at higher risk of poor outcomes, but this is due mainly to the higher incidence of multiple pregnancies (12, 13). Although success with ART treatment is surely associated with the number of embryos transferred (14), a policy of single-embryo transfer (SET) in stimulated cycles becomes more popular and is nowadays the most effective measure to reduce the incidence of multiple pregnancies in Europe (15, 16). With an increasing implementation of SET in more and more countries, multiple pregnancies have reduced dramatically.

Data available from three meta-analyses (17–19) show that ART singleton pregnancies had a higher risk of adverse pregnancy outcomes when compared with those after spontaneous conception. Of note, these three reviews included some case-control studies and did not focus on maternal complications. Case-control studies are prone to recall and selection biases, which limit the strength and quality of such evidence. Additionally, they only took whether the confounding factors were matched into account when exploring heterogeneity sources. Three years ago a review (20) of 30 cohort studies, which to our knowledge is the latest meta-analysis around this topic to date, supported that ART singleton pregnancies were associated with an increased risk of maternal complications and adverse pregnancy outcomes. However, this review (20) did not give attention to the risk of placenta previa, placental abruption, postpartum hemorrhage, polyhydramnios, and oligohydramnios. Similarly, when exploring heterogeneity sources, it did not take other confounding factors into account, except for whether the confounding factors were matched.

In fact, many subsequent cohort studies (2, 4, 6–8, 10, 12, 21–28) with adequate sample sizes that examined the association between ART singleton pregnancies and obstetric risks have yielded mixed results, with some showing similar outcomes to spontaneous conceptions (2, 7, 8, 21, 28) and others showing poorer outcomes (4, 6, 10, 12, 22–27). These studies involved 107,694 ART and 1,294,580 spontaneously conceived (SC) singleton pregnancies and accounted for 200.6% of the ART infants and 131.3% of the SC infants vs. studies already included in the previous meta-analysis. If these newer literatures could be included in the future meta-analysis, it is bound to increase the statistical power, which will help to find a statistically significant difference for obstetric risks, especially for rare outcomes; furthermore, this will also help to provide sufficient numbers of studies to examine obstetric risks within subgroups with

greater confidence and to explore possible explanations for heterogeneity. Our study aimed at providing up-to-date evidence to determine whether there are any increases in pregnancy-related complications and adverse pregnancy outcomes in singleton pregnancies obtained by IVF and/or ICSI when compared with SC pregnancies and identify potential heterogeneity moderators by subgroup and sensitivity analysis.

MATERIALS AND METHODS

Search Strategy

The present study was approved by the institutional review board of Maternal and Child Health Hospital of Hunan Province. We attempted to report this meta-analysis in accordance with the Meta-Analysis of Observational Studies in Epidemiology guidelines (29). Unrestricted searches were conducted, with an end date parameter of March 2015, of PubMed, Google Scholar, Cochrane Libraries, China Biology Medicine disc, Chinese Scientific Journals Fulltext Database (CQVIP), China National Knowledge Infrastructure, and Wanfang Database, to identify studies that assessed outcomes in singleton pregnancies resulting from ART. We used and combined the following search terms: “(Assisted reproductive technology OR ART OR Assisted conception OR Assisted reproduction OR In vitro fertilization OR IVF OR Test tube baby OR Intracytoplasmic sperm injection OR ICSI OR Artificial insemination OR Intrauterine insemination OR IUI OR Cervical canal insemination OR Embryo transfer) AND (Pregnancy outcomes OR Pregnancy complications OR Birth outcomes OR Neonatal outcomes OR Perinatal outcomes OR Obstetric outcomes OR Adverse outcomes OR Perinatal mortality OR Perinatal morbidity OR Preterm OR Low birth weight OR Congenital malformation OR Anomalies OR Birth defect OR Pregnancy-induced hypertension OR Gestational diabetes mellitus OR Placenta previa OR Placenta abruption OR Premature rupture of membranes OR Antepartum hemorrhage OR Postpartum hemorrhage).” Reference lists of the retrieved articles were also reviewed. The grey literature and conference abstracts were not searched. We did not contact authors of the primary studies for additional information.

Definitions

In the present study, ART singleton pregnancies were defined as the exposed group, and SC singleton pregnancies were defined as the unexposed group. We defined ART as being conceived by ICSI and/or IVF. We defined the SC group as pregnant women with no history of infertility in their records and no infertility treatment or whose spontaneous pregnancies have arisen after ovulation induction (OI) and intrauterine insemination (IUI). The outcomes of interest were pregnancy-related complications and adverse pregnancy outcomes. The complications involved were pregnancy-induced hypertension, gestational diabetes mellitus, placenta previa, placental abruption, premature rupture of membranes, antepartum hemorrhage, postpartum hemorrhage, polyhydramnios, oligohydramnios, and cesarean sections. The adverse pregnancy outcomes involved were preterm birth (PTB;

defined as birth at <37 weeks' gestation); very preterm birth (VPTB; defined as birth at <32 weeks' gestation); low birth weight (LBW; defined as birth weight <2,500 g); very low birth weight (VLBW; defined as birth weight <1,500 g); small for gestational age (SGA; defined as birth weight below the 10th percentile of the national reference curve); perinatal mortality (defined as stillbirth, fetal death, or neonatal death); congenital malformations (CM; defined as abnormalities that were probably of prenatal origin, including structural, chromosomal, and genetic defects); and intrauterine growth restriction (IUGR; defined as growth below the third percentile for gestational age). Because variations in the definition of outcomes exist across countries and cultures, it is extremely difficult to define uniform standards. The early literature did not always define birth outcomes, and in such cases we relied on the outcome terminology in the original articles.

Study Selection

We first performed an initial screening of titles or abstracts. A second screening was based on full-text review. Studies were considered eligible if they [1] were published in Chinese or English; [2] had a prospective or retrospective cohort design; [3] compared obstetric risks of ART singleton pregnancies with those conceived naturally; [4] had use of IVF and/or ICSI as the exposure of interest; [5] had use of pregnancy-related complications and adverse pregnancy outcomes as outcomes of interest; and [6] reported relative risks (RRs) and odd ratios (ORs), with corresponding 95% confidence intervals (CIs) (or data to calculate them). We excluded review articles, non-peer-reviewed local and/or federal government reports, and conference abstracts and presentations. If the same population was studied in more than one study, we included the study with the longest follow-up time or the most information.

Data Extraction and Quality Assessment

Two independent reviewers (J.Q. and X.L.) extracted data and assessed study quality. Any disagreements were resolved through discussion among the authors until consensus was reached. Data extraction was performed by using a standardized data collection form. We extracted any reported RRs or ORs of outcomes for ART-conceived singletons, compared with SC singletons. Furthermore, we extracted characteristics for each study. Information was recorded as follows: first author's name; publication year; study period; geographic region; sample source (population vs. clinic-based studies); study design (prospective vs. retrospective cohort study); sample size of ART and SC group; whether patients who achieved a pregnancy with OI and IUI were included in the SC group (yes, no, or not stated); type of ART; whether the confounding factors were adjusted and/or matched (matched and/or adjusted vs. crude); quality score; and reported pregnancy-related complications and adverse pregnancy outcomes.

The principles of the Newcastle-Ottawa Scale were adapted to assess the quality of included studies (30). In statistics, the scale is a tool used for assessing the quality of non-

randomized studies included in a systematic review and/or meta-analysis. Using the tool, each study is judged on eight items, categorized into three groups: the selection of the study groups; the comparability of the groups; and the ascertainment of outcome of interest for cohort studies. Stars awarded for each quality item serve as a quick visual assessment. Stars are awarded such that the highest quality studies can be awarded as many as nine stars. When the study gains seven or more stars, it is considered of higher methodologic quality.

Statistical Analysis

Relative risk was used to measure the association between ART and poor outcomes. Homogeneity of effect size across studies was tested by using the Q statistics at the $P < .10$ level of significance. The I^2 statistic, which is a quantitative measure of inconsistency across studies, was also calculated (significance level at $I^2 > 50\%$) (31, 32). The combined RR and the corresponding 95% CI were calculated using either fixed-effects models or, in the presence of heterogeneity, random-effects models (33).

Subgroup analyses according to whether the confounding factors were adjusted and/or matched, study design, geographic region, sample source, sample size, quality score, whether patients who achieved a pregnancy with OI and IUI were included in the SC group, and type of ART were performed to assess the potential effect modification of these variables on outcomes. We also conducted a sensitivity analysis to investigate the influence of a single study on the overall risk estimate by omitting one study at a time. Potential publication bias was assessed by Begg's funnel plots and Egger's linear regression test (34).

Statistical tests were declared significant for a two-sided P value not exceeding .05, except where otherwise specified. Egger's linear regression test was performed using SAS statistical software, version 8.2 (SAS Institute). Other analyses were performed by Review Manager version 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration).

RESULTS

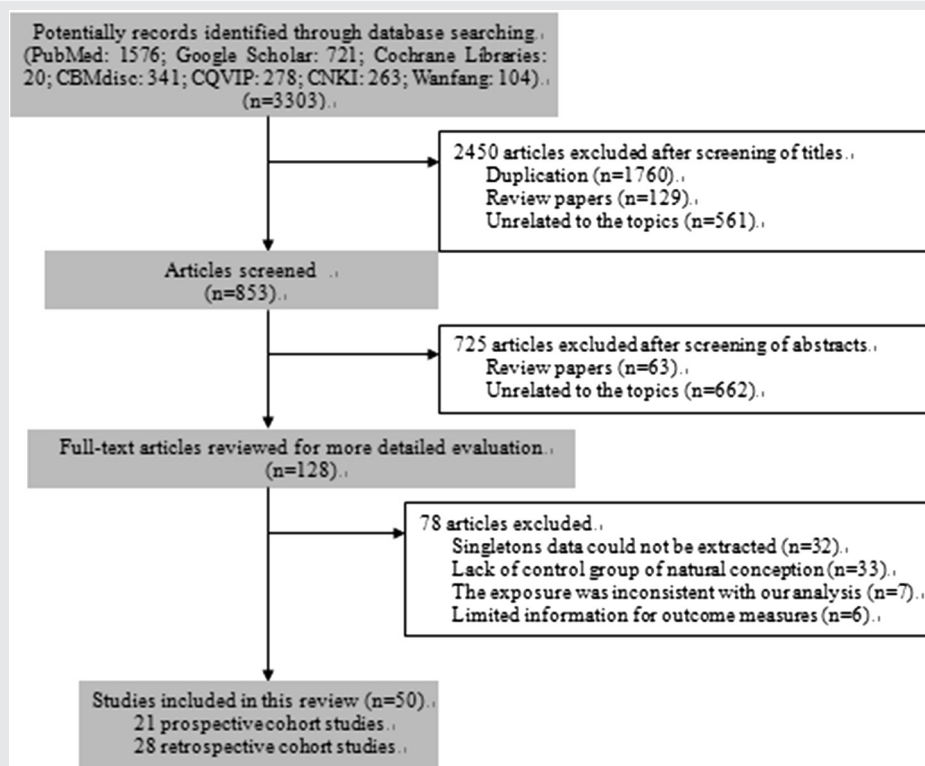
Literature Search

We initially searched 3,303 potentially eligible records; most were excluded after the first screening based on titles or abstracts because they were duplicates, reviews, or not relevant to our analysis. After full-text review of 128 studies, 32 studies were excluded because singletons data could not be extracted. An additional 33 studies that lacked a control group of natural conception were excluded. Seven studies in which the exposure was inconsistent with our analysis and six studies having limited information for outcomes were also excluded. Finally, we identified 50 eligible studies (2, 4, 6–8, 10, 12, 21–28, 35–69), including 21 prospective cohort studies and 28 retrospective cohort studies (Fig. 1).

