Assisted reproductive technology and risk of adverse obstetric outcomes in dichorionic twin pregnancies: a systematic review and meta-analysis

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Objective: To examine whether dichorionic twin pregnancies after assisted reproductive technology (ART) were at higher risk of adverse obstetric outcomes compared with those conceived naturally.
Design: Meta-analysis.
Setting: University-affiliated teaching hospital.
Patient(s): Dichorionic twin pregnancies conceived with ART and naturally.
Intervention(s): Studies comparing obstetric outcomes in dichorionic twin pregnancies conceived by ART and naturally were identified by searching PubMed, Google Scholar, Cochrane Libraries, and Chinese databases through July 2015 with no restrictions. Either a fixed-effects 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): Maternal complications and adverse pregnancy outcomes.
Result(s): Fifteen cohort studies involving 6,420 dichorionic twins after ART and 13,650 dichorionic twins conceived naturally were included. Most of maternal complications were similar in both groups, but placenta previa (relative risk [RR] = 2.99, 95% confidence interval [CI] 1.51–5.92; $I^2 = 0$) was significantly more common in the ART group. For neonatal outcomes, the ART group experienced higher risk of preterm birth (RR = 1.13, 95% CI 1.00–1.29; $I^2 = 75\%$), very preterm birth (RR = 1.39, 95% CI 1.07–1.82; $I^2 = 71\%$), low birth weight (RR = 1.11, 95% CI 1.00–1.23; $I^2 = 61\%$), and congenital malformations (RR = 1.26, 95% CI 1.09–1.46; $I^2 = 26\%$). In addition, the ART group had a higher proportion of elective cesarean sections (RR = 1.79, 95% CI 1.49–2.16; $I^2 = 60\%$), but had a similar proportion for emergency cesarean sections. Relevant heterogeneity moderators have been identified by subgroup analysis. No evidence of publication bias was observed.
Conclusion(s): The rates of placenta previa, elective cesarean section, preterm birth, very preterm birth, low birth weight, and congenital malformations were significantly higher in dichorionic twin pregnancies after ART. (Fertil Steril® 2016;105:1180–92. ©2016 by American Society for Reproductive Medicine.)
Key Words: In vitro fertilization, intracytoplasmic sperm injection, neonatal outcomes, obstetric outcomes, dichorionic twins

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In the past 36 years, assisted reproductive technology (ART), such as IVF and/or intracytoplasmic sperm injection (ICSI), has become a widespread option for the treatment of human infertility. More than 200,000 babies are born worldwide each year by ART (1, 2), and at present, approximately 5 million babies are born as a result of all forms of conception (3). Twin pregnancies resulting from ART have increased worldwide in recent years because of increased requests for ART and the transfer of two or three embryos to achieve a higher pregnancy rate (PR) (4). This increase has occurred despite efforts aimed at limiting the incidence of multiple pregnancies after ART by using single ET (5). Pressure to achieve higher PRs with infertility treatment has resulted in an unacceptably high multiple pregnancy rate (6).The final effect is reflected by data showing that 21.8% of all deliveries after ART occur in pregnancies with more than one fetus (7).

The increased rate of twins born as a result of ART is "the most serious complication" of ART treatment (8). It is well documented that twin pregnancies (either monochorionic or dichorionic) have a poorer maternal and neonatal outcomes than singleton pregnancies (9, 10), with higher rates of perinatal morbidity and mortality (11, 12). In addition, consistent evidence from meta-analyses (13–17) has shown that singleton pregnancies after ART are at greater risk of adverse obstetric outcomes than those conceived naturally. However, data are conflicting on the outcomes of ART twin pregnancies compared with spontaneously conceived (SC) twin pregnancies. Most studies comparing ART and SC twin pregnancies reported similar perinatal outcomes (5, 18–23). Some studies (4, 11, 24–26) reported a higher risk of poor perinatal outcomes for ART twins. Even other studies (27, 28) found better perinatal outcomes after ART. Differences in the study population and management methods of twin pregnancies, and especially whether or not monochorionicity was considered as a risk factor for adverse outcomes, are the main reasons for the inconsistent findings.

It is well known that the occurrence of monochorionicity among twin pregnancies after ART is quite rare compared with SC twin pregnancies (about 2% vs. 22%, respectively), and monochorionic pregnancies have worse perinatal outcomes (21, 29, 30). Theoretically, the lower proportion of monochorionic twins in pregnancies from ART may somewhat offset the adverse effect of ART in twins. Therefore the chorionicity should be considered as an intermediate that modifies the relation between ART and adverse obstetric outcomes in twin pregnancies. Although several studies (4, 5, 11, 20, 21, 31–40) have been performed to address whether dichorionic twin pregnancies after ART have greater risk of adverse outcomes compared with those conceived naturally, their results are often inconsistent. Not long ago, we have performed a meta-analysis to compare obstetric risks of twin pregnancies from ART versus spontaneous conception (41). However, at that time, we did not take chorionicity into account when evaluating the relation between ART and poor outcomes. The present study aimed at examining whether dichorionic twin pregnancies after IVF and/or ICSI have a higher risk of adverse obstetric outcomes compared with those conceived naturally by conducting a systematic review and meta-analysis.

