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Risk of preeclampsia in pregnancies resulting from double gamete donation and from oocyte donation alone

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ABSTRACT

Introduction: Pregnancies after gamete donation are at higher risk of developing pre-eclampsia (PE) than those achieved by IVF with patient's own gametes. We aim to assess whether pregnancies achieved with both oocyte and sperm donation (double donation, DD) are at an increased risk of developing PE and gestational hypertension (GH) compared to those achieved by oocyte donation alone (OD).
Materials and methods: Retrospective cohort study of 433 patients who reached the 20th week of gestation with either DD (n = 81) or OD (n = 352) between March 2013 and April 2016 at a fertility clinic. The risk of preterm PE, term PE, and gestational hypertension (GH) are presented as unadjusted and adjusted odds ratio (OR).
Results: DD have a higher risk of preterm PE than OD, with an OR of 3.02 (95%CI 1.11–8.24; p = 0.031). We found no difference in the risk of term PE (OR 0.26, 95%CI 0.03–1.98; p = 0.19) or of GH (OR 1.23, 95% CI 0.63–2.43; p = 0.55).
Discussion: Pregnancies with DD are at higher risk of developing preterm PE than OD alone. Patients, and physicians treating them, should be made aware of the elevated risk of PE in these gestations, in order to start prophylactic measures during the first weeks of pregnancy.

1. Introduction

Despite pre-eclampsia (PE) complicates between 2 and 7% of all gestations [1–3], its still unknown etiology can be explained by two different theories: the vascular theory suggests that oxidative stress and other related factors cause endothelial damage and impaired trophoblast invasion of the myometrial arteries, which in turn leads to disrupted placentation [4]. On the other hand, the immunological theory postulates that the vascular dysfunction is the result of a maladaptation of the mother to fetal agents, and rests on the observation that the trophoblastic cells invading the decidua during early pregnancy express HLA-C antigens (both maternal and paternal), which are polymorphic. The HLA-C is a strong ligand for the killer immunoglobulin receptor (KIR) which is present on the surface of the uterine natural killer cells (uNK) and modulates proangiogenic and endothelial factors that promote changes in the spiral arteries to supply proper blood flow to the fetus. Some maternal KIR genotypes (especially the AA genotype) combined with certain trophoblastic HLA-C allotypes (particularly HLA-C2) can favor a dysfunction of uNK, which is associated with an altered maternal blood supply to the placenta, inducing disorders like PE and fetal growth restriction [5,6]. Several histological findings of chronic villitis of immune origin have been associated with PE [7].

Some epidemiological evidence supports this theory: a longer exposure to the partner's sperm and the lack of barrier contraceptives use have both been reported to decrease the prevalence of PE [8–11], although the clinical relevance of this protective effect has been questioned [12,13]. Similarly, previous pregnancies or miscarriages with the same partner have been reported to have a protective effect against PE [14,15]. Furthermore, primigravity or conception with a new partner are associated with higher rates of PE [15].

Numerous studies have reported higher rates of PE in women who achieve pregnancy after either oocyte donation (OD) [1–3,16–20] or sperm donation [1,3,17]. The conceptus trophoblastic HLA-C is less recognizable to the immunological system of the mother when donated oocytes are used [2]. Furthermore, some authors hypothesize an association between the need for oocyte donation *per se* and PE, as circulating antibodies against granulosa cells and the zona pellucida have been detected in patients presenting ovarian failure, a classical indication for OD independently from sperm donation [21]. Moreover, it is not clear whether the altered ovarian function of patients needing OD

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or double donation (DD) could be related to vascular or immunological changes that could independently predispose to PE [19,22].

Assisted reproduction treatments by which embryos obtained from both donated sperm and oocytes are transferred to a woman uterus have increased in the last decades due to demographic and societal changes such as increased maternal age, single motherhood, and same sex family formation [23]. If poor immunological recognition causes PE, it would be reasonable to assume an increase of this pathology in pregnancies achieved by DD, since in these cases the mother has not been in contact with the fetal antigens, and there is no protective effect provided by the continuous exposure to the partner semen.

The aim of this study is to assess whether there is an increased risk of PE and in pregnancies achieved with both OD and sperm donation compared to pregnancies achieved by OD and partner sperm. An additional analysis of gestational hypertension (GH) risk has been also carried out.

2. Materials and methods

2.1. Study design

This is a retrospective cohort study of 433 patients having achieved a pregnancy through assisted reproductive technology (OD or DD) between March 2013 and April 2016 at a large referral fertility center. Data has been obtained through a questionnaire emailed to the patients at their 20th week of gestation in preparation for the delivery and sent for up to 3 times to patients that failed to reply after having delivered. The questionnaire was filled in by the patient with the help of her obstetrician/gynecologist

2.2. Ethical approval

Permission to conduct the study was granted by the Ethics Committee for Clinical Research of Clinica Eugin.

