GYNECOLOGY

Oocyte donation pregnancies and the risk of preeclampsia or gestational hypertension: a systematic review and metaanalysis

Pourya Masoudian, BHSc; Ahmed Nasr, MD, MSc; Joseph de Nanassy, MD; Karen Fung-Kee-Fung, MD, MHPE; Shannon A. Bainbridge, PhD; Dina El Demellawy, MD, PhD

The purpose of this study was to determine whether pregnancies that were achieved via oocyte donation, compared with pregnancies achieved via other assisted reproductive technology methods or natural conception, demonstrate increased risk of preeclampsia or gestational hypertension. Comparative studies of pregnancies that were achieved with oocyte donation vs other methods of assisted reproductive technology or natural conception with preeclampsia or gestational hypertension were included as 1 of the measured outcomes. Abstracts and unpublished studies were excluded. Two reviewers independently selected studies, which were assessed for quality with the use of methodological index for non-randomized studies, and extracted the data. Statistical analysis was conducted. Of the 523 studies that were reviewed initially, 19 comparative studies met the predefined inclusion and exclusion criteria and were included in the metaanalysis, which allowed for analysis of a total of 86,515 pregnancies. Our pooled data demonstrated that the risk of preeclampsia is higher in oocyte-donation pregnancies compared with other methods of assisted reproductive technology (odds ratio, 2.54; 95% confidence interval, 1.98—3.24; $P < .0001$) or natural conception (odds ratio, 4.34; 95% confidence interval, 3.10—6.06; $P < .0001$). The risk of gestational hypertension was also increased significantly in oocyte donation pregnancies in comparison with other methods of assisted reproductive technology (odds ratio, 3.00; 95% confidence interval, 2.44—3.70; $P < .0001$) or natural conception (odds ratio, 7.94; 95% confidence interval, 1.73—36.36; $P = .008$). Subgroup analysis that was conducted for singleton and multiple gestations demonstrated a similar risk for preeclampsia and gestational hypertension in both singleton and multiple gestations. This metaanalysis provides further evidence that supports that egg donation increases the risk of preeclampsia and gestational hypertension compared with other assisted reproductive technology methods or natural conception.

Key words: gestational hypertension, oocyte donation, preeclampsia

Introduced for the first time in the early 1980s, oocyte donation enables women with diminished ovarian reserve, premature ovarian failure, genetic disorders, and surgical menopause to become pregnant.[1-3] In 2012, there were approximately 20,000 attempts at pregnancy with the use of oocyte donation in the United States.[4] This number has been increasing over the past decade.[5] However, several adverse pregnancy outcomes have been correlated with pregnancies that were achieved after successful oocyte transfer compared with other conception methods, such as first-trimester bleeding, preterm birth, low birthweight, and intrauterine growth restriction.[6-9] Hypertensive disorders, such as preeclampsia and gestational hypertension, are other important examples of such complications that usually occur after the 20 weeks of gestation.[7-9]

Hypertensive disorders during pregnancy affect 5—10% of all pregnancies in the United States[10]; gestational hypertension is the most common cause of hypertension in pregnancy. Approximately 15% of gestational hypertension cases proceed to chronic hypertension after pregnancy,[11] and 10—50% of patients who initially are diagnosed with gestational hypertension will be diagnosed with preeclampsia in 1—5 weeks after the diagnosis.[12,13] Pregnancy outcomes of mild gestational hypertension are similar to those of the general obstetrics population.[13,14] However, severe gestational hypertension and preeclampsia are significant causes of maternal deaths each year, along with significant fetal morbidities worldwide.[15-17]

Observations of gestational hypertensive complications among oocyte donation pregnancies were first reported in the late 1980s.[18] However, conclusive evidence for association remains a challenge to substantiate because of intrinsic confounding variables within this patient population. Gestational hypertensive disorders are associated independently with inherent characteristics

From the Departments of Pediatric Pathology (Drs de Nanassy and El Demellawy and Mr Masoudian) and Pediatric Surgery (Dr Nasr), Children's Hospital of Eastern Ontario, Faculty of Medicine; the Department of Obstetrics and Gynecology (Dr Fung-Kee-Fung), The Ottawa Hospital, Faculty of Medicine; and the Faculty of Health Sciences (Dr Bainbridge), University of Ottawa, Ottawa, Ontario, Canada.

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Corresponding author: Dina El Demellawy MD PhD FRCPC. deldemellawy@cheo.on.ca

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of the recipients of oocyte donation, such as advanced maternal age, primiparity, primary cause of infertility (eg, maternal obesity), and ensuing multiple gestations.[19-25] This is especially a concern when several comparative studies have made little attempt to match for these variables across study populations or adjust for them in their subsequent analysis.