MATERIALS AND METHODS

Literature Search

We performed a meta-analysis according to the MOOSE guidelines (42). The present study was approved by the Institutional Review Board of Maternal and Child Health Hospital of Hunan province. The studies that compared maternal and neonatal outcomes in dichorionic twin pregnancies conceived by ART and spontaneously were identified by searching PubMed, Google Scholar, Cochrane Libraries, China Biology Medicine disc (CBMdisc), Chinese Scientific Journals Fulltext Database (CQVIP), China National Knowledge Infrastructure (CNKI), and Wanfang Database through July 2015 with no restrictions. We used the following search terms: assisted reproductive technology/ART, assisted conception, assisted reproduction, in vitro fertilization/IVF, test tube baby, intracytoplasmic sperm injection/ICSI, artificial insemination, intrauterine insemination/IUI, cervical canal insemination, embryo transfer, frozen embryo transfer, pregnancy/birth outcome, complication, maternal/neonatal/perinatal/obstetric outcome, adverse/poor outcome, mortality/morbidity, preterm/low birth weight, congenital malformation/anomalies/birth defect, and twin. In addition we reviewed references in seminal papers, review articles, and medical textbooks. We did not search gray literatures and conference abstracts, and did not contact authors of the primary studies for additional information.

Outcome Measures

The main outcome measures for the present study were maternal complications and adverse pregnancy outcomes. The maternal complications involved were pregnancy-induced hypertension or preeclampsia, gestational diabetes mellitus, placenta previa, placental abruption, premature rupture of membranes, antepartum hemorrhage, postpartum hemorrhage, oligohydramnios, polyhydramnios, and cesarean sections. The adverse pregnancy outcomes involved were: preterm birth (PTB; defined as birth at <37 weeks of gestation); very PTB (VPTB; defined as birth at <32 weeks of gestation); low birth weight (LBW; defined as birth weight $<2,500$ g); very LBW (VLBW; defined as birth weight $<1,500$ g); small for gestational age (SGA; defined as birth weight $<10\%$); 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); intrauterine growth restriction (IUGR; defined as growth below the third percentile for gestational age); neonatal respiratory distress syndrome (NRDS); and admission to neonatal intensive care unit (NICU). Because variations in the definition of outcome measures exist across countries and cultures, it is extremely difficult to define uniform standards. The early literatures did not always define

birth outcomes and in such cases we relied on the outcome terminology in the original articles.

Study Selection

Two authors (J.B.Q. and H.W.) independently conducted the studies selection. We first performed an initial screening of titles or abstracts. A second screening was based on full-text review. Studies were considered eligible for inclusion if they: [1] were published in Chinese or English language; [2] had a prospective or retrospective cohort design; [3] compared maternal and neonatal outcomes in dichorionic twin pregnancies conceived by ART and spontaneously; [4] had use of IVF and/or ICSI as the exposure of interest; [5] had use of maternal complications and adverse pregnancy outcomes as outcomes of interest; and [6] reported relative risks (RRs), odd ratios (ORs), and the corresponding 95% confidence interval (CI) (or data to calculate them). In our study, only dichorionic twin pregnancies were considered and distinguished into those conceived by ART (either IVF or ICSI) and those conceived naturally. Singleton pregnancies, triplet pregnancies, multiple pregnancies, and monochorionic twin pregnancies were excluded. We excluded review articles, nonpeer-reviewed local/government reports, conference abstract, and presentation in the present study. Multiple articles from the same center and/or authors were analyzed to determine whether the most recent publication was an accumulation that included cases reported in earlier publications. If this was evident from our review, then we used only the most recent publication. We also assessed potential studies to ensure that there was no duplication of case series.

Data Extraction and Quality Assessment

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

We adapted the principles of the Newcastle-Ottawa scale (NOS) to appraise the quality of included studies (43). In statistics, the scale is a tool used for assessing the quality of nonrandomized 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 are awarded up to nine stars. When the study gains at least seven stars, it is considered of higher methodological quality.

Statistics

Relative risk was used to measure the association between ART and adverse 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 $I^2>50\%$) (44, 45). The combined RR and the corresponding 95% CI were calculated using either fixed-effects models or, in the presence of heterogeneity, random-effects models (46).

Sensitivity analysis was conducted to explore possible explanations for heterogeneity and examine the influence of various exclusion criteria on the overall risk estimate. We performed a sensitivity analysis by omitting studies that had a prospective cohort design or with a sample size >2,000. Subgroup analyses according to whether the confounding factors were adjusted and/or matched, geographic region, sample source, 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. Potential publication bias was assessed by Begg's funnel plots and Egger's linear regression tests (47). The subgroup analysis and publication bias assessment were only performed for these outcomes with the number of included studies at seven or more.

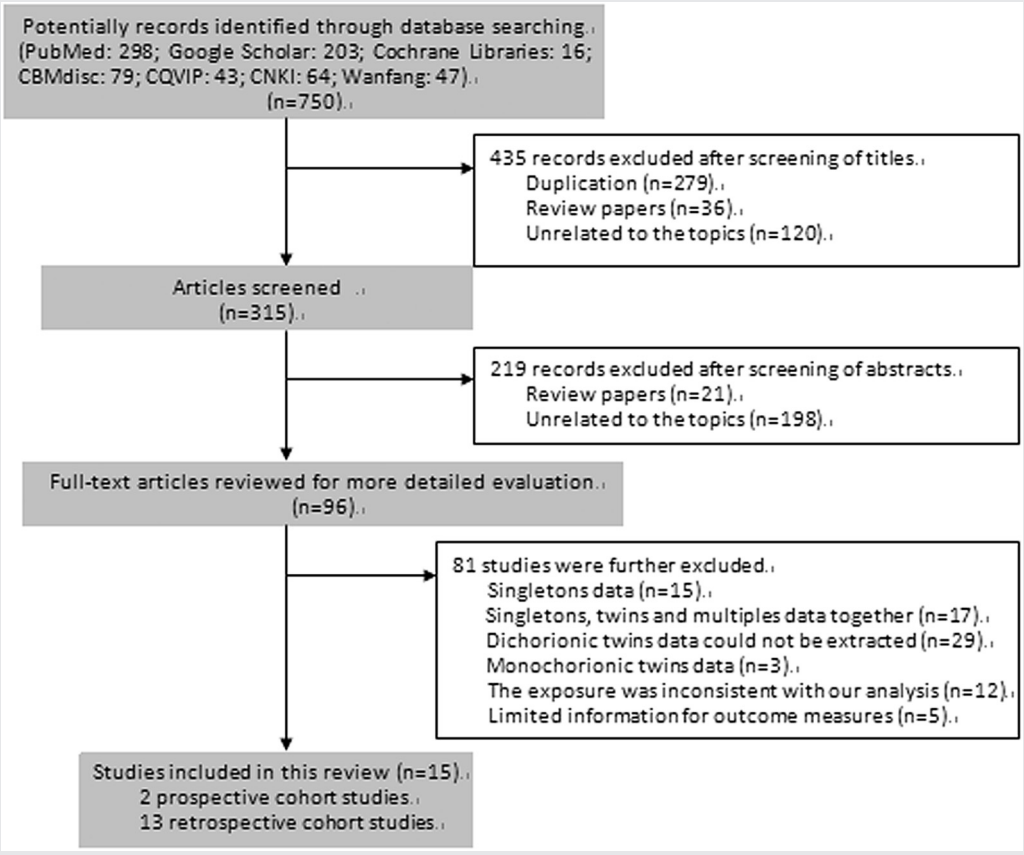
Statistical tests were declared significant for a two-sided P value not exceeding .05, except where otherwise specified. Egger's linear regression test was performed using the SAS statistical software, version 8.2 (SAS Institute). Other analyses were performed by Review Manager-version 5.0 (The Nordic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