2.3. Study population and participants

Patients of OD and DD with a fresh embryo transfer during the timeframe of the study, with a pregnancy reaching the 20th week of gestation were included in the study.

PE was defined as hypertension (arterial tension > 140/90 mmHg in at least 2 determinations taken at least 6 h apart) associated with proteinuria (> 300 mg protein in a 24 h urine), diagnosed at or after 20 weeks of pregnancy (Bulletins–Obstetrics 2002). Preterm PE was defined as that requiring delivery before 37 weeks of pregnancy, while in term PE delivery occurred at or after 37 weeks.

GH was defined by hypertension diagnosed by the same criteria than for PE but without proteinuria.

All patients underwent endometrial preparation with either oral (6mg/24 h) or transdermal (150 mcg/72 h) estrogens. In the menstrual cycle previous to the embryo transfer, they were administered a GnRHa depot (3.75 mg of triptorelin depot) in the mesoluteal phase, if they had regular cycles, or in the 17th day of oral contraceptives administration in case their periods were irregular. Progesterone (400 mg/12 h) was started the day of the donor's oocytes pick-up.

2.4. Statistical analysis

The risk of preterm PE, term PE and GH in DD compared to OD is presented as odds ratio (OR), with the associated confidence interval (95% CI) and p-value (Mantel-Haenszel Chi^2). In addition, a multivariable analysis has been performed for each study outcome, adjusting for the potential confounding factors age, primigravity and multiple pregnancy.

All statistical analyses were performed using SPSS version 22.0. A p-value ≤ 0.05 was set as statistically significant.

Table 1
Demographic characteristics overall and by study group.

	Overall (n = 433)	DD (n = 81)	OD (n = 352)	p-value*
Age, Mean (SD)	41.9 (4.5)	42.6 (3.7)	41.7 (4.6)	NS
BMI, Mean (SD)	23.2 (3.9)	23.4 (3.9)	23.2 (3.9)	NS
Primigravity, n (%)	251 (58.0)	58 (71.6)	193 (54.8)	0.006
Miscarriage history, n (%)	157 (36.3)	21 (25.9)	136 (38.6)	NS
Previous ART treatment offspring				
- 0, n (%)	366 (85.3)	78 (96.3)	291 (82.7)	
- 1, n (%)	39 (9.1)	2 (2.5)	37 (10.5)	NS
- 2+, n (%)	24 (5.6)	1 (1.2)	24 (6.8)	

DD: double donation (oocyte and sperm).
OD: oocyte donation.
* Student's *t*-test or Pearson's Chi^2.

3. Results

3.1. Demographic characteristics

A total of 1793 patients met the inclusion criteria and were sent the questionnaire, and 434 completed and returned it. The response rate was 24.2%. Supplementary Table 1 compares responders and non-responders characteristics and known PE risk factors. To note, no higher incidence of PE risk were found in non-responders. Information about non responders was obtained as part of the standard protocol of our center, where general information about patient's characteristics and pregnancy outcomes are registered in the clinic's database. Demographic characteristics of patients included in the study are presented in Table 1. On average, women were 41.9 years old, and 84.3% of them were childless.

3.2. Cycle and pregnancy characteristics

All oocytes in DD cycles were inseminated with frozen donor sperm, while 86.8% of frozen partner sperm was used in OD cycles. The proportion of frozen semen used is a consequence of patients living out of state, thus storing a semen sample on their first visit for future use. In most cases (90.3%), 2 embryos were transferred, and the majority of embryo transfers were on day 2–3 of development (90.3%). All embryos were transferred fresh (Table 2).

Overall, 22.6% of pregnancies were multiple, 93.5% ended in a live birth and C-section delivery was performed in 64.3% of cases. No significant differences were observed between study groups (Table 2).

3.3. Preeclampsia and gestational hypertension

Thirty-six cases of PE (8 in DD and 28 in OD) were registered. Of those, 16 were preterm PE, a condition statistically higher in the DD group (7/8 in DD and 12/28 in OD, p = 0.044). Regarding GH, 60 cases were reported (13 in DD and 47 in OD) (Table 3). DD pregnancies resulted in an OR of 2.68 [95%CI 1.02, 7.04, p = 0.038] for preterm PE, and OR of 0.26 [95%CI 0.03, 2.01, p = 0.17] for term PE; GH in DD pregnancies resulted in an OR of 1.24 [95%CI 0.64, 2.42, p = 0.53].

The risk of preterm PE associated to DD remained significant after adjustment for age, primigravity and multiple pregnancy, with an OR of 3.02 (95%CI 1.11–8.24; p = 0.031), and non significant for term PE and GH (Table 4).

4. Discussion

In the present study we found a high overall risk of PE and GH in the population studied, as expected after our previous report [16]. Interestingly, we also found an increased incidence of preterm PE in DD gestations compared to OD gestations, a finding not previously reported