Study Characteristics

The characteristics of included studies, which involved 161,370 ART singleton births and 2,280,241 SC singleton

FIGURE 1



Flow chart showing the meta-analysis studies selection.

Qin. Poor outcomes in assisted pregnancies. *Fertil Steril* 2016.

births, and were published between 1993 and 2014, are summarized in Table 1. Twenty-nine studies (58%) were conducted in Europe, 9 (18%) in Asia, 7 (14%) in Australia, 3 (6%) in the United States, and 2 (4%) in Canada. The sizes of the exposed and unexposed cohorts ranged from 41 to 5,581 (total 161,370) and from 52 to 826,909 (total 2,280,241) across studies, respectively. The studies with a sample size of more than 2,000 accounted for 62%. The sample source varied across studies, with more than half (56%) based on population. Five studies (10%) (4, 6, 27, 48, 65) included patients who achieved a pregnancy with OI and IUI in the SC group. Nineteen studies (38%) did not include these patients in the SC group, but the remaining studies (52%) did not indicate whether such patients were included.

Thirty-two studies (64%) were considered of higher methodologic quality, achieving a quality score ≥ 7 out of 9; these 32 studies contributed 97.8% of the ART infants and 96.7% of the SC infants. Eleven studies (22%) did not adjust and/or match any factors when estimating the effect of ART singletons on obstetric outcomes, whereas other studies adjusted and/or matched for a wide range of potential confounders for poor outcomes, such as maternal age, education, parity, race, occupation, smoking during pregnancy, socioeconomic status, date of delivery, area of residence, and obstetric and medical history, as well as fetal sex, year of birth, and number at birth.

ART and Risk of Pregnancy-related Complications

Overall, the ART singleton pregnancies compared with the SC singleton pregnancies had a significantly increased risk of developing pregnancy-induced hypertension (RR 1.30 [95% CI 1.04–1.62]; $P=.02$), gestational diabetes mellitus (RR 1.31 [95% CI 1.13–1.53]; $P=.0004$), placenta previa (RR 3.71 [95% CI 2.67–5.16]; $P<.00001$), placental abruption (RR 1.83 [95% CI 1.49–2.24]; $P<.00001$), antepartum hemorrhage (RR 2.11 [95% CI 1.86–2.38]; $P<.00001$), postpartum hemorrhage (RR 1.29 [95% CI 1.06–1.57]; $P=.01$), polyhydramnios (RR 1.74 [95% CI 1.24–2.45]; $P=.001$), oligohydramnios (RR 2.14 [95% CI 1.53–3.01]; $P<.0001$), and cesarean sections (RR 1.58 [95% CI 1.48–1.70]; $P=.001$). However, substantial heterogeneity was observed for pregnancy-induced hypertension ($I^2 = 79\%$), placenta previa ($I^2 = 81\%$), postpartum hemorrhage ($I^2 = 65\%$), and cesarean sections ($I^2 = 92\%$) (Table 2).

ART and Risk of Adverse Pregnancy Outcomes

Overall, the ART singleton pregnancies compared with the reference group experienced a significantly increased risk of developing PTB (RR 1.71 [95% CI 1.59–1.83]; $P<.00001$), VPTB (RR 2.12 [95% CI 1.73–2.59]; $P<.00001$), LBW (RR 1.61 [95% CI 1.49–1.75]; $P<.00001$), VLBW (RR 2.12 [95% CI 1.84–2.43]; $P<.00001$), SGA (RR 1.35 [95% CI

TABLE 1

Characteristics of 50 cohort studies of ART and risk of maternal complications and adverse pregnancy outcomes in singleton pregnancies.

First author/publication year (study period) (reference)	Geographic region	Sample source ^a	Study design	ART singletons (n)	SC singletons (n)	Grouped by sample size (ART plus SC group)	Whether patients who achieved a pregnancy with OI and IUI were included in the SC group?	Type of ART	Adjusted, matched, or crude data	Quality score ^b	Reported pregnancy-related complications and adverse pregnancy outcomes
Olivennes F/1993 (1987–1989) (35)	France	Clinic	Retrospective cohort	162	5,096	>2,000	No	IVF	Crude	2	Pregnancy-induced hypertension, premature rupture of membranes, cesarean sections, PTB, VPTB, LBW, VLBW, SGA, PM
Verlaenen H/1995 (1998–1994) (36)	Belgium	Clinic	Retrospective cohort	140	140	<500	No	IVF	Matched	1	Pregnancy-induced hypertension, PTB, IUGR, LBW, VLBW, PM, CM
Wennerholm UB/1996 (1992–1995) (37)	Sweden	Clinic	Retrospective cohort	140	9,753	>2,000	Not stated	ICSI	Matched	2	LBW, VLBW
Wennerholm UB/1997 (1990–1995) (38)	Sweden	Clinic	Retrospective cohort	320	160	<500	Not stated	IVF	Matched	2	cesarean sections, PTB, VPTB, LBW, SGA
Reubinoff BE/1997 (1983–1993) (39)	Israel	Clinic	Retrospective cohort	260	260	500–2,000	Not stated	IVF	Matched	2	Placenta previa, premature rupture of membranes, pregnancy-induced hypertension, gestational diabetes mellitus, antepartum hemorrhage, cesarean sections, PTB, LBW, SGA
Dhont M/1997 (1991–1997) (40)	Belgium	Population	Retrospective cohort	311	622	500–2,000	Not stated	IVF/ICSI ^c	Matched	1	Cesarean sections, PTB, VPTB, LBW, VLBW, PM, CM
Westergaard HB/1999 (1994–1996) (41)	Denmark	Population	Prospective cohort	1,298	1,298	>2,000	Not stated	IVF/ICSI ^c	Matched	1	cesarean sections, PM, CM, PTB, LBW, VLBW
Dhont M/1999 (1992–1997) (42)	Belgium	Population	Retrospective cohort	3,048	3,048	>2,000	No	IVF/ICSI ^c	Matched	1	cesarean sections, PM, CM, PTB, VPTB, LBW, VLBW
Koudstaal J/2000 (1992) (43)	Netherlands	Clinic	Retrospective cohort	307	307	500–2,000	No	IVF	Matched	2	cesarean sections, PTB, LBW, SGA
Perri T/2001 (1996) (44)	Israel	Clinic	Retrospective cohort	95	190	<500	Not stated	IVF/ICSI ^c	Matched	2	PTB, cesarean sections
Isaksson R/2002 (1993–1999) (45)	Finland	Clinic	Retrospective cohort	69	345	<500	Not stated	IVF/ICSI ^c	Matched	2	cesarean sections, PTB, LBW, VLBW, SGA, PM, CM, placenta previa, placental abruption, pregnancy-induced hypertension, gestational diabetes mellitus
Koivurova S/2002 (1990–1995) (46)	Finland	Population	Prospective cohort	153	287	<500	Not stated	IVF	Matched	1	PTB, VPTB, LBW, VLBW, CM
Wang JX/2002 (1986–1998) (47)	Australia	Clinic	Prospective cohort	1,019	1,019	>2,000	No	IVF/ICSI ^c	Matched	1	Cesarean sections, PTB, VPTB, CM, antepartum hemorrhage
Hansen M/2002 (1993–1997) (48)	Australia	Clinic	Prospective cohort	713	3,906	>2,000	Yes	IVF; ICSI	Adjusted only for CM	1	cesarean sections, PM, PTB, LBW, VLBW, CM
Place I/2003 (1998–2000) (49)	Belgium	Clinic	Prospective cohort	118	59	<500	No	IVF; ICSI	Matched	2	CM

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TABLE 1

Continued.

First author/publication year (study period) (reference)	Geographic region	Sample source ^a	Study design	ART singletons (n)	SC singletons (n)	Grouped by sample size (ART plus SC group)	Whether patients who achieved a pregnancy with OI and IUI were included in the SC group?	Type of ART	Adjusted, matched, or crude data	Quality score ^b	Reported pregnancy-related complications and adverse pregnancy outcomes
Ochsenkuhn R/2003 (1991–1996) (50)	Germany	Clinic	Retrospective cohort	163	322	<500	Not stated	IVF	Matched	2	Cesarean sections, antepartum hemorrhage, pregnancy-induced hypertension, gestational diabetes mellitus, PTB, LBW, VLBW, PM
Katalinic A/2004 (1998–2000) (51)	Germany	Population	Prospective cohort	2,055	7,861	>2,000	Not stated	ICSI	Crude	1	Cesarean sections, PTB, LBW, VLBW, CM, placenta previa, placental abruption, premature rupture of membranes, oligohydramnios, polyhydramnios, pregnancy-induced hypertension
Li FL/2005 (2000–2004) (52)	China	Clinic	Prospective cohort	115	1,095	500–2,000	Not stated	IVF	Matched	2	LBW, VLBW, PM, CM
Klemetti R/2005 (1996–1999) (53)	Finland	Population	Prospective cohort	2,930	26,489	>2,000	No	IVF	Adjusted	1	CM
Olson CK/2005 (1989–2002) (54)	USA	Clinic	Retrospective cohort	645	4,590	>2,000	No	IVF	Matched; Adjusted for CM	1	Cesarean sections, LBW, VLBW, VPTB, CM
Bonduelle M/2005 (2000–2005) (55)	UK, Belgium, Sweden, Denmark, and Greece	Population	Prospective cohort	977	538	500–2,000	Not stated	IVF; ICSI	Matched	1	Cesarean sections, CM
Agarwal P/2005 (1998–2003) (56)	Singapore	Clinic	Prospective cohort	41	147	<500	Not stated	ICSI	Matched	2	PTB, VPTB, LBW, VLBW, pregnancy-induced hypertension, placenta previa
Ombelet W/2005 (1997–2003) (57)	Belgium	Population	Retrospective cohort	1,655	3,278	>2,000	Not stated	ICSI	Matched	1	PTB, VPTB, LBW, VLBW, PM, CM
Kapiteijn K/2006 (1980–1995) (58)	Netherlands	Population	Retrospective cohort	2,239	6,343	>2,000	No	IVF	Adjusted	1	PTB, VPTB, LBW, VLBW
Romundstad LB/2006 (1988–2002) (59)	Norway	Population	Retrospective cohort	5,581	826,909	>2,000	Not stated	IVF/ICSI ^c	Adjusted	1	Placenta previa
Buckett WM/2007 (1998–2003) (60)	Canada	Clinic	Prospective cohort	237	338	500–2,000	Not stated	IVF; ICSI	Matched	2	LWB, VLBW, PTB, VPTB
Poikkeus P/2007 (1997–2003) (61)	Finland	Population	Prospective cohort	499	15,037	>2,000	Not stated	IVF/ICSI ^c	Crude	2	Cesarean sections, PTB, VPTB, LBW, VLBW, SGA, PM, pregnancy-induced hypertension, gestational diabetes mellitus, premature rupture of membranes, placenta previa, placental abruption

Qin. Poor outcomes in assisted pregnancies. *Fertil Steril* 2016.

TABLE 1

Continued.

