OBSTETRICS

The 'immunologic theory' of preeclampsia revisited: a lesson from donor oocyte gestations

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OBJECTIVE: To determine the prevalence of placental complications in patients conceived through donor versus autologous oocytes.

STUDY DESIGN: A retrospective cohort study including 2 groups of patients who conceived through in vitro fertilization using: (1) donor oocyte (n = 139) and (2) autologous oocyte (n = 126). Only singleton gestations were included. The rate of placental complications including preeclampsia, gestational hypertension, and intrauterine growth restriction was compared between these 2 groups.

RESULTS: The women who conceived using donor oocytes were older compared with women who conceived using autologous oocytes (median maternal age 45 vs 41, $P < .01$). The rate of hypertensive diseases of pregnancy including gestational hypertension and preeclampsia was significantly higher in ovum donor recipients compared with women conceived with autologous oocytes (25% vs 10%, $P < .01$). Similarly, the rate of intrauterine growth restriction was also higher among patients conceived through oocyte donation although it did not reach statistical significance (9.3% vs 4%, $P = .08$). When maternal age was restricted to ≤45 years, the rate of hypertensive diseases of pregnancy remained significantly higher among ovum donor compared with autologous oocyte recipients (22% vs 10%, $P = .02$). Adjustment for maternal age, gravidity, parity, and chronic hypertension revealed that oocyte donation was independently associated with higher rate of hypertensive diseases of pregnancy ($P = .01$).

CONCLUSION: Patients conceived through oocyte donation have an increased risk for placental complications of pregnancy. These findings support the 'immunologic theory' suggesting that immunologic intolerance between the mother and the fetus may play an important role in the pathogenesis of preeclampsia.

Key words: donor oocyte, obstetric outcome, preeclampsia, pregnancy induced hypertension

Cite this article as: Levron Y, Dviri M, Segol I, et al. The 'immunologic theory' of preeclampsia revisited: a lesson from donor oocyte gestations. Am J Obstet Gynecol 2014;210:x-ex-x-ex.

Preeclampsia complicates 3-5% of pregnancies and is one of the worldwide leading causes of maternal and neonatal morbidity and mortality.[1-7] Despite the considerable morbidity and mortality associated with this condition, the cause of preeclampsia has remained unknown. It is generally agreed, that the placenta plays a major role in the pathogenesis of preeclampsia, as delivery of the placenta results in resolution of the condition.[2,8] Normal placentation requires development of immune tolerance between the fetus and the mother. It has been postulated that preeclampsia may result from an abnormal maternal immune response to novel paternally derived fetal antigens.[2,9-11] Preeclampsia is more common in first pregnancies, after a change in paternity or prolonged interval between pregnancies and among women using barrier contraceptives.[12-14] In addition, women who conceived via surgically obtained sperm and were never exposed to their partner's sperm had a 3-fold increased risk of preeclampsia compared with women who were exposed to their partner's sperm.[15] The aforementioned observations support the hypothesis that maternal immunological intolerance plays a key factor in the pathogenesis of preeclampsia.

Ovum donor recipients can serve as a unique model to examine the immunologic theory because of the completely different genetic makeup of the mother and the developing fetus. Previous studies have demonstrated inconsistent outcomes when comparing obstetric complications between women undergoing in vitro fertilization (IVF) with and without ovum donation, which may result from the relatively small sample size and inappropriate control groups.[16-18] Moreover, the increased prevalence of obstetric complications in ovum donor pregnancies may be attributed, in part, to several confounding factors such as advance maternal age, which characterizes most of the oocyte recipients, as well as the IVF itself, because assisted reproductive technology alone has been associated with increased risk of pregnancy complications.[19,20] Therefore, it is still uncertain whether the use of donor oocytes by itself increases the risk of placental complications such as gestational hypertension, preeclampsia, and intrauterine growth restriction (IUGR).

Prompted by the aforementioned observations we aimed to determine whether the rate of placental complications in women conceived through donor oocyte differs from that of women

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Received Feb. 10, 2014; revised March 10, 2014; accepted March 17, 2014.

The authors report no conflict of interest.

Presented at the 32nd annual meeting of the SMFM, Feb. 6-11, 2012, Dallas, TX (abstract #790).

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2014.03.044

who conceived through IVF with autologous oocytes.

Materials and Methods

This is a retrospective cohort study of all women who had conceived through oocyte donation and received prenatal care and delivered at a single tertiary medical center between 2005 and 2011. The study was approved by the Institutional Research Ethics Board of Sheba Medical Center.

The study group included 139 women who conceived using donor oocytes and whose pregnancies continued beyond the first trimester and were compared with a control group, consisting of 126 women over 38 years old, who had conceived via IVF with autologous oocytes during the same time period and delivered at the same center. Only singleton gestations were included because multiple gestations are an established risk factor for preeclampsia and gestational hypertension. Pregnancies that were complicated by congenital anomalies or chromosomal abnormalities were excluded.