A previous metaanalysis was done to encompass studies that were published before 2010 without any subgroup analyses to control for the confounders.[26] In the past 5 years, there have been many more published studies that investigate the occurrence of hypertensive disorders in oocyte donation pregnancies. Therefore, our objective was to conduct a systematic review and metaanalysis of the existing literature to determine whether the risk of preeclampsia or gestational hypertension was increased in pregnancies that were achieved via oocyte donation, compared with other assisted reproductive technology (ART) methods or natural conception.

Methods

This metaanalysis was conducted according to the Metaanalysis of Observational Studies in Epidemiology guidelines.[27]

Literature search

A literature search was done by the investigators in PubMed, MEDLINE, Embase, and CENTRAL from January 1989 to July 15, 2015. In addition, Google, Google Scholar, and references of selected articles were used to identify other studies. We used the following keywords: preeclampsia, pregnancy-induced hypertension, gestational hypertension, pregnancy complication, egg, oocyte, ovum, donation, and donor.

Eligibility criteria

We included comparative studies that described pregnancies that were achieved through oocyte donation with the subsequent generation of preeclampsia or gestational hypertension as an outcome and compared them with pregnancies that were achieved through other methods of ART or natural conception. *Gestational hypertension* is defined as a new-onset elevated blood pressure (mild, ≥140/90 mm Hg; severe, ≥160/110 mm Hg) after 20 weeks of gestation without proteinuria or end-organ failure.[28] Before 2013, preeclampsia was diagnosed when gestational hypertension was accompanied by proteinuria (≥0.3 g/24 h).[29] In 2013, the American College of Obstetricians and Gynecologists (ACOG) replaced proteinuria as a necessary criterion for preeclampsia diagnosis with signs and symptoms of end-organ injuries.[28] The definitions of *preeclampsia* and *gestational hypertension* that were used for inclusion were based on the regional standards and guidelines in place at the time of each study.

Comorbidities (such as, gestational diabetes mellitus, HELLP (hemolysis, elevated liver enzymes, and low platelet count syndrome), morbid obesity, preterm labor, and multiple gestations) were not exclusion criteria. Abstracts, reviews, case studies, editorials, and noncomparative primary studies were excluded. The studies that had nonspecific "hypertensive disorders" as their outcome were also excluded. No language restrictions were applied.

Quality assessment

The Methodological Index for Non-Randomized Studies (MINORS)[30] was used to assess the quality of nonrandomized studies. This framework consists of 12 items that evaluate a study's validity, methods, and completeness of reporting elements. In the MINORS criteria, a comparative study is assigned a score of 0−2 for each of the 12 items included, for a maximum score of 24. Higher scores are indicative of greater methodologic quality.

Two investigators assessed each study independently and compared their scores afterwards to reach a consensus. If an agreement could not be reached, a third investigator was consulted.

Data extraction

The data from oocyte donation pregnancies, which lasted at least until week 20 of gestation, along with the control group, were extracted in a 2 × 2 contingency table. The data for nonoocyte donation ART (such as, in vitro fertilization, intracytoplasmic sperm injection, and insemination) were collected under the ART label. The data on spontaneous conception groups who did not use any type of assisted reproduction were collected separately under the natural conception label. Another investigator confirmed the extracted data independently. Disagreements were resolved by consulting a third investigator.

Data synthesis

Studies were classified into 4 groups based on their outcomes and control groups: (1) preeclampsia as the outcome and other methods of ART as the control, (2) preeclampsia as the outcome and natural conception as the control, (3) gestational hypertension as the outcome and other ART methods as the control, and (4) gestational hypertension as the outcome and natural conception as the control. It was possible for a study to be assigned to >1 group depending on whether they included both preeclampsia and gestational hypertension as the outcome or both ART and natural conception as the control.

Metaanalysis was performed with Review Manager software (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The Mantel-Haenszel model was used to analyze the dichotomous variables to produce an odds ratio (OR) for each outcome with a 95% confidence interval (CI). For each outcome, the heterogeneity of the study was assessed with the use of Chi^2 test and I^2 statistics. When no degree of heterogeneity was detected ($I^2 = 0\%$), we used a fixed-effects model. When some degree of heterogeneity was present ($I^2 > 0\%$), we used a random-effects model. Funnel plot analysis was used to assess publication bias by plotting ORs against standard errors.

Results

Study characteristics

The conducted search identified 523 studies for initial review, of which 19 were deemed to meet preidentified inclusion and exclusion criteria (Figure 1).[7-9,31-46] There were no randomized control trials found. From the 19 selected studies,