RESULTS

Literature Search

We initially searched 750 potentially eligible records from 7 databases. Of these, most were excluded after the first screening based on titles or abstracts, mainly because they were duplicates, reviews, or not relevant to our analysis. After full-text review of 96 studies, 15 studies were excluded because they only focused on singleton pregnancies. An additional 17 studies in which singletons, twins, and multiples data were not separated were excluded. Twenty-nine studies in which dichorionic twins data could not be extracted, 3 studies that only considered monochorionic twin pregnancies, 12 studies in which the exposure was inconsistent with our analysis, and 5 studies having limited information for outcome measures were also excluded. Finally, 15 studies including 2 prospective cohort studies (4, 5) and 13 retrospective cohort studies (11, 20, 21, 31–40) were included in our review (Fig. 1).

FIGURE 1



Flow chart of study selection.

Qin. Adverse outcomes in assisted twin pregnancies. Fertil Steril 2016.

Study Characteristics

The characteristics of included studies involving 6,420 dichorionic twins conceived with ART and 13,650 dichorionic twins conceived naturally and published between 2003 and 2014 (Table 1). Seven studies (46.7%) were conducted in Europe, six (40%) in Asia, and two (13.3%) in Australia. For sample sources, 5 studies (33.3%) were population based, and 10 (66.7%) were clinic based. The size of ART infants ranged from 76 to 1,650 (total 6,420) and SC infants from 54 to 4,134 (total 13,650). The sample size in more than half studies (53.3%) was less than 500.

Among the 15 studies included, those reporting complications and/or adverse outcomes were as follows: 7 pregnancy-induced hypertension or preeclampsia; 4 gestational diabetes mellitus; 4 placenta previa; 2 placental abruption; 5 premature rupture of membranes; only 1 antepartum hemorrhage; 3 postpartum hemorrhage; only 1 polyhydramnios; only 1 oligohydramnios; 5 cesarean sections; 12 PTB; 10 VPTB; 9 LBW; 7 VLBW; 3 SGA; 10 perinatal mortality; 14 CM; 3 IUGR; 5 NRDS; and 8 NICU admissions.

Three studies (20%) (21, 31, 36) included patients who achieved a pregnancy with OI and IUI in the SC group, and the remaining studies did not include these patients in the SC group. Eleven studies (73.3%) were considered of higher methodological quality, achieving a quality score ≥ 7 out of 9; these 11 studies contributed 89.8% of the ART infants and 94.1% of the SC infants. Four studies (26.7%) (20, 33, 34, 39) did not adjust and/or match any factors when estimating the effect of ART on obstetric outcomes, whereas other studies at least adjusted and/or matched for maternal age.

ART and Risk of Maternal Complications

Pregnancy-induced hypertension or preeclampsia and gestational diabetes mellitus. Of the seven studies, three showed a positive association between ART and risk of pregnancy-induced hypertension or preeclampsia. For gestational diabetes mellitus, three studies (total 4) showed a positive association between ART and risk of gestational diabetes mellitus. Overall, there were no significant statistical differences between the two groups for developing pregnancy-induced hypertension or preeclampsia (RR = 1.04, 95% CI 0.86–1.25; P=.70) and gestational diabetes mellitus (RR = 1.13, 95% CI 0.78–1.65; P=.51), without the evidence of heterogeneity (all $I^2 = 0$) (Table 2).

Placenta previa, placental abruption, and premature rupture of membranes. Four studies (total 4) showed a

TABLE 1

Characteristics of 15 cohort studies of ART and risk of adverse obstetric outcomes in dichorionic twin pregnancies.

