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

Jiabi Qin, M.D., Ph.D.,[a,b] Xiaoying Liu, M.D.,[b] Xiaoqi Sheng, M.D.,[a] Hua Wang, M.D.,[a] and Shiyou Gao, M.D.[c]

[a] Division of Medical Genetics, Maternal and Child Health Hospital of Hunan Province; [b] Department of Epidemiology and Health Statistics, School of Public Health, Central South University; and [c] Reproductive Center, Maternal and Child Health Hospital of Hunan Province, Hunan, People's Republic of China

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

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/qinj-art-singleton-pregnancy-complications/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Received June 12, 2015; revised September 5, 2015; accepted September 9, 2015; published online October 9, 2015.
J.Q. has nothing to disclose. X.L. has nothing to disclose. X.S. has nothing to disclose. H.W. has nothing to disclose. S.G. has nothing to disclose.
J.Q. was supported by the Project Funded by China Postdoctoral Science Foundation (2015M572248) and Hunan Provincial Science and Technology Plan Project (2015RS4055). The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.
J.Q. and X.L. should be considered similar in author order.
Reprint requests: Jiabi Qin, M.D., Ph.D., Maternal and Child Health Hospital of Hunan Province, Division of Medical Genetics, 53 Xiangchun Road, Changsha, Hunan 410008, People's Republic of China (E-mail: qinjiabi123@hotmail.com).

Fertility and Sterility® Vol. 105, No. 1, January 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.09.007

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;