First author/publication year (study period) (reference)	Geographic region	Sample source ^a	Study design	ART singletons (n)	SC singletons (n)	Grouped by sample size (ART plus SC group)	Whether patients who achieved a pregnancy with OI and IUI were included in the SC group?	Type of ART	Adjusted, matched, or crude data	Quality score ^b	Reported pregnancy-related complications and adverse pregnancy outcomes
Schieve LA/2007 (1997–1998) (62)	USA	Population	Retrospective cohort	1,400	1,400	>2,000	No	IVF/ICSI ^c	Matched	1	Pregnancy-induced hypertension, gestational diabetes mellitus, placenta previa, placental abruption, cesarean sections, PTB, VPTB, LBW, VLBW
Palermo GD/2008 (1993–2006) (63)	USA	Clinic	Retrospective cohort	229	194	<500	Not stated	ICSI	Matched	2	CM
Apantaku O/2008 (1999–2004) (64)	UK	Clinic	Retrospective cohort	88	88	<500	No	IVF/ICSI ^c	Matched	2	PTB, cesarean section, LBW, VLBW, CM
Fujii M/2010 (2006) (8)	Japan	Population	Retrospective cohort	1,408	53,939	>2,000	No	IVF	Adjusted except for placenta previa	1	PM, LBW, SGA, CM, placenta previa
Halliday JL/2010 (1991–2004) (4)	Australia	Population	Retrospective cohort	6,946	20,838	>2,000	Yes	IVF; ICSI	Matched and adjusted	1	CM
Pinborg A/2010 (1995–2007) (65)	Denmark	Population	Prospective cohort	11,286	4,800	>2,000	Yes	IVF; ICSI	Crude	1	Cesarean sections, LBW, VLBW, PTB, VPTB, PM, CM
Wisborg K/2010 (1989–2006) (12)	Denmark	Population	Prospective cohort	742	16,525	>2,000	No	IVF/ICSI ^c	Adjusted	1	PM
Wen SW/2010 (1996–2005) (2)	Canada	Clinic	Retrospective cohort	568	1,100	500–2,000	Not stated	IVF/ICSI ^c	Matched and adjusted	1	CM, PM, VPTB, IUGR
Healy DL/2010 (1991–2004) (66)	Australia	Population	Retrospective cohort	6,730	24,619	>2,000	No	IVF/ICSI ^c	Matched and adjusted	1	Cesarean section, placenta previa, placental abruption, antepartum hemorrhage, postpartum hemorrhage
Pelkonen S/2010 (1995–2006) (67)	Finland	Population	Prospective cohort	4,772	31,243	>2,000	Not stated	IVF/ICSI ^c	Crude	1	Cesarean section, PTB, VPTB, LBW, VLBW, SGA, PM
Henningsen AK/2011 (1994–2008) (68)	Denmark	Population	Prospective cohort	3,881	3,880	>2,000	Not stated	IVF/ICSI ^c	Adjusted	1	PTB, VPTB, LBW, VLBW
Zeng MY/2011 (2005–2011) (69)	China	Clinic	Retrospective cohort	52	52	<500	Not stated	IVF/ICSI ^c	Crude	2	PTB, placenta previa, premature rupture of membranes, pregnancy-induced hypertension, gestational diabetes mellitus
Hayashi M/2012 (2001–2005) (22)	Japan	Population	Retrospective cohort	4,570	4,264	>2,000	No	IVF	Matched	1	Cesarean sections, PTB, VPTB, LBW, VLBW, SGA, PM, pregnancy-induced hypertension, placental abruption, placenta previa, postpartum hemorrhage
Hansen M/2012 (1994–2002) (6)	Australia	Population	Retrospective cohort	1,972	205,641	>2,000	Yes	IVF/ICSI ^c	Adjusted only for CM	1	Cesarean sections, PTB, VPTB, LBW, VLBW, CM, PM
Sagot P/2012 (2000–2009) (25)	France	Population	Retrospective cohort	903	4,044	>2,000	No	IVF	Matched and adjusted	1	CM

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TABLE 1

Continued.

First author/publication year (study period) (reference)	Geographic region	Sample source ^a	Study design	ART singletons (n)	SC singletons (n)	Grouped by sample size (ART plus SC group)	Whether patients who achieved a pregnancy with OI and IUI were included in the SC group?	Type of ART	Adjusted, matched, or crude data	Quality score ^b	Reported pregnancy-related complications and adverse pregnancy outcomes
Kuivasaari-Pirinen P/2012 (1996–2007) (21)	Finland	Population	Retrospective cohort	255	26,870	>2,000	Not stated	IVF/ICSI ^c	Crude	2	Gestational diabetes mellitus, placental abruption, placenta previa, PTB, LBW, SGA
Davies MJ/2012 (1986–2002) (26)	Australia	Population	Retrospective cohort	4,333	295,220	>2,000	No	IVF; ICSI	Adjusted only for CM	1	cesarean sections, PTB, VPTB, PM, CM
Farhi A/2013 (2006–2008) (7)	Israel	Population	Prospective cohort	509	587	500–2,000	Not stated	IVF; ICSI	Adjusted	1	Pregnancy-induced hypertension, gestational diabetes mellitus, cesarean sections, PTB, LBW, SGA, CM
Fedder J/2013 (1995–2009) (27)	Denmark	Population	Prospective cohort	17,216	33,852	>2,000	Yes	IVF; ICSI	Crude	1	Cesarean sections, LBW, VLBW, PTB, VPTB, PM, CM
Malchau SS/2013 (1995–2010) (10)	Denmark	Clinic	Prospective cohort	16,732	33,437	>2,000	Not stated	IVF; ICSI	Crude	1	Cesarean sections, SGA, PTB, VPTB, LBW, VLBW, CM, pregnancy-induced hypertension
Wennerholm UB/2013 (1982–2007) (23)	Denmark, Norway and Sweden	Population	Prospective cohort	48,889	288,542	>2,000	Not stated	IVF/ICSI ^c	Crude	1	LBW, VLBW, PTB, VPTB, SGA, PM
Poon WB/2013 (2001–2012) (28)	Singapore	Clinic	Retrospective cohort	261	15,985	>2,000	No	IVF/ICSI ^c	Crude	2	Cesarean sections, antepartum hemorrhage; oligohydramnios; polyhydramnios; gestational diabetes mellitus; PTB, VPTB, LBW, VLBW, CM
Marino JL/2014 (1986–2002) (24)	Australia	Population	Prospective cohort	2,338	293,684	>2,000	No	IVF; ICSI	Adjusted	1	PM, PTB, VPTB, LBW, VLBW, SGA

^a Population vs. clinic-based sample.^b Each study was assigned a score out of 9; 1 = higher-quality studies with scores ≥ 7 , 2 = low-quality with scores < 7 .^c These articles did not estimate obstetric risks in IVF and ICSI pregnancies separately.Qin. Poor outcomes in assisted pregnancies. *Fertil Steril* 2016.

TABLE 2

Meta-analysis of association between ART and pregnancy-related complications in singleton pregnancies.								
Pregnancy-related complication	No. of studies	ART singletons (n)	SC singletons (n)	RR (95% CI) from fixed-effects models	RR (95% CI) from random-effects models	Measure of heterogeneity		
						Q	P	I ² (%)
Pregnancy-induced hypertension	13	26,652	68,948	1.25 (1.17–1.34)	1.30 (1.04–1.62)	57.97	<.00001	79
Gestational diabetes mellitus	9	3,468	60,858	1.31 (1.13–1.53)	1.31 (1.11–1.54)	8.53	.38	6
Placenta previa	12	22,920	961,703	3.31 (2.96–3.70)	3.71 (2.67–5.16)	58.86	<.00001	81
Placental abruption	7	15,578	80,396	1.83 (1.49–2.24)	1.87 (1.45–2.40)	7.70	.26	22
Premature rupture of membranes	5	3,028	28,306	0.91 (0.81–1.03)	1.31 (0.72–2.38)	12.99	.01	69
Antepartum hemorrhage	5	8,433	42,205	2.11 (1.86–2.38)	2.40 (1.79–3.21)	7.56	.11	47
Postpartum hemorrhage	2	11,300	28,883	1.24 (1.13–1.36)	1.29 (1.06–1.57)	2.84	.09	65
Polyhydramnios	2	2,316	23,846	1.74 (1.24–2.45)	1.74 (1.24–2.45)	0.35	.55	0
Oligohydramnios	2	2,316	23,846	2.14 (1.53–3.01)	2.14 (1.53–3.01)	0.00	.97	0
Caesarean sections	28	81,810	695,735	1.57 (1.54–1.59)	1.58 (1.48–1.70)	334.66	<.00001	92

Note: RR = relative risk.
Qin. Poor outcomes in assisted pregnancies. Fertil Steril 2016.

1.20–1.52]; $P < .00001$), CM (RR 1.37 [95% CI 1.29–1.45]; $P < .00001$), and perinatal mortality (RR 1.64 [95% CI 1.41–1.90]; $P < .00001$). However, substantial evidence of heterogeneity was found for these outcomes (all I^2 values $\geq 41\%$) (Table 3).

Subgroup Analysis for Pregnancy-related Complications

Subgroup analysis for pregnancy-related complications is summarized in Supplemental Table 1 (available online). After subgroup analysis, whether patients who achieved a pregnancy with OI and IUI were included in the SC group, geographic region, and type of ART were identified as the first three of the most relevant heterogeneity moderators. These differences for risks of developing placenta previa (test for subgroup differences [TSD]: $\chi^2 = 44.39$, $P < .00001$; $I^2 = 93.2\%$) and cesarean sections (TSD: $\chi^2 = 13.61$, $P = .003$; $I^2 = 77.9\%$) in the ART singleton pregnancies were statistically significant between different geographic regions. Additionally, there were statistically significant differences for risk of developing placenta previa in the ART singleton pregnan-

cies for whether patients who achieved a pregnancy with OI and IUI were included in the SC group (TSD: $\chi^2 = 25.04$, $P < .00001$; $I^2 = 96.0\%$) and type of ART (TSD: $\chi^2 = 10.99$, $P = .004$; $I^2 = 81.8\%$).

Subgroup Analysis for Adverse Pregnancy Outcomes

Subgroup analysis for adverse pregnancy outcomes is summarized in Supplemental Table 2. After subgroup analysis, geographic region, whether the confounding factors were adjusted and/or matched, and whether patients who achieved a pregnancy with OI and IUI were included in the SC group were identified as the first three of the most relevant heterogeneity moderators. These differences for risks of developing VPTB (TSD: $\chi^2 = 16.22$, $P = .001$; $I^2 = 81.5\%$), LBW (TSD: $\chi^2 = 61.51$, $P < .00001$; $I^2 = 95.1\%$), VLBW (TSD: $\chi^2 = 44.03$, $P < .00001$; $I^2 = 93.2\%$), and SGA (TSD: $\chi^2 = 15.42$, $P = .0004$; $I^2 = 87.0\%$) in the ART singleton pregnancies were statistically significant between different geographic regions. There were statistically significant differences for risks of developing LBW (TSD: $\chi^2 = 13.32$, $P = .0003$; $I^2 = 92.5\%$),

TABLE 3

Meta-analysis of association between ART and adverse pregnancy outcomes in singleton pregnancies.								
Adverse pregnancy outcome	No. of studies	ART singletons (n)	SC singletons (n)	RR (95% CI) from fixed-effects models	RR (95% CI) from random-effects models	Measure of heterogeneity		
						Q	P	I ² (%)
Preterm birth	36	133,338	1,289,549	1.70 (1.67–1.74)	1.71 (1.59–1.83)	171.67	<.00001	80
Very preterm birth	25	128,547	1,253,013	2.75 (2.62–2.88)	2.12 (1.73–2.59)	234.52	<.00001	90
Low birth weight	36	130,147	1,062,445	1.69 (1.64–1.73)	1.61 (1.49–1.75)	175.76	<.00001	80
Very low birth weight	30	127,088	980,322	2.18 (2.06–2.30)	2.12 (1.84–2.43)	88.63	<.00001	67
Small for gestational age	14	81,090	753,771	1.49 (1.44–1.54)	1.35 (1.20–1.52)	72.20	<.00001	82
Perinatal mortality	22	106,267	1,262,997	1.57 (1.46–1.70)	1.64 (1.41–1.90)	38.24	.01	45
Congenital malformations	28	77,697	724,300	1.32 (1.27–1.36)	1.37 (1.29–1.45)	45.43	.01	41
Intrauterine growth restriction	2	708	1,240	1.08 (0.60–1.97)	1.11 (0.32–3.94)	4.49	.03	78

Qin. Poor outcomes in assisted pregnancies. Fertil Steril 2016.