First author/ publication year (study period)	Geographic region	Sample source	Study design	ART twins (n)	SC twins (n)	Whether patients who achieved a pregnancy with OI and IUI were included in the SC group?	ART type	Pregnancy-related complications and adverse pregnancy outcomes	Adjusted or matched factors	Grouped by sample size (ART plus SC group)	Quality score[a]
Smithers/2003 (1991–1999)	Australia	Population	Retrospective cohort	1,028	4,134	Yes	IVF	Placenta previa; antepartum hemorrhage; preeclampsia or eclampsia; premature rupture of membranes; cesarean sections; PTB; VPTB; CM	Adjusted for maternal age and parity, except for CM	>2,000	1
Pinborg/2004 (1995–2000)[b]	Denmark	Population	Retrospective cohort	1,650	3,546	Yes	IVF/ICSI	PTB; VPTB; LBW; VLBW; CM; perinatal mortality; NICU admissions	Maternal age and parity	>2,000	1
Kuwata/2004 (1990–2001)	Japan	Clinic	Retrospective cohort	232	188	No	IVF; ICSI	CM	Maternal age	<500	1
Ho/2005 (2002–2003)	Taiwan	Clinic	Retrospective cohort	140	54	No	IVF	PTB; LBW; VLBW; CM; perinatal mortality; SGA; NICU admissions	None	<500	2
Ombelet/2005 (1997–2003)	Belgium	Population	Retrospective cohort	470	907	No	ICSI	PTB; VPTB; LBW; VLBW; CM; perinatal mortality; NRDS; NICU admissions	Parity, maternal age, place of birth, date of birth, and fetal sex	500–2,000	1
Joy/2008 (2002–2003)[b]	UK	Clinic	Retrospective cohort	76	170	No	IVF/ICSI	LBW; CM	None	<500	2
Zhang/2008 (1998–2005)	China	Clinic	Retrospective cohort	86	150	No	IVF	Premature rupture of membrane; placenta previa; postpartum hemorrhage; preeclampsia or eclampsia; PTB; LBW; CM; perinatal mortality	None	<500	2

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TABLE 1

Continued.

First author/ publication year (study period)	Geographic region	Sample source	Study design	ART twins (n)	SC twins (n)	Whether patients who achieved a pregnancy with OI and IUI were included in the SC group?	ART type	Pregnancy-related complications and adverse pregnancy outcomes	Adjusted or matched factors	Grouped by sample size (ART plus SC group)	Quality score[a]
Vasario/2010 (2004–2008)	Italy	Clinic	Prospective cohort	168	278	No	IVF	Pregnancy-induced hypertension; gestational diabetes mellitus; placenta previa; postpartum hemorrhage; premature rupture of membrane; PTB; VPTB; CM; perinatal mortality; NRDS; cesarean sections; IUGR; NICU admissions	Maternal age and parity	<500	1
Yang/2011 (1995–2008)	South Korea	Clinic	Retrospective cohort	134	286	No	IVF	Preeclampsia or eclampsia; premature rupture of membrane; placenta previa; placental abruption; PTB; VPTB; LBW; VLBW; CM; SGA; perinatal mortality; NICU admissions	Maternal age and parity	<500	1
Hansen/2012 (1994–2002)[b]	Australia	Population	Retrospective cohort	939	1,619	Yes	IVF/ICSI	Perinatal mortality; PTB; VPTB; LBW; VLBW; CM	Maternal age, parity, and date of fetal birth	>2,000	1

Qin. Adverse outcomes in assisted twin pregnancies. Fertil Steril 2016.

TABLE 1

Continued.

First author/ publication year (study period)	Geographic region	Sample source	Study design	ART twins (n)	SC twins (n)	Whether patients who achieved a pregnancy with OI and IUI were included in the SC group?	ART type	Pregnancy-related complications and adverse pregnancy outcomes	Adjusted or matched factors	Grouped by sample size (ART plus SC group)	Quality score[a]
Moini/2012 (2008–2010)[b]	Iran	Clinic	Prospective cohort	460	340	No	IVF/ICSI	Pregnancy-induced hypertension; gestational diabetes mellitus; placental abruption; oligohydramnion; polyhydramnion; postpartum hemorrhage; premature rupture of membranes; cesarean sections; PTB; VPTB; LBW; VLBW; CM; NRDS; IUGR; perinatal mortality; NICU admissions	Adjust for maternal age and BMI for VPTB, VLBW, perinatal mortality, and NICU admissions	500–2,000	1
Sagot/2012 (2000–2009)	France	Population	Retrospective cohort	168	550	No	IVF	CM	Maternal age and gestational diabetes	500–2,000	1
Hu/2012 (2009–2011)	China	Clinic	Retrospective cohort	175	262	No	IVF	PTB; VPTB; CM; NRDS; SGA; perinatal mortality	Maternal age	<500	1
Egic/2014 (2009–2012)	Serbia	Clinic	Retrospective cohort	352	430	No	IVF	Pregnancy-induced hypertension; gestational diabetes mellitus; PTB; VPTB; cesarean sections; NICU admissions	None	<500	2
Geisler/2014 (2009–2012)[b]	Ireland	Clinic	Retrospective cohort	342	736	No	IVF/ICSI	Pregnancy-induced hypertension; gestational diabetes mellitus; cesarean sections; PTB; VPTB; LBW; VLBW; IUGR; CM; NRDS; perinatal mortality; NICU admissions	Adjusting for maternal age, parity, type of antenatal care for pregnancy-induced hypertension, gestational diabetes mellitus, and cesarean sections	500–2,000	1

Note: ART = assisted reproductive technology; BMI = body mass index; CM = congenital malformations; ICSI = intracytoplasmic sperm injection; IUGR = intrauterine growth restriction; LBW = low birth weight; NICU = neonatal intensive care unit; NRDS = neonatal respiratory distress syndrome; OI = ovulation induction; PTB = preterm birth; SC = spontaneously conceived; SGA = small for gestational age; VLBW = very low birth weight; VPTB = very preterm birth.

[a] Each study was assigned a score of 1–9; 1 = higher quality studies with scores ≥7, 2 = low quality with scores <7.

[b] These articles did not estimate obstetric risks in IVF and ICSI dichorionic twin pregnancies separately.

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TABLE 2

Meta-analysis of association between ART and maternal complications in dichorionic twin pregnancies.

