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ORIGINAL ARTICLE: ASSISTED REPRODUCTION

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

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Key Words: In vitro fertilization, intracytoplasmic sperm injection, neonatal outcomes, obstetric outcomes, dichorionic twins



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- Received October 15, 2015; revised December 15, 2015; accepted December 22, 2015.
 J.B.Q. has nothing to disclose. H.W. has nothing to disclose. X.S. has nothing to disclose. Q.X. has nothing to disclose. S.G. has nothing to disclose.
 J.B.Q. was supported by the Project Funded by China Postdoctoral Science Foundation (2015M572248) and Hunan Provincial Science and Technology Plan Project (2015R54055).
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 Fertility and Sterility@ Vol. ■, No. ■, 2016 0015-0282/\$36.00
 Copyright ©2016 American Society for Reproductive Medicine, Published by Elsevier Inc. http://dx.doi.org/10.1016/j.fertnstert.2015.12.131

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n 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).

136 The increased rate of twins born as a result of ART is "the 137 most serious complication" of ART treatment (8). It is well 138 documented that twin pregnancies (either monochorionic or 139 dichorionic) have a poorer maternal and neonatal outcomes 140 than singleton pregnancies (9, 10), with higher rates of 141 perinatal morbidity and mortality (11, 12). In addition, 142 consistent evidence from meta-analyses (13-17) has shown 143 that singleton pregnancies after ART are at greater risk of 144 adverse obstetric outcomes than those conceived naturally. 145 However, data are conflicting on the outcomes of ART twin 146 pregnancies compared with spontaneously conceived (SC) 147 twin pregnancies. Most studies comparing ART and SC twin 148 pregnancies reported similar perinatal outcomes (5, 18-23). 149 Some studies (4, 11, 24-26) reported a higher risk of poor 150 perinatal outcomes for ART twins. Even other studies 151 (27, 28) found better perinatal outcomes after ART. 152 Differences in the study population and management 153 methods of twin pregnancies, and especially whether or not 154 monochorionicity was considered as a risk factor for 155 adverse outcomes, are the main reasons for the inconsistent 156 findings.

157 It is well known that the occurrence of monochorionicity 158 among twin pregnancies after ART is quite rare compared 159 with SC twin pregnancies (about 2% vs. 22%, respectively), 160 and monochorionic pregnancies have worse perinatal out-161 comes (21, 29, 30). Theoretically, the lower proportion of 162 monochorionic twins in pregnancies from ART may 163 somewhat offset the adverse effect of ART in twins. 164 Therefore the chorionicity should be considered as an 165 intermediate that modifies the relation between ART and 166 adverse obstetric outcomes in twin pregnancies. Although 167 several studies (4, 5, 11, 20, 21, 31-40) have been 168 performed to address whether dichorionic twin pregnancies 169 after ART have greater risk of adverse outcomes compared 170 with those conceived naturally, their results are often 171 inconsistent. Not long ago, we have performed a meta-172 analysis to compare obstetric risks of twin pregnancies from 173 ART versus spontaneous conception (41). However, at that 174 time, we did not take chorionicity into account when evalu-175 ating the relation between ART and poor outcomes. The pre-176 sent study aimed at examining whether dichorionic twin 177 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 metaanalysis.

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 pregnancyinduced 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

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