SGA (TSD: $\chi^2 = 8.85$, $P = .003$; $I^2 = 88.7\%$), and CM (TSD: $\chi^2 = 5.17$, $P = .02$; $I^2 = 80.7\%$) in the ART singleton pregnancies for whether the confounding factors were adjusted and/or matched. Additionally, there were statistically significant differences for risks of developing LBW (TSD: $\chi^2 = 15.75$, $P = .0004$; $I^2 = 87.3\%$) and VLBW (TSD: $\chi^2 = 8.24$, $P = .02$; $I^2 = 75.7\%$) in the ART singleton pregnancies for whether patients who achieved a pregnancy with OI and IUI were included in the SC group.

Sensitivity Analysis

Sensitivity analyses were conducted to explore potential sources of heterogeneity in the association between ART and obstetric risks and to examine the influence of various exclusion criteria on the overall risk estimate. Exclusion of five studies (4, 6, 27, 48, 65) in which patients achieved a pregnancy with OI and IUI in the SC group, yielded similar results (Supplemental Tables 1 and 2). Exclusion of any one study at a time yielded consistent results, with a narrow range from 1.30 (95% CI 1.00–1.74) to 1.41 (95% CI 1.22–1.64) for pregnancy-induced hypertension; 1.26 (95% CI 1.05–1.50) to 1.34 (95% CI 1.15–1.56) for gestational diabetes mellitus; 3.09 (95% CI 2.32–4.11) to 3.78 (95% CI 2.62–5.46) for placenta previa, 1.74 (95% CI 1.36–2.23) to 2.06 (95% CI 1.64–2.60) for placental abruption, 0.89 (95% CI 0.79–1.00) to 1.59 (95% CI 0.77–3.29) for premature rupture of membranes; 2.04 (95% CI 1.80–2.32) to 2.82 (95% CI 2.10–3.78) for antepartum hemorrhage; 1.55 (95% CI 1.45–1.65) to 1.60 (95% CI 1.50–1.71) for cesarean sections; 1.68 (95% CI 1.57–1.80) to 1.73 (95% CI 1.62–1.85) for PTB; 2.04 (95% CI 1.67–2.51) to 2.19 (95% CI 1.80–2.68) for VPTB; 1.59 (95% CI 1.47–1.73) to 1.64 (95% CI 1.52–1.78) for LBW; 2.06 (95% CI 1.79–2.36) to 2.17 (95% CI 1.89–2.48) for VLBW; 1.30 (95% CI 1.17–1.45) to 1.38 (95% CI 1.22–1.55) for SGA; 1.58 (95% CI 1.38–1.81) to 1.70 (95% CI 1.47–1.96) for perinatal mortality; and 1.32 (95% CI 1.27–1.38) to 1.39 (95% CI 1.29–1.48) for CM.

Publication Bias

The Begg's funnel plot did not show any substantial asymmetry. Egger's regression test also indicated little evidence of publication bias ($P = .312$ for pregnancy-induced hypertension; .202 for gestational diabetes mellitus; .178 for placenta previa; .130 for placental abruption; .166 for premature rupture of membranes; .240 for antepartum hemorrhage; .512 for cesarean sections; .704 for PTB, .439 for VPTB, .801 for LBW, .301 for VLBW, .155 for SGA, .780 for CM, and .326 for perinatal mortality).

DISCUSSION

Assisted reproductive technology was introduced into medical practice with little formal evaluation of its effects on maternal and fetal well-being (57). Earlier reviews have suggested that ART pregnancies are associated with higher risks. However, there have been recent advances in the way ART is done, leading to some controversy as to whether ART singletons are associated with higher obstetric risks. In particular,

along with the increasing implementation of SET, more and more researchers are interested in this topic. Our meta-analysis of 50 cohort studies involving 161,370 ART singletons and 2,280,241 SC singletons, with sufficient statistical power, aimed at providing the updated evidence to address the question of whether an increased risk of pregnancy-related complications and adverse pregnancy outcomes exists in ART singleton pregnancies compared with those conceived naturally. An improved understanding of this issue may have important clinical implications, given the possibility that the clear results might be useful for counseling ART patients and properly designing the consent forms.

Findings from our study indicated that the singleton pregnancies created with ART experienced a significantly increased risk, of 30% for pregnancy-induced hypertension, 31% for gestational diabetes mellitus, 271% for placenta previa, 83% for placental abruption, 111% for antepartum hemorrhage, 29% for postpartum hemorrhage, 74% for polyhydramnios, 114% for oligohydramnios, 58% for cesarean sections, 71% for PTB, 112% for VPTB, 61% for LBW, 112% for VLBW, 35% for SGA, 64% for perinatal mortality, and 37% for CM, compared with those created naturally. The following outcomes' risk increased further: placental abruption, perinatal mortality, and CM, when data were restricted to matched and/or adjusted studies; LBW and VLBW when data were restricted to high-quality studies; gestational diabetes mellitus, placenta previa, cesarean sections, VPTB, LBW, VLBW, and perinatal mortality when data were restricted to studies with large sample sizes; pregnancy-induced hypertension, placenta previa, placental abruption, cesarean sections, PTB, VPTB, LBW, VLBW, SGA, and perinatal mortality when data were restricted to prospective cohort studies; pregnancy-induced hypertension, placenta previa, LBW, VLBW, and perinatal mortality when data were restricted to population-based studies; pregnancy-induced hypertension, placenta previa, LBW, and CM when data were restricted to studies having the use of ICSI as the exposure of interest; and PTB, VPTB, LBW, VLBW, SGA, and perinatal mortality when data were restricted to studies having the use of IVF as the exposure of interest.

To date there are five existing reviews (17–20, 70) of outcomes for singleton pregnancies created by IVF and/or ICSI. Our findings are generally consistent with previous reviews. However, our study has important strengths. This review is the most up to date on this subject. With the accumulating evidence and enlarged sample size, we have enhanced statistical power to provide more precise and reliable risk estimates. In our study, 62% of the studies included in this subgroup analysis had a large sample size (>2,000); more than half of studies (64%) were considered of higher methodologic quality; and these high-quality studies contributed 97.8% of the ART infants and 96.7% of the SC infants. All the included original studies used a cohort study design, which minimizes recall and selection biases. Moreover, the association between ART and obstetric risk persists and remains statistically significant in sensitivity analysis based on various exclusion criteria. The most relevant heterogeneity moderators have been identified by subgroup

analysis. Additionally, our study indicated that singleton pregnancies after ART carry an increased risk of placenta previa, placental abruption, postpartum hemorrhage, polyhydramnios, and oligohydramnios, which has not been confirmed by previous reviews.

The underlying mechanisms involved in the association between ART and poor outcomes in the singleton pregnancies are uncertain. One possible explanation is that ART procedures or maternal factors associated with infertility or a combination of these bring about increased risks of adverse outcomes in the ART pregnancies. Some studies have shown that factors associated with ART procedures themselves, such as the medications used to induce ovulation or to maintain the pregnancy in the early stages, the culture media composition, the length of time in culture, the freezing and thawing of embryos, the potential for polyspermic fertilization, the delayed fertilization of the oocyte, altered hormonal environment at the time of implantation, and the manipulation of gametes and embryos or a combination of these, may increase the risk of adverse outcomes (6, 48, 71–73). However, some studies have concluded that the ART procedures associated with IVF and ICSI are not responsible for these adverse outcomes. This viewpoint is supported by studies of subfertile women who conceived without the aid of ART and yet exhibited an increased risk of PTB (22, 24, 58, 74–76), LBW (24, 74–76), perinatal mortality (24, 77), CM (74, 78), pregnancy-induced hypertension or preeclampsia (74–76), gestational diabetes (74), and cesarean delivery (74–76). In addition, it has been hypothesized that the invasive infertility treatments may cause health problems in the mothers and their offspring, and the more invasive the procedure, the more harmful it may be (2). The uncertainty of underlying mechanisms between ART and obstetric risks warrants further research.

Substantial heterogeneity was observed among studies of ART and obstetric risks, which was not surprising given the differences in study population and methodology. In the present review, subgroup analysis was used to explore heterogeneity sources. Our subgroup analyses have identified main heterogeneity moderators, including whether patients who achieved a pregnancy with OI and IUI were included in the SC group, geographic region, whether the confounding factors were adjusted and/or matched, and type of ART. Previous studies (2, 48, 54) showed that differences in the obstetric management, diagnosis of adverse outcomes, length of follow-up, ethnic background, socioeconomic situation, maternal education, food and life habits, ART procedures, and prenatal care services exist in different geographic regions, which may lead to substantial heterogeneity. Furthermore, the pregnancies occurring after OI and IUI have been reported to more frequently have poorer outcomes (22, 24, 25). Therefore, if the SC category included patients who achieved a pregnancy with OI and IUI, the SC pregnancies will have an increased incidence of adverse outcomes. Our study has confirmed the above hypothesis.

Potential limitations of this study should be considered. First, some included studies may have considered patients who achieved a pregnancy with OI and IUI to be in the SC category. The results may have been an underestimation of

the association between ART and adverse outcomes, because singleton pregnancies occurring after OI and IUI have been reported to more frequently have poorer outcomes compared with those conceived naturally (22, 24, 25). Although we carried out subgroup analysis according to whether patients who achieved a pregnancy with OI and IUI were included in the SC group, more than half of the included studies (52%) did not specify whether they were included, thereby restricting our analysis. In fact, when data were restricted to studies that did not include these patients in the SC group, the risk of gestational diabetes mellitus, placental abruption, PTB, VPTB, LBW, VLBW, and perinatal mortality was increased further.

Second, there was substantial heterogeneity among studies for association between ART singleton pregnancies and obstetric risks. Nevertheless, we were able to detect the major source of heterogeneity through the subgroup analysis and the sensitivity analysis. The sensitivity analysis that omitted one study at a time and calculated the combined RR for the remaining studies yielded consistent results. After subgroup analysis, the heterogeneity was obviously decreased. However, our estimates have to be viewed with caution because of heterogeneity. Third, a number of the outcomes, especially for pregnancy-related complications, relied on between 2 and 7 of the 50 total studies, so more studies should be included in future reviews, to provide further support for our results.

Fourth, residual confounding is of concern. Uncontrolled or unmeasured risk factors potentially produce biases. In our review, 11 studies (22%) did not adjust and/or match any factors when estimating the effect of ART singletons on obstetric outcomes, whereas other studies adjusted and/or matched for a wide range of potential confounders for poor outcomes, such as maternal age, education, parity, race, occupation, smoking during pregnancy, socioeconomic status, date of delivery, area of residence and obstetric and medical history as well as fetal sex, year of birth, and number at birth. Although restricting analysis to studies that have matched or adjusted confounding factors did not materially alter the combined risk estimate, we still cannot rule out the possibility that residual confounding, including vanishing twins, obesity, allogenic nature of the fetus, and pregnancy intention, could affect the results, because these factors do not explain all of the obstetric risk. Besides, potential publication bias could influence the findings, but little evidence of publication bias was observed. Last but not least, because the present review only included studies published in Chinese or English, additional research in other populations is warranted to generalize the findings.

In conclusion, the present study, which includes a large proportion of participants, giving it sufficient statistical power, aimed to address the question of whether singleton pregnancies obtained by ART carry an increased risk of adverse obstetric outcomes, compared with those conceived naturally. Although the role of potential bias and evidence of heterogeneity should be carefully evaluated, our study indicated that ART singleton pregnancies are associated with higher risks of pregnancy-related complications and adverse pregnancy outcomes when compared with those conceived naturally.