Maternal complication	Studies (n)	Unlike sex twins (n)		Fixed-effects models, RR (95% CI)	Random-effects models, RR (95% CI)	Heterogeneity		
		ART group	SC group			Q	P value	I^2
Pregnancy-induced hypertension or preeclampsia	7	2,570	6,354	1.04 (0.86–1.25)	1.04 (0.86–1.25)	4.72	.58	0
Gestational diabetes mellitus	4	1,322	1,784	1.13 (0.78–1.65)	1.13 (0.78–1.65)	1.40	.71	0
Placenta previa	4	1,416	4,848	2.99 (1.51–5.92)	2.99 (1.51–5.92)	1.25	.74	0
Placental abruption	2	594	626	1.33 (0.30–5.82)	1.33 (0.30–5.82)	0.85	.36	0
Premature rupture of membranes	5	1,876	5,188	1.20 (0.97–1.49)	1.20 (0.97–1.49)	2.89	.58	0
Postpartum hemorrhage	3	714	768	1.08 (0.62–1.87)	1.08 (0.62–1.87)	0.25	.88	0
Cesarean section	5	2,350	5,918	1.24 (1.18–1.31)	1.58 (1.15–2.16)	98.54	< .00001	96%
Elective cesarean section	2	1,370	4,870	1.79 (1.49–2.16)	1.87 (1.37–2.55)	2.50	.11	60%
Emergency cesarean section	2	1,370	4,870	1.64 (1.34–2.01)	1.76 (0.93–3.36)	9.58	.002	90%

Note: ART = assisted reproductive technology; CI = confidence interval; RR = relative risk; SC = spontaneously conceived.

Qin. Adverse outcomes in assisted twin pregnancies. Fertil Steril 2016.

positive relation between ART and risk of placenta previa, only one of which had significant statistical differences. Only two studies (4, 35) reported placental abruption. For premature rupture of membranes, four studies (total 5) showed a positive association between ART and risk of premature rupture of membranes, only one of which had significant statistical differences. Overall, the risk of developing placental abruption (RR = 1.33, 95% CI 0.30–5.82; P=.71) and premature rupture of membranes (RR = 1.20, 95% CI 0.97–1.49; P=.10) was similar in the ART group compared with the reference group, without the evidence of heterogeneity (all I^2 = 0). However, the ART group experienced a significantly increased risk of developing placenta previa (RR = 2.99, 95% CI 1.51–5.92; P=.002), without the evidence of heterogeneity (I^2 = 0) (Table 2).

Antepartum and postpartum hemorrhage. Only one study (31) in which the RR in relation to ART was 1.73 (95% CI 1.05–2.86) reported antepartum hemorrhage. For postpartum hemorrhage, two studies (total 3) showed a positive association between ART and risk of postpartum hemorrhage. Overall, the risk of developing postpartum hemorrhage was similar between the two groups (RR = 1.08, 95% CI 0.62–1.87; P=.79), without the evidence of heterogeneity (I^2 = 0) (Table 2).

Cesarean sections. Three studies (total 5) showed a significantly positive association between ART and risk of cesarean section. Overall, the ART pregnancies were more likely to be delivered by cesarean sections than those conceived naturally (RR = 1.58, 95% CI 1.15–2.16; P=.004), with substantial evidence of heterogeneity (I^2 = 96%). Of note, the ART group compared with the reference group had a higher proportion of elective cesarean sections (RR = 1.79, 95% CI 1.49–2.16; P<.00001), but they had a similar proportion for emergency cesarean sections (RR = 1.76, 95% CI 0.93–3.36; P=.08) (Table 2).

Polyhydramnios and oligohydramnios. Only one study (4) reported polyhydramnios and oligohydramnios, and it did not show that the risk of developing polyhydramnios and oligohydramnios was significantly increased in the ART group compared with the reference group.

ART and Risk of Adverse Pregnancy Outcomes

Preterm birth and very preterm birth. For PTB, four studies (total 12) showed a significantly positive relation between ART and risk of PTB. For VPTB, three studies (total 10) indicated a significantly positive association with ART. Overall, the ART pregnancies had a higher risk of developing PTB (RR = 1.13, 95% CI 1.00–1.29; P=.05) and VPTB (RR = 1.39, 95% CI 1.07–1.82; P=.01) than those conceived spontaneously, with substantial evidence of heterogeneity (I^2 = 75% and 71% for PTB and VPTB, respectively) (Table 3).

Low birth weight and very low birth weight. Of the nine studies reporting LBW, seven showed a positive association with ART, only two of which had significantly statistical differences. For VLBW, only two studies (total 7) hinted at a significantly positive relationship with ART. Overall, the

TABLE 3

Meta-analysis of association between ART and adverse pregnancy outcomes in dichorionic twin pregnancies.

Adverse pregnancy outcomes	Number of studies (n)	The number of unlike sex twins		RR (95% CI) from fixed-effects models	RR (95% CI) from random-effects models	Measure of heterogeneity		
		ART group	SC group			*Q*	*P* value	I^2
Preterm birth	12	5,944	12,742	1.08 (1.02–1.13)	1.13 (1.00–1.29)	43.50	<.00001	75%
Very preterm birth	10	5,718	12,538	1.39 (1.24–1.57)	1.39 (1.07–1.82)	31.44	.0002	71%
Low birth weight	9	4,297	7,808	1.09 (1.03–1.16)	1.11 (1.00–1.23)	20.34	.009	61%
Very low birth weight	7	4,135	7,488	1.28 (1.10–1.50)	1.36 (0.96–1.94)	20.71	.002	71%
Small for gestational age	3	449	602	1.25 (0.91–1.70)	1.25 (0.91–1.70)	1.76	.41	0
Perinatal mortality	10	4,564	8,178	1.60 (1.20–2.13)	1.38 (0.83–2.30)	20.93	.01	57%
Congenital malformations	14	6,068	13,220	1.26 (1.09–1.46)	1.32 (1.07–1.62)	17.63	.17	26%
Intrauterine growth restriction	3	970	1,354	1.08 (0.88–1.34)	1.05 (0.74–1.50)	4.67	.10	57%
NICU admissions	8	3,716	6,577	1.17 (1.07–1.27)	1.15 (0.95–1.40)	22.86	.002	69%
Neonatal respiratory distress syndrome	5	1,615	2,523	1.39 (1.14–1.69)	1.26 (0.91–1.73)	8.22	.08	51%

Note: ART = assisted reproductive technology; CI = confidence interval; NICU = neonatal intensive care unit; RR = relative risk; SC = spontaneously conceived.

