European Journal of Obstetrics & Gynecology and Reproductive Biology 222 (2018) 1–6

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Outcomes of pregnancies achieved by double gamete donation: A comparison with pregnancies obtained by oocyte donation alone

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ARTICLE INFO

Article history:
Received 7 June 2017
Received in revised form 9 December 2017
Accepted 13 December 2017
Available online xxx

Keywords:
Double gamete donation
Oocyte donation
Advanced maternal age
Perinatal outcome
Preeclampsia

ABSTRACT

Objective: Women increasingly resort to oocyte donation to become pregnant. The high risk of preeclampsia found in oocyte donation pregnancies and the separate risk of preeclampsia associated with sperm donation may be cumulative in double donation pregnancies. We aimed to study the obstetrical and perinatal outcomes of pregnancies obtained by double donation (both oocyte and sperm) in comparison with those obtained by oocyte donation alone (oocyte donation and partner's sperm).
Study design: This cohort study included all women aged 43 and older who became pregnant after oocyte donation and gave birth between 2010 and 2016 in a tertiary maternity center. Primary outcomes were preeclampsia and hypertensive gestational disorders. Secondary outcomes were gestational diabetes, placental abnormalities, postpartum hemorrhage, perinatal death, and preterm delivery. We used univariate and multivariate analysis to compare IVF with double donation and IVF with oocyte donation alone for obstetric and perinatal outcomes.
Results: 247 women, 53 with double donations and 194 with oocyte donations alone, gave birth to 339 children. We observed no significant differences between groups for any obstetric or perinatal complications, except for the risk of gestational diabetes, which was more frequent in women with double donations compared with oocyte donation alone (26.4% vs. 12.9%, $P = 0.02$) and remained significant after adjustment (aOR = 2.80 95%CI[1.26-6.17]). Rates of gestational hypertension and preeclampsia were high, but similar between groups (20.7% vs. 26.3%, $P = 0.41$, and 18.9% vs. 17.5%, $P = 0.82$).
Conclusion: Women undergoing oocyte donation should be fully informed of its high rates of obstetric and perinatal risks. However, except for a higher observed risk of gestational diabetes, double donation does not appear to be associated with a higher risk of complications than oocyte donation alone.

Introduction

Maternal age at delivery is rising continuously in most Western countries [1,2]. As fecundity drops rapidly after the age of 35 years and the success rate of IVF with autologous oocytes decreases after the age of 40, women resort in growing numbers to ART with oocyte donation to become pregnant. Currently, oocyte donation yields high live birth rates, even at very advanced maternal ages [3–5]. The number of women receiving double gamete donation (both oocyte and sperm) has also grown steadily; they may be single women or have either a female or an infertile male partner; they often are nulliparous and of very advanced age [6].

Oocyte donation pregnancies are associated with various obstetric and perinatal complications, in particular gestational hypertension and preeclampsia [7–9]. Indeed, regardless of maternal age, oocyte donation is strongly associated with the risk of gestational hypertensive disorders [10,11]. However, women pregnant after oocyte donation often accumulate several risk factors for these disorders, because they frequently resort to this ART after 40 years. Advanced maternal age is a known independent risk factor for gestational hypertension and preeclampsia, but is also associated with a high frequency of cardiovascular risk factors,

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https://doi.org/10.1016/j.ejogrb.2017.12.026
0301-2115/

including obesity, high blood pressure and type 2 diabetes mellitus. The pathogenesis of preeclampsia involves immunological mechanisms [12]: in normal pregnancies, the maternal immune system achieves tolerance of the paternal antigens, then of the fetal antigens, allowing implantation and early placenta growth [13]. Partial failure of these immunoregulation mechanisms can cause poor placentation and dysfunctional uteroplacental perfusion, increasing the risk of placental preeclampsia [14,15]. In the case of oocyte donation, the embryo is only carrying foreign HLA: the donor's antigens and the paternal antigens. As a consequence, oocyte donation increases the risk of failure of the maternal immunoregulation mechanisms to accommodate the embryo, leading to inappropriate immune adaptation to the fetus, and abnormal placentation. Numerous studies suggest that maternal tolerance to paternal antigens begins with vaginal exposure to partner's seminal plasma; the risk of preeclampsia has been shown to be related to the duration of this exposure [16–18]. The importance of pre-conceptual exposure to semen can explain why pregnancies obtained with donor sperm are associated with increased risk of preeclampsia compared with partner sperm [13,19–21].