Obstetricians should manage these pregnancies as high risk. However, the mechanisms leading to these adverse outcomes in infertile women remain unclear and require further study for elucidation.

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SUPPLEMENTAL TABLE 1

Subgroup analysis for pregnancy-related complications.					
	Pregnancy-induced hypertension (n = 13) 1.30 (1.04–1.62) $\chi^2 = 57.97, P < .00001$; $I^2 = 79\%$	Gestational diabetes mellitus (n = 9) 1.31 (1.13–1.53) $\chi^2 = 8.53, P = .38$; $I^2 = 6\%$	Placenta previa (n = 12) 3.71 (2.67–5.16) $\chi^2 = 58.86, P < .00001$; $I^2 = 81\%$	Placental abruption (n = 7) 1.83 (1.49–2.24) $\chi^2 = 7.70, P = .26$; $I^2 = 22\%$	Caesarean sections (n = 28) 1.58 (1.48–1.70) $\chi^2 = 334.66, P < .00001$; $I^2 = 92\%$
Whether the confounding factors were adjusted or matched	TSD: $\chi^2 = 0.49, P = .48$; $I^2 = 0\%$	TSD: $\chi^2 = 0.75, P = .39$; $I^2 = 0\%$	TSD: $\chi^2 = 1.12, P = .29$; $I^2 = 11.1\%$	TSD: $\chi^2 = 0.10, P = .75$; $I^2 = 0\%$	TSD: $\chi^2 = 14.50, P = .0001$; $I^2 = 93.1\%$
Adjusted and/or matched	1.20 (0.79–1.81) (n = 8) $\chi^2 = 26.58, P = .0004$; $I^2 = 74\%$	1.20 (0.93–1.55) (n = 5) $\chi^2 = 5.25, P = .26$; $I^2 = 24\%$	3.13 (1.89–5.16) (n = 7) $\chi^2 = 40.87, P < .00001$; $I^2 = 85\%$	1.95 (1.19–3.21) (n = 4) $\chi^2 = 7.12, P = .07$; $I^2 = 58\%$	1.40 (1.27–1.54) (n = 17) $\chi^2 = 74.85, P < .00001$; $I^2 = 79\%$
Crude	1.41 (1.17–1.70) (n = 5) $\chi^2 = 10.22, P = .04$; $I^2 = 61\%$	1.38 (1.14–1.67) (n = 4) $\chi^2 = 2.53, P = .47$; $I^2 = 0\%$	4.53 (2.84–7.23) (n = 5) $\chi^2 = 14.22, P = .007$; $I^2 = 72\%$	1.90 (1.38–2.63) (n = 3) $\chi^2 = 0.48, P = .79$; $I^2 = 0\%$	1.80 (1.65–1.96) (n = 11) $\chi^2 = 182.87, P < .00001$; $I^2 = 95\%$
Study design	TSD: $\chi^2 = 2.65, P = .10$; $I^2 = 62.3\%$	TSD: $\chi^2 = 0.01, P = .94$; $I^2 = 0\%$	TSD: $\chi^2 = 7.38, P = .007$; $I^2 = 86.4\%$	TSD: $\chi^2 = 0.07, P = .78$; $I^2 = 0\%$	TSD: $\chi^2 = 0.45, P = .50$; $I^2 = 0\%$
Retrospective cohort studies	1.07 (0.75–1.53) (n = 8) $\chi^2 = 19.90, P = .006$; $I^2 = 65\%$	1.32 (1.08–1.61) (n = 7) $\chi^2 = 6.41, P = .38$; $I^2 = 6\%$	3.14 (2.19–4.50) (n = 9) $\chi^2 = 44.74, P < .00001$; $I^2 = 82\%$	1.79 (1.39–2.31) (n = 5) $\chi^2 = 7.15, P = .13$; $I^2 = 44\%$	1.56 (1.40–1.74) (n = 17) $\chi^2 = 192.50, P < .00001$; $I^2 = 92\%$
Prospective cohort studies	1.49 (1.24–1.80) (n = 5) $\chi^2 = 10.27, P = .04$; $I^2 = 61\%$	1.30 (1.03–1.66) (n = 2) $\chi^2 = 2.12, P = .15$; $I^2 = 53\%$	6.36 (4.43–9.12) (n = 3) $\chi^2 = 0.25, P = .88$; $I^2 = 0\%$	1.90 (1.36–2.66) (n = 2) $\chi^2 = 0.47, P = .49$; $I^2 = 0\%$	1.63 (1.50–1.78) (n = 11) $\chi^2 = 122.19, P < .00001$; $I^2 = 92\%$
Geographic region	TSD: $\chi^2 = 0.23, P = .89$; $I^2 = 0\%$	TSD: $\chi^2 = 0.36, P = .84$; $I^2 = 0\%$	TSD: $\chi^2 = 44.39, P < .00001$; $I^2 = 93.2\%$	TSD: $\chi^2 = 6.75, P = .08$; $I^2 = 55.6\%$	TSD: $\chi^2 = 13.61, P = .003$; $I^2 = 77.9\%$
Asia	1.32 (0.78–2.24) (n = 5) $\chi^2 = 16.75, P = .002$; $I^2 = 76\%$	1.36 (1.05–1.77) (n = 4) $\chi^2 = 3.30, P = .35$; $I^2 = 9\%$	2.60 (2.17–3.10) (n = 5) $\chi^2 = 7.4, P = .11$; $I^2 = 46\%$	1.21 (0.79–1.85) (n = 1) Not applicable	1.74 (1.17–2.58) (n = 5) $\chi^2 = 52.02, P < .00001$; $I^2 = 92\%$
Europe	1.36 (1.11–1.68) (n = 7) $\chi^2 = 15.08, P = .02$; $I^2 = 60\%$	1.25 (1.01–1.56) (n = 4) $\chi^2 = 4.87, P = .18$; $I^2 = 38\%$	5.80 (4.78–7.03) (n = 5) $\chi^2 = 0.29, P = .99$; $I^2 = 0\%$	1.93 (1.40–2.66) (n = 4) $\chi^2 = 0.94, P = .81$; $I^2 = 0\%$	1.58 (1.45–1.72) (n = 16) $\chi^2 = 133.94, P < .00001$; $I^2 = 89\%$
Oceania	Not applicable	Not applicable	2.27 (1.82–2.83) (n = 1) Not applicable	2.02 (1.41–2.89) (n = 1) Not applicable	1.75 (1.52–2.02) (n = 5) $\chi^2 = 75.89, P < .00001$; $I^2 = 95\%$
North America	1.50 (1.04–2.16) (n = 1) Not applicable	1.40 (0.97–2.02) (n = 1) Not applicable	3.80 (1.60–9.02) (n = 1) Not applicable	3.80 (1.60–9.02) (n = 1) Not applicable	1.19 (1.01–1.40) (n = 2) $\chi^2 = 4.08, P = .04$; $I^2 = 75\%$
Sample source	TSD: $\chi^2 = 0.06, P = .80$; $I^2 = 0\%$	TSD: $\chi^2 = 0.62, P = .43$; $I^2 = 0\%$	TSD: $\chi^2 = 0.72, P = .39$; $I^2 = 0\%$	TSD: $\chi^2 = 0.52, P = .47$; $I^2 = 0\%$	TSD: $\chi^2 = 1.70, P = .19$; $I^2 = 41.0\%$
Population-based studies	1.35 (0.92–1.98) (n = 5) $\chi^2 = 42.39, P < .00001$; $I^2 = 91\%$	1.27 (1.07–1.51) (n = 4) $\chi^2 = 3.03, P = .39$; $I^2 = 1\%$	3.90 (2.77–5.48) (n = 8) $\chi^2 = 53.58, P < .00001$; $I^2 = 87\%$	1.82 (1.48–2.23) (n = 6) $\chi^2 = 7.18, P = .21$; $I^2 = 30\%$	1.53 (1.40–1.67) (n = 15) $\chi^2 = 292.78, P < .00001$; $I^2 = 95\%$
Clinic-based studies	1.34 (1.23–1.47) (n = 8) $\chi^2 = 9.77, P = .20$; $I^2 = 28\%$	1.47 (1.072–2.02) (n = 5) $\chi^2 = 4.88, P = .30$; $I^2 = 18\%$	2.01 (0.66–6.15) (n = 4) $\chi^2 = 4.51, P = .21$; $I^2 = 33\%$	5.00 (0.32–78.12) (n = 1) Not applicable	1.68 (1.51–1.87) (n = 13) $\chi^2 = 40.50, P < .0001$; $I^2 = 70\%$
Sample size	TSD: $\chi^2 = 0.35, P = .84$; $I^2 = 0\%$	TSD: $\chi^2 = 4.09, P = .13$; $I^2 = 51.1\%$	TSD: $\chi^2 = 3.02, P = .22$; $I^2 = 33.7\%$	TSD: $\chi^2 = 0.52, P = .47$; $I^2 = 0\%$	TSD: $\chi^2 = 0.73, P = .70$; $I^2 = 0\%$
<500	1.31 (0.69–2.49) (n = 5) $\chi^2 = 7.85, P = .10$; $I^2 = 49\%$	0.53 (0.19–1.44) (n = 3) $\chi^2 = 0.41, P = .82$; $I^2 = 0\%$	3.09 (0.86–11.11) (n = 3) $\chi^2 = 2.67, P = .26$; $I^2 = 25\%$	5.00 (0.32–78.12) (n = 1) Not applicable	1.52 (1.26–1.85) (n = 5) $\chi^2 = 4.34, P = .36$; $I^2 = 8\%$

Qin. Poor outcomes in assisted pregnancies. Fertil Steril 2016.

SUPPLEMENTAL TABLE 1

Continued.