The medical files of all women were reviewed for the variables of interest. Demographic and clinical data of the patients were retrieved and included age, gravity, parity, and information regarding medical conditions such as chronic hypertension, diabetes, and thrombophilia. Maternal characteristics and their pregnancy outcomes were abstracted from the obstetric electronic charts. Pregnancy outcome measures included preterm delivery less than 34 weeks of gestation, gestational hypertension, preeclampsia, IUGR, gestational diabetes as well as gestational age at delivery, birthweight, and mode of delivery and were compared between the 2 groups.

Gestational hypertension was defined as blood pressure $\geq$140/90 mm Hg measured on 2 occasions at least 4 hours apart, occurring after 20 weeks of gestation in a previously normotensive woman, and preeclampsia was diagnosed when gestational hypertension was accompanied by proteinuria ($\geq$300 mg/24 hours or 2+ dipstick).[21] Hypertensive diseases of pregnancy was defined as the presence of gestational hypertension or preeclampsia. IUGR was defined as birthweight below the 10th percentile. Gestational diabetes was diagnosed when there were 2 abnormal values in the oral glucose tolerance test.

Normality of the data was tested using Shapiro-Wilk or Kolmogorov-Smirnov tests. Comparison of continuous variables between the 2 groups was conducted using Mann-Whitney U test or Student t test as appropriate. The χ^2 or Fisher exact tests were used for comparison of categorical variables. Logistic regression analysis was used to examine the relationship between hypertensive diseases of pregnancy and the presence of donor oocytes vs autologous oocytes. Adjustment was conducted for maternal age, gravidity, parity, and presence of chronic hypertension. Significance was accepted at $P < .05$. Statistical analyses were conducted using the IBM Statistical Package for the Social Sciences (IBM SPSS v.19; IBM Corporation Inc, Armonk, NY).

Results

Between 2005 and 2011, 139 women who conceived using donor oocytes (IVF-DO group) have delivered in our hospital and were matched to 126 women over 38 years old who conceived via IVF using autologous oocytes during the same time period (IVF-AO group). Table 1 describes the patients' characteristics. The recipients of donor oocytes were older compared with women using autologous oocytes (median maternal age 45 vs 41, $P < .01$). However, both groups were similar regarding the rate of nulliparity as well as the rate of preexisting medical conditions such as chronic hypertension, diabetes, and thrombophilia. The pregnancy outcomes of both groups are described in Table 2. The median gestational age at delivery and birthweight were similar among both groups.

The rate of hypertensive diseases of pregnancy (gestational hypertension or preeclampsia) and gestational hypertension were significantly higher in donor oocyte recipients compared with women who conceived with autologous oocytes (25% vs 10%, $P < .01$; and 16% vs 5.5%, $P < .01$, respectively). Previous abortions did not seem to be protective among ovum donor recipients as 17 of 61 (28%) ovum donor recipients with previous abortions were complicated by gestational hypertension or preeclampsia. Moreover, although the rates of preeclampsia and IUGR were higher in the donor oocyte recipients compared with controls, the differences did not reach statistical significance (9.3% vs 4.8%, $P = .15$, and 9.3% vs 4%, $P = .08$, respectively).

Early-onset preeclampsia before 34 weeks of gestation was also more common among ovum donor recipients (4.3% vs 0.8%) although this difference did not reach statistical significance ($P = .07$). Comparison of only nulliparous women among both groups revealed similarly increased rates of hypertensive diseases of pregnancy among nulliparous ovum-donor recipients compared with nulliparous controls (28% vs 12.5%, $P = .03$). The 2 groups did not differ with regard to the rates of preterm labor, gestational diabetes, and placental abruption. The rate of cesarean section was significantly higher among patients in the IVF-DO group (85% vs 56%, $P < .01$); in 55% of them cesarean section was performed because of maternal request. The other major indications for cesarean section among ovum donor recipients included abnormal presentation (14%), arrest of labor (8%), and fetal distress (6%).

To overcome the difference in maternal age between the groups, a subgroup analysis of patients under 45 years old was performed and revealed that the rate of hypertensive diseases of pregnancy remained significantly higher among donor oocyte recipients compared with autologous oocyte recipients (22% vs 10%, $P = .02$, Table 3). Multiple linear regression analysis was used to examine the relationship between hypertensive disease of pregnancy and any placental disease of pregnancy (gestational hypertension, preeclampsia, or IUGR) and the presence of donor oocytes vs autologous oocytes, while adjusting for maternal age, gravidity, parity, and presence of chronic hypertension (Table 4). The final regression model revealed that oocyte donation was independently associated with higher rate of hypertensive diseases of pregnancy (adjusted odds ratio 2.52;