Qin. Adverse outcomes in assisted twin pregnancies. Fertil Steril 2016.

ART group compared with the SC group experienced a significantly increased risk of developing LBW (RR = 1.11, 95% CI 1.00–1.23; P=.05), but had a similar risk of developing VLBW (RR = 1.36, 95% CI 0.96–1.94; P=.08), with substantial evidence of heterogeneity (I^2 = 61% and 71% for LBW and VLBW, respectively) (Table 3).

Perinatal mortality. Six studies (total 10) showed a positive relationship with ART, only three of which had significantly statistical differences. Overall, there were no significantly statistical differences for risk of developing perinatal mortality (RR = 1.38, 95% CI 0.83–2.30; P=.21) between the two groups. Substantial heterogeneity was observed (I^2 = 57%) (Table 3).

Congenital malformations. Of the 14 studies reporting CM, 3 showed a significantly positive association with ART. Overall, the ART group compared with the reference group experienced a significantly higher risk of developing CM (RR = 1.26, 95% CI 1.09–1.46; P=.002), without the evidence of heterogeneity (I^2 = 26%) (Table 3).

Small for gestational age, intrauterine growth restriction, and neonatal respiratory distress syndrome. For SGA, two studies (total 3) showed a positive relation between ART and risk of SGA. For IUGR, only one study (total 3) suggested a significantly positive association with ART. For NRDS, two studies (total 5) indicated a significantly positive association with ART. The overall combined RRs in relation to ART were 1.25 (95% CI 0.91–1.70; P=.17) for SGA, 1.08 (95% CI 0.88–1.34; P=.45) for IUGR, and 1.26 (95% CI 0.91–1.73; P=.16) for NRDS. There was no evidence of heterogeneity except for NRDS (I^2 = 51%) (Table 3).

Admission to neonatal intensive care unit. Of the eight studies reporting NICU admission, only three showed a significantly positive association with ART. Overall, the ART group compared with the reference group was at a similar risk for NICU admission (RR = 1.15, 95% CI 0.95–1.40; P=.14), with substantial evidence of heterogeneity (I^2 = 69%) (Table 3).

Subgroup Analysis

Subgroup analysis for adverse obstetric outcomes was summarized in Supplemental Table 1. After subgroup analysis, geographic region, whether the confounding factors were adjusted and/or matched, type of ART, sample sources, and whether patients who achieved a pregnancy with OI and IUI were included in the SC group as the first five of the most relevant heterogeneity moderators have been identified. These differences for risks of developing LBW (test for subgroup differences: $\chi^2 = 13.39$, P=.001; I^2 = 85.1%) and VLBW (test for subgroup differences: χ^2 = 18.48, $P<.0001$; I^2 = 89.2%) in the ART pregnancies were statistically significant between different geographic regions. There was statistically significant difference for the risk of developing CM (test for subgroup differences: χ^2 = 3.94, P=.05; I^2 = 74.6%) in the ART pregnancies for whether the confounding factors were adjusted and/or matched. Also, there was statistically significant difference for the risk of developing perinatal mortality

(test for subgroup differences: $\chi^2 = 5.05$, $P=.02$; $I^2 = 80.2\%$) in the ART pregnancies for type of ART.

Sensitivity Analyses

Sensitivity analyses were conducted to explore potential sources of heterogeneity in the association between ART and adverse obstetric outcomes and to examine the influence of various exclusion criteria on the overall risk estimate. Exclusion of two studies (4, 5) that had a prospective cohort design yielded similar results, and the new combined RRs in relation to ART were 1.02 (95% CI 0.83–1.25; $I^2 = 6\%$) for pregnancy-induced hypertension or preeclampsia; 1.11 (95% CI 0.66–1.87; $I^2 = 0$) for gestational diabetes mellitus; 3.19 (95% CI 1.57–6.48; $I^2 = 0$) for placenta previa; 1.28 (95% CI 0.97–1.68; $I^2 = 16\%$) for premature rupture of membranes; 2.04 (95% CI 1.44–2.89; $I^2 = 89\%$) for cesarean sections; 1.16 (95% CI 1.03–1.30; $I^2 = 65\%$) for PTB; 1.32 (95% CI 1.03–1.69; $I^2 = 69\%$) for VPTB; 1.14 (95% CI 1.02–1.28; $I^2 = 53\%$) for LBW; 1.28 (95% CI 0.88–1.87; $I^2 = 73\%$) for VLBW; 1.32 (95% CI 0.71–2.44; $I^2 = 61\%$) for perinatal mortality; 1.25 (95% CI 1.08–1.45; $I^2 = 37\%$) for CM; 1.09 (95% CI 0.89–1.34; $I^2 = 73\%$) for NICU admission; and 1.14 (95% CI 0.63–2.07; $I^2 = 67\%$) for NRDS.