Subgroup variable	Pregnancy-induced hypertension (n = 13) 1.30 (1.04–1.62) $\chi^2 = 57.97, P < .00001; I^2 = 79\%$	Gestational diabetes mellitus (n = 9) 1.31 (1.13–1.53) $\chi^2 = 8.53, P = .38; I^2 = 6\%$	Placenta previa (n = 12) 3.71 (2.67–5.16) $\chi^2 = 58.86, P < .00001; I^2 = 81\%$	Placental abruption (n = 7) 1.83 (1.49–2.24) $\chi^2 = 7.70, P = .26; I^2 = 22\%$	Caesarean sections (n = 28) 1.58 (1.48–1.70) $\chi^2 = 334.66, P < .00001; I^2 = 92\%$
500–2,000	1.44 (1.01–2.05) (n = 2) $\chi^2 = 0.04, P = .83; I^2 = 0\%$	1.14 (0.78–1.66) (n = 2) $\chi^2 = 1.55, P = .21; I^2 = 35\%$	0.50 (0.05–5.00) (n = 1) Not applicable	Not applicable	1.43 (1.03–2.00) (n = 5) $\chi^2 = 24.94, P < .0001; I^2 = 84\%$
>2,000	1.26 (0.97–1.65) (n = 6) $\chi^2 = 49.42, P < .00001; I^2 = 90\%$	1.39 (1.17–1.64) (n = 4) $\chi^2 = 2.49, P = .48; I^2 = 0\%$	3.90 (2.77–5.48) (n = 8) $\chi^2 = 53.58, P < .00001; I^2 = 87\%$	1.82 (1.48–2.23) (n = 6) $\chi^2 = 7.18, P = .21; I^2 = 30\%$	1.62 (1.50–1.74) (n = 18) $\chi^2 = 303.96, P < .00001; I^2 = 94\%$
Quality score	TSD: $\chi^2 = 1.18, P = .28; I^2 = 15.4\%$	TSD: $\chi^2 = 0.42, P = .52; I^2 = 0\%$	TSD: $\chi^2 = 0.40, P = .53; I^2 = 0\%$	TSD: $\chi^2 = 0.70, P = .40; I^2 = 0\%$	TSD: $\chi^2 = 1.73, P = .19; I^2 = 42.1\%$
High	1.17 (0.90–1.53) (n = 6) $\chi^2 = 39.87, P < .00001; I^2 = 87\%$	1.22 (0.92–1.61) (n = 2) $\chi^2 = 1.36, P = .24; I^2 = 26\%$	3.48 (2.38–5.09) (n = 6) $\chi^2 = 46.35, P < .00001; I^2 = 89\%$	1.83 (1.31–2.55) (n = 4) $\chi^2 = 6.59, P = .09; I^2 = 54\%$	1.54 (1.43–1.66) (n = 18) $\chi^2 = 302.34, P < .00001; I^2 = 94\%$
Low	1.58 (0.99–2.52) (n = 7) $\chi^2 = 13.69, P = .03; I^2 = 56\%$	1.36 (1.13–1.63) (n = 7) $\chi^2 = 6.75, P = .34; I^2 = 11\%$	5.16 (3.42–7.77) (n = 6) $\chi^2 = 7.66, P = .18; I^2 = 35\%$	2.42 (1.22–4.80) (n = 3) $\chi^2 = 0.41, P = .81; I^2 = 0\%$	1.75 (1.47–2.08) (n = 10) $\chi^2 = 27.16, P = .001; I^2 = 67\%$
Whether patients who achieved a pregnancy with OI and IUI were included in the SC group	TSD: $\chi^2 = 3.60, P = .06; I^2 = 72.2\%$	TSD: $\chi^2 = 1.60, P = .21; I^2 = 37.6\%$	TSD: $\chi^2 = 25.04, P < .00001; I^2 = 96.0\%$	TSD: $\chi^2 = 0.18, P = .67; I^2 = 0\%$	TSD: $\chi^2 = 3.68, P = .16; I^2 = 45.7\%$
Yes	Not applicable	Not applicable	Not applicable	Not applicable	1.78 (1.49–2.12) (n = 4) $\chi^2 = 70.63, P < .00001; I^2 = 96\%$
No	0.95 (0.63–1.45) (n = 4) $\chi^2 = 12.12, P = .007; I^2 = 75\%$	1.51 (1.16–1.95) (n = 2) $\chi^2 = 0.30, P = .58; I^2 = 0\%$	2.50 (2.18–2.87) (n = 4) $\chi^2 = 4.83, P = .18; I^2 = 38\%$	1.90 (1.12–3.23) (n = 3) $\chi^2 = 6.57, P = .04; I^2 = 70\%$	1.47 (1.33–1.62) (n = 11) $\chi^2 = 92.60, P < .00001; I^2 = 89\%$
Not stated	1.47 (1.25–1.74) (n = 9) $\chi^2 = 13.88, P = .08; I^2 = 42\%$	1.22 (1.01–1.48) (n = 7) $\chi^2 = 6.63, P = .36; I^2 = 9\%$	5.63 (4.66–6.80) (n = 8) $\chi^2 = 8.14, P = .32; I^2 = 14\%$	1.93 (1.40–2.66) (n = 4) $\chi^2 = 0.94, P = .81; I^2 = 0\%$	1.60 (1.42–1.81) (n = 13) $\chi^2 = 115.96, P < .00001; I^2 = 90\%$
Type of ART	TSD: $\chi^2 = 2.58, P = .28; I^2 = 22.4\%$	TSD: $\chi^2 = 1.86, P = .40; I^2 = 0\%$	TSD: $\chi^2 = 10.99, P = .004; I^2 = 81.8\%$	TSD: $\chi^2 = 5.49, P = .06; I^2 = 63.5\%$	TSD: $\chi^2 = 0.18, P = .92; I^2 = 0\%$
IVF	1.12 (0.81–1.54) (n = 7) $\chi^2 = 34.32, P < .00001; I^2 = 83\%$	1.07 (0.70–1.65) (n = 3) $\chi^2 = 3.74, P = .15; I^2 = 46\%$	2.49 (1.75–3.55) (n = 3) $\chi^2 = 4.91, P = .09; I^2 = 59\%$	1.21 (0.79–1.85) (n = 1) Not applicable	1.55 (1.43–1.67) (n = 13) $\chi^2 = 57.67, P < .00001; I^2 = 79\%$
ICSI	1.39 (1.27–1.53) (n = 4) $\chi^2 = 3.30, P = .35; I^2 = 9\%$	0.99 (0.61–1.61) (n = 1) Not applicable	6.56 (4.16–1.35) (n = 2) $\chi^2 = 0.20, P = .66; I^2 = 0\%$	1.81 (1.26–2.60) (n = 1) Not applicable	1.51 (1.27–1.81) (n = 7) $\chi^2 = 136.92, P < .00001; I^2 = 96\%$
IVF/ICSI	1.55 (1.22–1.98) (n = 6) $\chi^2 = 10.30, P = .07; I^2 = 51\%$	1.32 (1.13–1.54) (n = 7) $\chi^2 = 4.79, P = .57; I^2 = 0\%$	4.04 (2.45–6.66) (n = 7) $\chi^2 = 36.50, P < .00001; I^2 = 84\%$	2.25 (1.67–3.04) (n = 5) $\chi^2 = 2.21, P = .70; I^2 = 0\%$	1.57 (1.47–1.67) (n = 20) $\chi^2 = 177.70, P < .00001; I^2 = 89\%$

Note: ART = assisted reproductive technology; ICSI = intracytoplasmic sperm injection; OI = ovulation induction; SC = spontaneously conceived; TSD = test for subgroup difference.

Qin. Poor outcomes in assisted pregnancies. Fertil Steril 2016.

SUPPLEMENTAL TABLE 2

Subgroup analysis for adverse pregnancy outcomes.

Subgroup variable	Preterm birth (n = 36) 1.71 (1.59–1.83) $\chi^2 = 171.67$, $P < .00001$; $I^2 = 80\%$	Very preterm birth (n = 25) 2.12 (1.73–2.59) $\chi^2 = 234.52$, $P < .00001$; $I^2 = 90\%$	Low birth weight (n = 36) 1.61 (1.49–1.75) $\chi^2 = 175.76$, $P < .00001$; $I^2 = 80\%$	Very low birth weight (n = 30) 2.12 (1.84–2.43) $\chi^2 = 88.63$, $P < .00001$; $I^2 = 67\%$	Small for gestational age (n = 14) 1.35 (1.20–1.52) $\chi^2 = 72.20$, $P < .00001$; $I^2 = 82\%$	Perinatal mortality (n = 22) 1.64 (1.41–1.90) $\chi^2 = 38.24$, $P = .01$; $I^2 = 45\%$	Congenital malformations (n = 28) 1.37 (1.29–1.45) $\chi^2 = 45.43$, $P = .01$; $I^2 = 41\%$
Whether the confounding factors were adjusted or matched	TSD: $\chi^2 = 0.97$, $P = .32$; $I^2 = 0\%$	TSD: $\chi^2 = 1.62$, $P = .20$; $I^2 = 38.4\%$	TSD: $\chi^2 = 13.32$, $P = .0003$; $I^2 = 92.5\%$	TSD: $\chi^2 = 3.77$, $P = .05$; $I^2 = 73.5\%$	TSD: $\chi^2 = 8.85$, $P = .003$; $I^2 = 88.7\%$	TSD: $\chi^2 = 0.04$, $P = .85$; $I^2 = 0\%$	TSD: $\chi^2 = 5.17$, $P = .02$; $I^2 = 80.7\%$
Adjusted and/or matched	1.64 (1.42–1.90) (n = 22) $\chi^2 = 93.12$, $P < .00001$; $I^2 = 77\%$	1.90 (1.43–2.52) (n = 15) $\chi^2 = 55.79$, $P < .00001$; $I^2 = 75\%$	1.40 (1.23–1.59) (n = 24) $\chi^2 = 88.87$, $P < .00001$; $I^2 = 74\%$	1.77 (1.34–2.34) (n = 19) $\chi^2 = 56.87$, $P < .00001$; $I^2 = 68\%$	1.20 (1.12–1.29) (n = 8) $\chi^2 = 8.24$, $P = .31$; $I^2 = 15\%$	1.66 (1.24–2.23) (n = 13) $\chi^2 = 21.65$, $P = .04$; $I^2 = 45\%$	1.42 (1.30–1.56) (n = 23) $\chi^2 = 34.07$, $P = .05$; $I^2 = 35\%$
Crude	1.78 (1.67–1.91) (n = 14) $\chi^2 = 55.36$, $P < .00001$; $I^2 = 77\%$	2.40 (1.92–2.98) (n = 10) $\chi^2 = 82.94$, $P < .00001$; $I^2 = 89\%$	1.87 (1.72–2.04) (n = 12) $\chi^2 = 48.36$, $P < .00001$; $I^2 = 77\%$	2.39 (2.13–2.68) (n = 11) $\chi^2 = 18.40$, $P = .05$; $I^2 = 46\%$	1.50 (1.33–1.68) (n = 6) $\chi^2 = 15.58$, $P = .008$; $I^2 = 68\%$	1.61 (1.35–1.92) (n = 9) $\chi^2 = 16.41$, $P = .04$; $I^2 = 51\%$	1.27 (1.22–1.33) (n = 5) $\chi^2 = 3.83$, $P = .43$; $I^2 = 0\%$
Study design	TSD: $\chi^2 = 2.20$, $P = .14$; $I^2 = 54.4\%$	TSD: $\chi^2 = 1.72$, $P = .19$; $I^2 = 41.9\%$	TSD: $\chi^2 = 6.09$, $P = .01$; $I^2 = 83.6\%$	TSD: $\chi^2 = 1.43$, $P = .23$; $I^2 = 30.2\%$	TSD: $\chi^2 = 1.13$, $P = .29$; $I^2 = 11.8\%$	TSD: $\chi^2 = 0.47$, $P = .49$; $I^2 = 0\%$	TSD: $\chi^2 = 0.10$, $P = .75$; $I^2 = 0\%$
Retrospective cohort studies	1.60 (1.38–1.84) (n = 20) $\chi^2 = 98.82$, $P < .00001$; $I^2 = 81\%$	1.87 (1.41–2.46) (n = 13) $\chi^2 = 59.17$, $P < .00001$; $I^2 = 80\%$	1.46 (1.26–1.69) (n = 20) $\chi^2 = 84.24$, $P < .00001$; $I^2 = 77\%$	1.87 (1.35–2.57) (n = 15) $\chi^2 = 56.51$, $P < .00001$; $I^2 = 75\%$	1.20 (1.08–1.32) (n = 8) $\chi^2 = 11.70$, $P = .11$; $I^2 = 40\%$	1.57 (1.33–1.86) (n = 12) $\chi^2 = 13.63$, $P = .25$; $I^2 = 19\%$	1.37 (1.28–1.47) (n = 15) $\chi^2 = 14.83$, $P = .39$; $I^2 = 6\%$
Prospective cohort studies	1.80 (1.68–1.91) (n = 16) $\chi^2 = 45.37$, $P < .00001$; $I^2 = 67\%$	2.39 (1.87–3.05) (n = 12) $\chi^2 = 99.01$, $P < .00001$; $I^2 = 89\%$	1.80 (1.66–1.94) (n = 16) $\chi^2 = 49.96$, $P < .0001$; $I^2 = 70\%$	2.30 (2.05–2.57) (n = 15) $\chi^2 = 23.30$, $P = .06$; $I^2 = 40\%$	1.41 (1.23–1.63) (n = 6) $\chi^2 = 40.46$, $P < .00001$; $I^2 = 88\%$	1.73 (1.38–2.15) (n = 10) $\chi^2 = 24.60$, $P = .003$; $I^2 = 63\%$	1.36 (1.24–1.48) (n = 13) $\chi^2 = 28.49$, $P = .005$; $I^2 = 58\%$
Geographic region	TSD: $\chi^2 = 5.58$, $P = .13$; $I^2 = 46.2\%$	TSD: $\chi^2 = 16.22$, $P = .001$; $I^2 = 81.5\%$	TSD: $\chi^2 = 61.51$, $P < .00001$; $I^2 = 95.1\%$	TSD: $\chi^2 = 44.03$, $P < .00001$; $I^2 = 93.2\%$	TSD: $\chi^2 = 15.42$, $P = .0004$; $I^2 = 87.0\%$	TSD: $\chi^2 = 7.22$, $P = .07$; $I^2 = 58.4\%$	TSD: $\chi^2 = 1.22$, $P = .75$; $I^2 = 0\%$
Asia	1.71 (1.29–2.26) (n = 7) $\chi^2 = 14.63$, $P = .02$; $I^2 = 59\%$	1.36 (1.17–1.59) (n = 3) $\chi^2 = 2.29$, $P = .32$; $I^2 = 13\%$	1.21 (1.12–1.31) (n = 7) $\chi^2 = 6.25$, $P = .40$; $I^2 = 4\%$	1.33 (1.11–1.58) (n = 4) $\chi^2 = 1.49$, $P = .68$; $I^2 = 0\%$	1.13 (1.02–1.26) (n = 4) $\chi^2 = 1.53$, $P = .67$; $I^2 = 0\%$	1.21 (0.92–1.59) (n = 3) $\chi^2 = 0.80$, $P = .67$; $I^2 = 0\%$	1.26 (0.94–1.68) (n = 4) $\chi^2 = 1.11$, $P = .77$; $I^2 = 0\%$
Europe	1.68 (1.56–1.81) (n = 22) $\chi^2 = 82.33$, $P < .00001$; $I^2 = 74\%$	1.98 (1.53–2.56) (n = 14) $\chi^2 = 123.26$, $P < .00001$; $I^2 = 89\%$	1.70 (1.56–1.85) (n = 23) $\chi^2 = 86.95$, $P < .00001$; $I^2 = 75\%$	2.16 (1.88–2.48) (n = 20) $\chi^2 = 37.72$, $P = .006$; $I^2 = 50\%$	1.52 (1.36–1.69) (n = 9) $\chi^2 = 17.37$, $P = .03$; $I^2 = 54\%$	1.75 (1.41–2.17) (n = 14) $\chi^2 = 29.37$, $P = .006$; $I^2 = 56\%$	1.29 (1.24–1.34) (n = 16) $\chi^2 = 21.57$, $P = .12$; $I^2 = 30\%$