The high risk of preeclampsia found in oocyte donation pregnancies and the separate risk of preeclampsia associated with sperm donation may be cumulative in double donation pregnancies. Because we wondered whether pregnancies due to double donation are at higher risk of such obstetric and perinatal complications as gestational hypertension and preeclampsia, we sought to study their obstetric and perinatal outcomes by comparing the obstetric and perinatal outcomes of pregnancies obtained by double donation and those obtained by oocyte donation alone. If higher risks are identified in double donation pregnancies, this essential information should be explained to women and couples who consider such ART.

Materials and methods

Study population

This retrospective cohort study at the Port Royal Maternity Hospital (Paris, France) included all women aged 43 and older who became pregnant after oocyte donation and gave birth after 20 weeks of gestation between January 2010 and March 2016. They were classified into two groups: those who had received a double gamete donation (both oocyte and sperm) and those with oocyte donation alone (oocyte donation and partner's sperm). Data were collected from the obstetric records. This study does not include women whose prenatal care began elsewhere and who were transferred because of adverse fetal or maternal conditions during pregnancy. Individual characteristics considered included age, geographic origin, prepregnancy body mass index (BMI), chronic hypertension, pregestational diabetes, previous caesarean delivery, parity, type of pregnancy (singleton or multiple), and tobacco use. We recorded the country of donation, donor age, and type of relationship (single or couple), when this information was available in the medical file. ART with double donation is currently not authorized in France, regardless of maternal age, (except for embryo donation, which remains very rare). Thus, all included women received their double donation abroad and then gave birth in our center.

Type of outcome measures

The primary outcomes were gestational hypertension and preeclampsia. Standard definitions were used for both [22]: gestational hypertension as systolic blood pressure level $\geq$140 mm Hg or a diastolic blood pressure level $\geq$90 mm Hg any time after 20 weeks of gestation, and preeclampsia as gestational hypertension plus proteinuria (300 mg or higher in a 24-h urine collection). In case of chronic hypertension, preeclampsia was diagnosed by the addition of proteinuria (300 mg or higher per 24 h).

Secondary outcomes included gestational diabetes (defined as hyperglycemia first diagnosed during pregnancy, identified after a 75-g glucose load according to the International association of diabetes and pregnancy study group guidelines [23]), gestational cholestasis, abruptio placenta, HELLP syndrome, threatened preterm labor (uterine contractions and ultrasound cervical length $<$25 mm before 37 weeks of gestation), preterm premature rupture of the membranes (pPROM), placental abnormalities (low-lying placenta, placenta previa, or placenta accreta), and hospitalization during pregnancy. Delivery outcomes included gestational age at delivery, preterm birth before 37 and 32 weeks of gestation, mode of onset of labor (spontaneous or induced), caesarean or vaginal delivery, postpartum hemorrhage (PPH) and severe PPH (defined by at least one of the following treatments: sulprostone, vessel ligation and other conservative surgery, embolization, and hysterectomy). Neonatal outcomes included birth weight, fetal growth restriction (FGR, defined as a birth weight $<$10th percentile on Lubchenco curves [24]), intrauterine fetal death (IUFD), termination of pregnancy (TOP), and transfer to the neonatal intensive care unit (NICU).

Ethics approval

The National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, CNIL n° 1755849) approved this study. Under French regulations, this study is exempt from IRB review because it is an observational study using anonymized data from medical records. Women are informed that their records can be used for the evaluation of medical practices and are explicitly informed that they can opt out of these studies.

Statistics

We used univariate and multivariate analyses to compare obstetric and neonatal outcomes according to mode of conception: double donation versus oocyte donation alone. Findings were considered statistically significant if $P < 0.05$. For univariate analysis, we used Student, Chi2, and Fisher exact tests, as appropriate. Multivariate analysis was conducted by logistic regression for preeclampsia (i.e., the primary outcome) and for gestational diabetes (the only obstetric outcome significantly associated with double donation in the univariate analysis). We adjusted for the women's characteristics that differed significantly between the two groups in the univariate analysis ($P < 0.1$) and the maternal characteristics known to be generally associated with risks. We used Stata version 12.0 software (College Station, TX, USA) for the analyses.

Results

Population characteristics

The study included 247 women, 53 pregnant by double donation, and 194 by oocyte donation with the partner's sperm. Table 1 summarizes their baseline characteristics. Mean maternal age was 47 years $\pm$ 3.3 in the double donation group and 46 $\pm$ 2.5 for those with oocyte donations only ($P = 0.16$). These characteristics did not differ significantly between the two groups, except for tobacco use and chronic hypertension, both significantly more frequent in double donation pregnancies. The nulliparity rate was