Further exclusion of 3 studies (21, 31, 36) with a sample size of >2,000 showed a somewhat greater risk of CM (RR = 1.50, 95% CI 1.12–2.01; $I^2 = 34\%$), but showed a somewhat lower risk of pregnancy-induced hypertension or preeclampsia (RR = 0.92, 95% CI 0.72–1.17; $I^2 = 0$), placenta previa (RR = 2.86, 95% CI 0.98–8.36; $I^2 = 0$), premature rupture of membranes (RR = 1.20, 95% CI 0.88–1.65; $I^2 = 0$), cesarean sections (RR = 1.40, 95% CI 1.07–1.84; $I^2 = 94\%$), PTB (RR = 1.09, 95% CI 0.93–1.28; $I^2 = 71\%$), VPTB (RR = 1.35, 95% CI 0.92–2.03; $I^2 = 60\%$), LBW (RR = 1.05, 95% CI 0.97–1.13; $I^2 = 29\%$), VLBW (RR = 1.17, 95% CI 0.88–1.54; $I^2 = 41\%$), perinatal mortality (RR = 1.18, 95% CI 0.58–2.40; $I^2 = 58\%$), and NICU admission (RR = 1.12, 95% CI 0.88–1.42; $I^2 = 69\%$).

Publication Bias

Visual inspection of Begg's funnel plots did not identify substantial asymmetry. The Egger's linear regression test also indicated no evidence of publication bias among studies of ART and adverse obstetric outcomes ($P=.283$ for pregnancy-induced hypertension or preeclampsia; .507 for PTB, .229 for VPTB; .260 for LBW; .411 for VLBW; .124 for perinatal mortality; .293 for CM; and .658 for NICU admissions).

DISCUSSION

During the past decades, ART has been transformed from a miracle to a standard and common part of medical practice. Although the initial skepticism surrounding ART has greatly waned, the perinatal outcome remains the focus of continuing critical scrutiny from the medical world and the public at large. We have observed the inconsistent findings from published studies on twin pregnancy outcomes obtained by ART and spontaneous conception. In most studies, however, the concrete chorionicity, regarded as an intermediate that modifies the relation between ART and pregnancy outcomes in twin pregnancies, has not been determined. Our meta-analysis, which included 15 cohort studies and involved 6,420 dichorionic twins resulting from ART and 13,650 dichorionic twins conceived naturally, is to verify whether dichorionic twin pregnancies after ART have a higher risk of adverse obstetric outcomes compared with those conceived naturally by complete and systematic literature search. To get homogeneous observations, monochorionic twin pregnancies and triplet pregnancies were excluded. It was possible to identify potential heterogeneity moderators by subgroup and sensitivity analyses. Our findings 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 the present study suggested that most maternal complications, such as pregnancy-induced hypertension or preeclampsia, gestational diabetes mellitus, placental abruption, premature rupture of membranes, and postpartum hemorrhage, were similar in the two groups, but placenta previa was significantly more common in the ART group. For neonatal outcomes, our study indicated that the risk of PTB, VPTB, LBW, and CM in the ART group was markedly increased by 15%, 39%, 11%, and 26%, respectively. The ART pregnancies were more likely to be delivered by cesarean sections than those conceived naturally. Of note, the ART group compared with the reference group had a higher proportion of elective cesarean sections, but had a similar proportion for emergency cesarean sections. When data were restricted to matched and/or adjusted studies, the risk of PTB, perinatal mortality, and CM increased further. In addition, the risk of PTB, LBW, perinatal mortality, and CM increased further when data were restricted to population-based studies or those with high quality. However, these results have to be viewed with caution because of some evidence of heterogeneity (I^2 range, 0–96%). These findings require confirmation when more data from larger multiple studies become available, because 53% of the studies included in this subgroup analysis had a small sample size (<500).

Following the worldwide introduction of ART, critical concern about the incidence of adverse obstetric outcomes prompted studies addressing this issue. At present, a public belief still holds that maternal and neonatal outcome of ART pregnancies is substantially worse compared with those created naturally (16, 41). This belief can be explained partly by the higher rate multiple pregnancies, which in turn is associated with a higher rate of perinatal mortality and morbidity (11, 12). It is already very clear that compared with SC pregnancies, ART leads to more multiple pregnancies, most of which are twin pregnancies (8, 12). It is worth noting that previous studies generally considered ART singleton pregnancies as having a higher risk of poor obstetric outcomes, such as antepartum hemorrhage, pregnancy-induced hypertension, premature rupture of membranes, gestational diabetes mellitus, PTB, LBW, CM, perinatal mortality, and SGA, than SC singleton pregnancies, which has been confirmed by several meta-analysis (13–17).

It is not yet clear, however, whether twin pregnancies resulting from ART must be considered at higher obstetric risk than those conceived naturally. Although the past few years have seen a rapidly growing interest in testing this hypothesis, studies comparing maternal and neonatal outcomes of ART and SC twin pregnancies have reported conflicting results. Most of studies reported comparable maternal outcomes for ART and SC twin pregnancies (4, 5, 19, 48, 49), whereas some (50–52) reported that maternal complications, such as gestational diabetes mellitus, pregnancy-induced hypertension, placenta previa, premature rupture of membranes, and anemia during pregnancy, were significantly more common in ART twin pregnancies. In terms of neonatal outcomes, some studies (21, 30, 36, 53, 54) have showed that ART twin pregnancies were at greater risk of LBW, PTB, CM, NRDS, and perinatal mortality; some other studies (5, 18, 19, 50, 55) did not accept these findings and reported that ART twin pregnancies compared with those conceived naturally had similar neonatal outcomes. Even some reports (4, 27, 56) have suggested better neonatal outcomes after ART. Accordingly, there had been contradictory results for twin pregnancies according to the conception methods, which may be due to differences in the study population, management methods of twin pregnancies, and especially whether or not monochorionicity was considered as a risk factor for adverse outcomes.