Qin. Poor outcomes in assisted pregnancies. Fertil Steril 2016.

SUPPLEMENTAL TABLE 2

Continued.

Subgroup variable	Preterm birth (n = 36) 1.71 (1.59–1.83) $\chi^2 = 171.67$, $P < .00001$; $I^2 = 80\%$	Very preterm birth (n = 25) 2.12 (1.73–2.59) $\chi^2 = 234.52$, $P < .00001$; $I^2 = 90\%$	Low birth weight (n = 36) 1.61 (1.49–1.75) $\chi^2 = 175.76$, $P < .00001$; $I^2 = 80\%$	Very low birth weight (n = 30) 2.12 (1.84–2.43) $\chi^2 = 88.63$, $P < .00001$; $I^2 = 67\%$	Small for gestational age (n = 14) 1.35 (1.20–1.52) $\chi^2 = 72.20$, $P < .00001$; $I^2 = 82\%$	Perinatal mortality (n = 22) 1.64 (1.41–1.90) $\chi^2 = 38.24$, $P = .01$; $I^2 = 45\%$	Congenital malformations (n = 28) 1.37 (1.29–1.45) $\chi^2 = 45.43$, $P = .01$; $I^2 = 41\%$
Oceania	1.75 (1.46–2.10) (n = 5) $\chi^2 = 33.87$, $P < .00001$; $I^2 = 88\%$	2.80 (2.16–3.61) (n = 4) $\chi^2 = 9.08$, $P = .03$; $I^2 = 67\%$	1.96 (1.80–2.14) (n = 3) $\chi^2 = 0.94$, $P = .63$; $I^2 = 0\%$	2.98 (2.53–3.50) (n = 3) $\chi^2 = 1.52$, $P = .47$; $I^2 = 0\%$	1.22 (1.11–1.34) (n = 1) Not applicable	1.85 (1.48–2.30) (n = 4) $\chi^2 = 1.59$, $P = .66$; $I^2 = 0\%$	1.44 (1.21–1.72) (n = 5) $\chi^2 = 18.17$, $P = .001$; $I^2 = 78\%$
North America	2.68 (2.08–3.44) (n = 2) $\chi^2 = 2.33$, $P = .13$; $I^2 = 57\%$	2.06 (1.41–3.00) (n = 4) $\chi^2 = 3.82$, $P = .28$; $I^2 = 21\%$	1.73 (1.41–2.14) (n = 3) $\chi^2 = 2.30$, $P = .32$; $I^2 = 13\%$	1.83 (1.16–2.89) (n = 3) $\chi^2 = 2.65$, $P = .27$; $I^2 = 24\%$	Not applicable	0.77 (0.18–3.29) (n = 1) Not applicable	1.44 (1.08–1.92) (n = 3) $\chi^2 = 0.68$, $P = .71$; $I^2 = 0\%$
Sample source	TSD: $\chi^2 = 2.99$, $P = .08$; $I^2 = 66.5\%$	TSD: $\chi^2 = 0.63$, $P = .43$; $I^2 = 0\%$	TSD: $\chi^2 = 0.41$, $P = .52$; $I^2 = 0\%$	TSD: $\chi^2 = 0.04$, $P = .85$; $I^2 = 0\%$	TSD: $\chi^2 = 1.15$, $P = .28$; $I^2 = 13.3\%$	TSD: $\chi^2 = 0.39$, $P = .53$; $I^2 = 0\%$	TSD: $\chi^2 = 0.22$, $P = .64$; $I^2 = 0\%$
Population-based studies	1.64 (1.52–1.77) (n = 20) $\chi^2 = 116.33$, $P < .00001$; $I^2 = 84\%$	2.01 (1.57–2.57) (n = 16) $\chi^2 = 215.63$, $P < .00001$; $I^2 = 93\%$	1.63 (1.48–1.79) (n = 20) $\chi^2 = 133.12$, $P < .00001$; $I^2 = 86\%$	2.16 (1.82–2.56) (n = 17) $\chi^2 = 76.65$, $P < .00001$; $I^2 = 79\%$	1.31 (1.11–1.53) (n = 8) $\chi^2 = 65.29$, $P < .00001$; $I^2 = 89\%$	1.66 (1.41–1.95) (n = 15) $\chi^2 = 33.48$, $P = .002$; $I^2 = 58\%$	1.32 (1.27–1.38) (n = 16) $\chi^2 = 17.76$, $P = .28$; $I^2 = 16\%$
Clinic-based studies	1.98 (1.62–2.41) (n = 16) $\chi^2 = 47.61$, $P < .0001$; $I^2 = 68\%$	2.36 (1.73–3.22) (n = 9) $\chi^2 = 14.02$, $P = .08$; $I^2 = 43\%$	1.53 (1.27–1.83) (n = 16) $\chi^2 = 37.69$, $P = .001$; $I^2 = 60\%$	2.21 (1.89–2.57) (n = 13) $\chi^2 = 11.96$, $P = .45$; $I^2 = 0\%$	1.49 (1.37–1.63) (n = 6) $\chi^2 = 6.91$, $P = .23$; $I^2 = 28\%$	1.39 (0.81–2.39) (n = 7) $\chi^2 = 4.55$, $P = .60$; $I^2 = 0\%$	1.42 (1.13–1.78) (n = 12) $\chi^2 = 27.43$, $P = .004$; $I^2 = 60\%$
Sample size	TSD: $\chi^2 = 0.30$, $P = .86$; $I^2 = 0\%$	TSD: $\chi^2 = 0.59$, $P = .74$; $I^2 = 0\%$	TSD: $\chi^2 = 5.63$, $P = .06$; $I^2 = 64.5\%$	TSD: $\chi^2 = 11.09$, $P = .004$; $I^2 = 82.0\%$	TSD: $\chi^2 = 0.07$, $P = .97$; $I^2 = 0\%$	TSD: $\chi^2 = 5.86$, $P = .05$; $I^2 = 65.9\%$	TSD: $\chi^2 = 2.49$, $P = .29$; $I^2 = 19.7\%$
<500	1.58 (0.95–2.65) (n = 9) $\chi^2 = 25.06$, $P = .002$; $I^2 = 68\%$	2.31 (0.72–7.42) (n = 3) $\chi^2 = 1.37$, $P = .50$; $I^2 = 0\%$	1.43 (1.05–1.96) (n = 7) $\chi^2 = 6.69$, $P = .35$; $I^2 = 10\%$	1.80 (0.95–3.42) (n = 6) $\chi^2 = 4.17$, $P = .53$; $I^2 = 0\%$	1.23 (0.56–2.70) (n = 2) $\chi^2 = 0.10$, $P = .75$; $I^2 = 0\%$	1.19 (0.36–3.90) (n = 3) $\chi^2 = 0.12$, $P = .94$; $I^2 = 0\%$	1.28 (0.83–1.99) (n = 6) $\chi^2 = 7.08$, $P = .21$; $I^2 = 29\%$
500–2,000	1.96 (1.10–3.48) (n = 5) $\chi^2 = 23.92$, $P < .0001$; $I^2 = 83\%$	1.40 (0.45–4.38) (n = 3) $\chi^2 = 8.92$, $P = .01$; $I^2 = 78\%$	1.12 (0.79–1.59) (n = 6) $\chi^2 = 12.21$, $P = .03$; $I^2 = 59\%$	0.62 (0.30–1.31) (n = 3) $\chi^2 = 0.20$, $P = .91$; $I^2 = 0\%$	1.38 (0.94–2.04) (n = 3) $\chi^2 = 5.44$, $P = .07$; $I^2 = 63\%$	0.54 (0.21–1.38) (n = 3) $\chi^2 = 0.40$, $P = .82$; $I^2 = 0\%$	1.55 (1.32–1.82) (n = 5) $\chi^2 = 0.26$, $P = .99$; $I^2 = 0\%$

Qin. Poor outcomes in assisted pregnancies. Fertil Steril 2016.

SUPPLEMENTAL TABLE 2

Continued.

