

Pregnancy-related complications and adverse pregnancy outcomes in multiple pregnancies resulting from assisted reproductive technology: a meta-analysis of cohort studies

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Objective: To provide an up-to-date comparison of pregnancy-related complications and adverse pregnancy outcomes of multiple pregnancies generated with assisted reproductive technology (ART) vs. spontaneous conception.

Design: Meta-analysis.

Setting: University-affiliated teaching hospital.

Patient(s): Multiple pregnancies conceived by ART or naturally.

Intervention(s): Searches through October 2014 were conducted on PubMed, Google Scholar, Cochrane Libraries, China Biology Medicine disc, Chinese Scientific Journals Fulltext Database, China National Knowledge Infrastructure, and Wanfang Data, to identify studies that met prestated 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): Thirty-nine cohort studies involving 146,008 multiple births were included in the meta-analysis. Multiple pregnancies from ART were associated with a higher risk of premature rupture of membranes (relative risk [RR] = 1.20, 95% confidence interval [CI]: 1.05–1.37; $I^2 = 15\%$); pregnancy-induced hypertension (RR = 1.11, 95% CI: 1.04–1.19; $I^2 = 6\%$); gestational diabetes mellitus (RR = 1.78, 95% CI: 1.25–2.55; $I^2 = 42\%$); preterm birth (RR = 1.08, 95% CI: 1.03–1.14; $I^2 = 83\%$); very preterm birth (RR = 1.18, 95% CI: 1.04–1.34; $I^2 = 79\%$); low birth weight (RR = 1.04, 95% CI: 1.01–1.07; $I^2 = 47\%$); very low birth weight (RR = 1.13, 95% CI: 1.01–1.25; $I^2 = 62\%$); and congenital malformation (RR = 1.11, 95% CI: 1.02–1.22; $I^2 = 30\%$). The relevant heterogeneity moderators have been identified by subgroup analysis. Sensitivity analysis yielded similar results. No evidence of publication bias was observed.

Conclusion(s): Although the role of potential bias and evidence of heterogeneity should be carefully evaluated, the present study suggests that multiple pregnancies generated via ART, vs. spontaneous conception, are associated with higher risks of pregnancy-related complications and adverse pregnancy outcomes. Further research is needed to determine which aspect of ART poses the most risk and how this risk can be minimized. (Fertil Steril® 2015;103: 1492–508. ©2015 by American Society for Reproductive Medicine.)

Key Words: Assisted reproductive technology, in vitro fertilization, intracytoplasmic sperm injection, adverse pregnancy outcomes, meta-analysis

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During the past 36 years, assisted reproductive technology (ART) has been transformed from a miracle to a standard and common part of medical practice. Over 200,000 babies are born worldwide each year via ART (1, 2), and to date, approximately 5 million in all (3). One of the consequences of the increasing popularity of ART is the progressive rise in the incidence of twin, triplet, and multiple pregnancies because of increased requests for the transfer of 2 or 3 embryos to achieve a higher pregnancy rate (4). This increase has occurred despite efforts aimed at limiting the incidence of multiple pregnancies after ART (e.g., using single embryo transfer [ET]). The transfer of ≥ 2 embryos, even in relatively young women, is particularly common where in vitro fertilization (IVF) treatments are quite expensive and couples wish to maximize their chances of achieving a pregnancy (5).

The final effect is reflected by data showing that 21.8% of all deliveries after ART occur in pregnancies with >1 fetus (6). In some countries, this proportion may be higher. For example, in 2000, of the 31,582 US births via ART reported, 44.5% were twins, 9.3% were triplets, and 0.6% were higher-order multiples (7). A large European registry reported 26.3% multiples after IVF and intracytoplasmic sperm injection (ICSI) (8). Although the initial skepticism surrounding ART has greatly waned, the perinatal outcome remains the focus of continuing critical scrutiny from both the medical world and the public at large.

Obstetric risks are well known to be more frequent in multiple (\geq twin) pregnancies than in singleton pregnancies (4, 9–11). Additionally, consistent evidence from meta-analyses (12, 13) has shown that ART singletons are associated with higher risks of poor perinatal outcomes, compared with spontaneously conceived (SC) singletons. However, whether multiple pregnancies after ART must be considered to be at higher obstetric risk than SC ones is still unclear. Although the past few years have seen a rapidly growing interest in addressing this issue, study results are often inconsistent.

Most studies comparing ART and SC twin pregnancies reported similar perinatal outcomes (5, 14–19); some studies reported a higher risk of poor perinatal outcomes for ART twins (4, 20–23); others found better perinatal outcomes after ART (24, 25). Ten years ago, 2 meta-analyses (26, 27), including case-control studies, addressed the issue and found conflicting results, particularly regarding incidence of preterm delivery and perinatal mortality. Case-control studies are prone to recall and selection biases, which limit the strength and quality of such evidence.

Many subsequent, prospective, cohort studies (5, 21, 24, 28) have yielded mixed results, with most showing a weak or null association between ART and obstetric risk in multiple pregnancies. Recently, several studies (4, 29–34) have observed a significantly positive association between the 2. Given the inconsistency of the existing literatures and the insufficient statistical power of primary studies, we conducted a meta-analysis of cohort studies to provide an up-to-date comparison of pregnancy-related complications and adverse pregnancy outcomes of the multiple pregnancies resulting from IVF and/or ICSI vs. spontaneous conceptions.

METHODS

Literature Search

Unrestricted searches were conducted, with an end-date parameter of 2014, of PubMed, Google Scholar, Cochrane Libraries, China Biology Medicine disc (CBMdisc), Chinese Scientific Journals Fulltext Database (CQVIP), China National Knowledge Infrastructure (CNKI), and Wanfang Data, to identify studies that assessed outcomes of multiple pregnancies generated via ART. The following search terms were used: 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, and birth defect. We reviewed references in seminal papers, review articles, and medical textbooks. The grey literature and conference abstracts were not searched.

We did not contact authors of the primary studies for additional information. We performed a meta-analysis that accorded with MOOSE (meta-analysis of observational studies in epidemiology) guidelines (35). The current study was approved by the Institutional Review Board of Maternal and Child Health Hospital of Hunan Province.

Outcome Measures

The outcomes of interest were pregnancy-related complications and adverse pregnancy outcomes. The complications involved were antepartum hemorrhage, postpartum hemorrhage, placenta previa, placental abruption, premature rupture of membranes, pregnancy-induced hypertension, gestational diabetes mellitus, anemia during pregnancy, oligohydramnios, and polyhydramnios. 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); neonatal respiratory distress syndrome (NRDS); and intrauterine growth restriction. Because of variations in the definition of outcome measures across countries and cultures, defining uniform standards is extremely difficult. The early literature did not always define birth outcomes, and in such cases, we relied on the outcome terminology in the original papers.

Selection Criteria

Studies were considered to have met eligibility criteria if they: (1) were published in Chinese or English; (2) had a prospective or retrospective cohort design; (3) compared obstetric risk of ART multiple pregnancies with those conceived naturally; (4) had use of IVF and/or ICSI as the exposure of interest; (5) had as outcomes of interest pregnancy-related complications and adverse pregnancy outcomes; and (6) reported

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