Monochorionic twins constitute up to one-third of all twin gestations (57). With the expansion of ART, there has been an increase in the incidence of monozygotic twinning (58, 59). Nevertheless, it has been reported that the occurrence of monozygotic twinning among ART pregnancies is still rare compare with among SC pregnancies (4, 5). Compared with dichorionic twins, monochorionic twins are at an increased risk for perinatal morbidity, because of their shared placenta, including growth discordance, twin-to-twin transfusion syndrome, fetal loss before 24 weeks of gestation, prematurity, neurological deficits, and perinatal death (21, 29, 30). Therefore, the chorionicity should be regarded as an intermediate for predicting the perinatal outcomes of twin pregnancies. The importance of the present study was that we only analyzed dichorionic twin pregnancies to avoid possible adverse effects of monochorionicity itself.

Although several studies (4, 5, 11, 20, 21,31–40) have been performed to address whether dichorionic twin pregnancies after ART have greater risk of adverse outcomes compared with those conceived naturally, their results are often inconsistent. For maternal complications, most studies (4, 5, 35, 39, 40) obtained similar outcomes for ART and SC dichorionic twin pregnancies. In contrast, some studies reported a higher risk of placenta previa (31), premature rupture of membranes (34), and antepartum hemorrhage (31) in dichorionic twin pregnancies after ART. Regarding neonatal outcomes, some studies reported PTB (11, 31, 34, 36), VPTB (4, 36, 40), LBW (11, 36), VLBW (4, 36, 40), perinatal mortality (4, 11, 36), CM (32, 37, 38), IUGR (4), NRDS (4, 40), and NICU admission (4, 21, 39) were significantly more common in dichorionic twin pregnancies resulting from ART. Other studies (5, 20, 33, 35) reported similar neonatal outcomes between the two groups. Considering that most of these studies had a small sample size, the present study was able to increase the sample size by collecting published cohort studies to enhance statistical power, which will help to find a statistically significant difference, especially for risk of rare outcomes. Recently we have published a meta-analysis (41) to compare obstetric risks of twin pregnancies from ART versus spontaneous conception and found that ART twin pregnancies were associated with a higher risk of premature rupture of membranes, pregnancy-induced hypertension, gestational diabetes mellitus, PTB, VPTB, LBW, VLBW, and CM. However, at that time, we did not analyze the impact of chorionicity on adverse outcomes. Up to now, to our knowledge, there is only one meta-analysis (60) that has took the effect of chorionicity on adverse outcomes into account when assessing obstetric risks of twin pregnancies after ART. Of note, that review (60) did not focus on other adverse outcomes except for CM, and it did not find statistically significant difference for risk of CM. Different from that review (60), the present study had a stronger statistical power and indicated that dichorionic twin pregnancies after ART had a significantly increased risk of CM compared with those conceived naturally.

Substantial heterogeneity was observed among studies of ART and obstetric risks in dichorionic twin pregnancies, which was not surprising given the differences in study population and management methods of twin pregnancies. In our review, subgroup analysis was used to explore heterogeneity sources. Our subgroup analyses have identified main heterogeneity moderators including geographic region, whether the confounding factors were adjusted and/or matched, type of ART, sample sources, and whether patients who achieved a pregnancy with OI and IUI were included in the SC group. Previous studies (4, 5, 27, 54) showed that differences in the obstetric management of twin pregnancies, 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 region, which may lead to substantial heterogeneity. In addition, the pregnancies occurring after OI and IUI have been reported to more frequently have poorer outcomes (37, 55, 61). Therefore, if the SC category included patients who achieved a pregnancy with OI and IUI, the SC pregnancies had an increased incidence of adverse outcomes. Our study has confirmed that hypothesis. When data were restricted to studies that did not include these patients in the SC group, the risk of CM was increased further.

There are several limitations in our study. First, more than half of the studies included in the present review had a small sample size, which implies that our findings require confirmation when more data from larger multiple studies become available. Second, most of included studies belonged to retrospective cohort design. Thereby, the retrospective nature of data collection and incomplete data on the specific reason for the iatrogenic deliveries should be considered as a limitation. Third, there was substantial heterogeneity among studies for association between ART and obstetric risks in dichorionic twin pregnancies. Nevertheless, we were able to detect the major source of heterogeneity through the

subgroup analysis and the sensitivity analysis. The sensitivity analysis yielded consistent results. After subgroup analysis, the heterogeneity was decreased. However, our estimates have to be viewed with caution because of heterogeneity. Fourth, a number of the outcomes, especially for maternal complications, relied on between 2 and 7 of the 15 total studies, therefore more studies should be included in future reviews to provide further support for our results. Fifth, residual confounding is of concern. Uncontrolled or unmeasured risk factors potentially produce biases. In our review, four studies (26.7%) did not adjust and/or match any factors when estimating the effect of ART on obstetric outcomes in dichorionic twin pregnancies, whereas other studies at least adjusted and/or matched for maternal age. Although restricting analysis to matched and/or adjusted data did not materially alter the combined risk estimate, we still cannot rule out the possibility that residual confounding, such as obstetric management of twin pregnancies, smoking during pregnancy, obesity, and pregnancy intention, could affect the results, because these factors do not explain all of the obstetric risk. Finally, because the present review only included studies published in Chinese or English language, additional research in other populations is warranted to generalize the findings.

In conclusion, the present study represents, to our knowledge, the first meta-analysis that comprehensively assessed obstetric outcomes of dichorionic twin pregnancies after ART. Our study aimed at addressing whether dichorionic twin pregnancies after ART have higher risk of adverse outcomes compared with those conceived naturally by complete and systematic literature search. Although the role of potential bias and evidence of heterogeneity should be carefully evaluated, finding from our study indicated that the risks of placenta previa, PTB, VPTB, LBW, and CM were significantly higher in dichorionic twin pregnancies after ART. In addition, the ART group was more likely to be delivered by cesarean section, especially by elective cesarean sections. A priority in the management of twin pregnancy should be accurate prediction and early detection of these complications, which may offer the opportunity for timely intervention and improved outcomes. Further well-designed and large population studies on ART and SC dichorionic twin pregnancies are needed to confirm these results.

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