Subgroup variable	Preterm birth (n = 36) 1.71 (1.59–1.83) $\chi^2 = 171.67$, $P < .00001$; $I^2 = 80\%$	Very preterm birth (n = 25) 2.12 (1.73–2.59) $\chi^2 = 234.52$, $P < .00001$; $I^2 = 90\%$	Low birth weight (n = 36) 1.61 (1.49–1.75) $\chi^2 = 175.76$, $P < .00001$; $I^2 = 80\%$	Very low birth weight (n = 30) 2.12 (1.84–2.43) $\chi^2 = 88.63$, $P < .00001$; $I^2 = 67\%$	Small for gestational age (n = 14) 1.35 (1.20–1.52) $\chi^2 = 72.20$, $P < .00001$; $I^2 = 82\%$	Perinatal mortality (n = 22) 1.64 (1.41–1.90) $\chi^2 = 38.24$, $P = .01$; $I^2 = 45\%$	Congenital malformations (n = 28) 1.37 (1.29–1.45) $\chi^2 = 45.43$, $P = .01$; $I^2 = 41\%$
>2,000	1.71 (1.60–1.82) (n = 22) $\chi^2 = 121.31$, $P < .00001$; $I^2 = 83\%$	2.19 (1.78–2.70) (n = 19) $\chi^2 = 216.69$, $P < .00001$; $I^2 = 92\%$	1.69 (1.55–1.84) (n = 23) $\chi^2 = 142.07$, $P < .00001$; $I^2 = 85\%$	2.22 (1.93–2.55) (n = 21) $\chi^2 = 72.90$, $P < .00001$; $I^2 = 73\%$	1.35 (1.19–1.54) (n = 9) $\chi^2 = 65.89$, $P < .00001$; $I^2 = 88\%$	1.69 (1.45–1.97) (n = 16) $\chi^2 = 32.44$, $P = .006$; $I^2 = 54\%$	1.35 (1.27–1.44) (n = 17) $\chi^2 = 33.81$, $P = .006$; $I^2 = 53\%$
Quality score	TSD: $\chi^2 = 1.20$, $P = .27$; $I^2 = 16.4\%$	TSD: $\chi^2 = 0.12$, $P = .73$; $I^2 = 0\%$	TSD: $\chi^2 = 0.44$, $P = .51$; $I^2 = 0\%$	TSD: $\chi^2 = 4.51$, $P = .03$; $I^2 = 77.8\%$	TSD: $\chi^2 = 1.17$, $P = .28$; $I^2 = 14.4\%$	TSD: $\chi^2 = 0.92$, $P = .34$; $I^2 = 0\%$	TSD: $\chi^2 = 0.32$, $P = .57$; $I^2 = 0\%$
High	1.65 (1.54–1.77) (n = 22) $\chi^2 = 118.70$, $P < .00001$; $I^2 = 82\%$	2.10 (1.69–2.61) (n = 19) $\chi^2 = 225.84$, $P < .00001$; $I^2 = 92\%$	1.63 (1.49–1.77) (n = 22) $\chi^2 = 139.85$, $P < .00001$; $I^2 = 85\%$	2.22 (1.92–2.58) (n = 20) $\chi^2 = 78.36$, $P < .00001$; $I^2 = 76\%$	1.30 (1.13–1.50) (n = 7) $\chi^2 = 63.30$, $P < .00001$; $I^2 = 91\%$	1.61 (1.38–1.88) (n = 17) $\chi^2 = 33.03$, $P = .007$; $I^2 = 52\%$	1.37 (1.29–1.46) (n = 22) $\chi^2 = 41.24$, $P = .005$; $I^2 = 49\%$
Low	1.93 (1.47–2.53) (n = 14) $\chi^2 = 45.51$, $P < .0001$; $I^2 = 71\%$	1.93 (1.33–2.79) (n = 6) $\chi^2 = 5.10$, $P = .40$; $I^2 = 2\%$	1.49 (1.16–1.91) (n = 14) $\chi^2 = 35.63$, $P = .0007$; $I^2 = 64\%$	1.44 (1.00–2.09) (n = 10) $\chi^2 = 5.41$, $P = .80$; $I^2 = 0\%$	1.50 (1.25–1.80) (n = 7) $\chi^2 = 8.90$, $P = .18$; $I^2 = 33\%$	2.19 (1.20–3.99) (n = 5) $\chi^2 = 4.02$, $P = .40$; $I^2 = 1\%$	1.22 (0.83–1.81) (n = 6) $\chi^2 = 4.05$, $P = .54$; $I^2 = 0\%$
Whether patients who achieved a pregnancy with OI and IUI were included in the SC group	TSD: $\chi^2 = 0.83$, $P = .66$; $I^2 = 0\%$	TSD: $\chi^2 = 3.53$, $P = .17$; $I^2 = 43.3\%$	TSD: $\chi^2 = 15.75$, $P = .0004$; $I^2 = 87.3\%$	TSD: $\chi^2 = 8.24$, $P = .02$; $I^2 = 75.7\%$	TSD: $\chi^2 = 1.48$, $P = .22$; $I^2 = 32.3\%$	TSD: $\chi^2 = 2.56$, $P = .28$; $I^2 = 21.9\%$	TSD: $\chi^2 = 1.19$, $P = .55$; $I^2 = 0\%$
Yes	1.74 (1.41–2.13) (n = 4) $\chi^2 = 35.26$, $P < .00001$; $I^2 = 91\%$	2.53 (2.23–2.86) (n = 3) $\chi^2 = 4.44$, $P = .11$; $I^2 = 55\%$	1.95 (1.83–2.08) (n = 4) $\chi^2 = 0.90$, $P = .82$; $I^2 = 0\%$	2.66 (2.33–3.02) (n = 4) $\chi^2 = 4.94$, $P = .18$; $I^2 = 39\%$	Not applicable	1.76 (1.48–2.08) (n = 4) $\chi^2 = 1.38$, $P = .71$; $I^2 = 0\%$	1.43 (1.24–1.64) (n = 5) $\chi^2 = 20.91$, $P = .0003$; $I^2 = 81\%$
No	1.80 (1.56–2.09) (n = 12) $\chi^2 = 55.29$, $P < .00001$; $I^2 = 80\%$	2.28 (1.75–2.96) (n = 10) $\chi^2 = 41.98$, $P < .00001$; $I^2 = 79\%$	1.63 (1.36–1.96) (n = 12) $\chi^2 = 73.17$, $P < .00001$; $I^2 = 85\%$	2.15 (1.53–3.02) (n = 10) $\chi^2 = 39.06$, $P < .0001$; $I^2 = 77\%$	1.27 (1.09–1.47) (n = 5) $\chi^2 = 10.60$, $P = .03$; $I^2 = 62\%$	1.91 (1.43–2.55) (n = 8) $\chi^2 = 16.06$, $P = .02$; $I^2 = 56\%$	1.31 (1.21–1.43) (n = 11) $\chi^2 = 13.78$, $P = .18$; $I^2 = 27\%$

Qin. Poor outcomes in assisted pregnancies. Fertil Steril 2016.

SUPPLEMENTAL TABLE 2

Continued.

Subgroup variable	Preterm birth (n = 36) 1.71 (1.59–1.83) $\chi^2 = 171.67$, $P < .00001$; $I^2 = 80\%$	Very preterm birth (n = 25) 2.12 (1.73–2.59) $\chi^2 = 234.52$, $P < .00001$; $I^2 = 90\%$	Low birth weight (n = 36) 1.61 (1.49–1.75) $\chi^2 = 175.76$, $P < .00001$; $I^2 = 80\%$	Very low birth weight (n = 30) 2.12 (1.84–2.43) $\chi^2 = 88.63$, $P < .00001$; $I^2 = 67\%$	Small for gestational age (n = 14) 1.35 (1.20–1.52) $\chi^2 = 72.20$, $P < .00001$; $I^2 = 82\%$	Perinatal mortality (n = 22) 1.64 (1.41–1.90) $\chi^2 = 38.24$, $P = .01$; $I^2 = 45\%$	Congenital malformations (n = 28) 1.37 (1.29–1.45) $\chi^2 = 45.43$, $P = .01$; $I^2 = 41\%$
Not stated	1.66 (1.50–1.84) (n = 20) $\chi^2 = 79.09$, $P < .00001$; $I^2 = 76\%$	1.74 (1.20–2.52) (n = 12) $\chi^2 = 112.45$, $P < .00001$; $I^2 = 90\%$	1.53 (1.37–1.70) (n = 20) $\chi^2 = 71.58$, $P < .00001$; $I^2 = 73\%$	1.86 (1.55–2.25) (n = 16) $\chi^2 = 31.57$, $P = .007$; $I^2 = 52\%$	1.42 (1.27–1.60) (n = 9) $\chi^2 = 21.16$, $P = .007$; $I^2 = 62\%$	1.45 (1.31–1.60) (n = 10) $\chi^2 = 14.40$, $P = .11$; $I^2 = 38\%$	1.32 (1.24–1.39) (n = 12) $\chi^2 = 10.73$, $P = .47$; $I^2 = 0\%$
Type of ART	TSD: $\chi^2 = 3.84$, $P = .15$; $I^2 = 47.9\%$	TSD: $\chi^2 = 1.83$, $P = .40$; $I^2 = 0\%$	TSD: $\chi^2 = 0.66$, $P = .72$; $I^2 = 0\%$	TSD: $\chi^2 = 3.01$, $P = .22$; $I^2 = 33.6\%$	TSD: $\chi^2 = 0.26$, $P = .88$; $I^2 = 0\%$	TSD: $\chi^2 = 1.32$, $P = .52$; $I^2 = 0\%$	TSD: $\chi^2 = 1.37$, $P = .51$; $I^2 = 0\%$
IVF	1.91 (1.68–2.18) (n = 16) $\chi^2 = 75.65$, $P < .00001$; $I^2 = 80\%$	2.18 (1.69–2.82) (n = 11) $\chi^2 = 44.44$, $P < .00001$; $I^2 = 77\%$	1.65 (1.42–1.91) (n = 19) $\chi^2 = 126.39$, $P < .00001$; $I^2 = 86\%$	2.28 (1.75–2.96) (n = 14) $\chi^2 = 51.79$, $P < .00001$; $I^2 = 675\%$	1.39 (1.19–1.64) (n = 9) $\chi^2 = 30.02$, $P = .0002$; $I^2 = 73\%$	1.91 (1.35–2.72) (n = 9) $\chi^2 = 23.64$, $P = .003$; $I^2 = 66\%$	1.32 (1.22–1.42) (n = 16) $\chi^2 = 27.13$, $P = .03$; $I^2 = 45\%$
ICSI	1.60 (1.43–1.80) (n = 10) $\chi^2 = 25.81$, $P = .002$; $I^2 = 65\%$	1.85 (1.46–2.35) (n = 7) $\chi^2 = 11.88$, $P = .06$; $I^2 = 50\%$	1.63 (1.44–1.84) (n = 11) $\chi^2 = 24.92$, $P = .006$; $I^2 = 60\%$	1.91 (1.66–2.19) (n = 10) $\chi^2 = 13.02$, $P = .16$; $I^2 = 31\%$	1.31 (1.18–1.46) (n = 3) $\chi^2 = 3.45$, $P = .18$; $I^2 = 42\%$	1.51 (1.18–1.93) (n = 4) $\chi^2 = 1.92$, $P = .59$; $I^2 = 0\%$	1.41 (1.30–1.52) (n = 12) $\chi^2 = 19.24$, $P = .06$; $I^2 = 43\%$
IVF/ICSI	1.75 (1.63–1.89) (n = 24) $\chi^2 = 114.45$, $P < .00001$; $I^2 = 80\%$	2.28 (1.88–2.77) (n = 17) $\chi^2 = 129.59$, $P < .00001$; $I^2 = 88\%$	1.72 (1.59–1.87) (n = 20) $\chi^2 = 75.10$, $P < .00001$; $I^2 = 75\%$	2.27 (1.98–2.61) (n = 18) $\chi^2 = 42.32$, $P = .0006$; $I^2 = 60\%$	1.40 (1.23–1.60) (n = 8) $\chi^2 = 41.81$, $P < .00001$; $I^2 = 83\%$	1.72 (1.44–2.05) (n = 15) $\chi^2 = 31.42$, $P = .005$; $I^2 = 55\%$	1.36 (1.27–1.46) (n = 18) $\chi^2 = 33.03$, $P = .01$; $I^2 = 49\%$

Qin. Poor outcomes in assisted pregnancies. Fertil Steril 2016.