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Risk of pre-eclampsia after fresh or frozen embryo transfer in patients undergoing oocyte donation

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ABSTRACT

Objectives: Different perinatal and neonatal adverse outcomes have been reported to be increased in frozen embryo transfer pregnancies compared with fresh embryo transfer with patient's own oocytes. Concerning preeclampsia, it has also been reported to be increased after frozen embryo transfer.
The objective of this study is to asses if there is an increased risk of preeclampsia and gestational hypertension in pregnancies achieved with oocyte donation after frozen embryo transfer compared to fresh embryo transfer.
Study design: Retrospective cohort study of 433 patients who underwent a cycle with donated oocytes either after fresh (n = 353) or frozen embryo transfer (n = 80) between March 2013 and April 2016 at a large fertility clinic. Participants are pregnant patients who reached the 20th week of gestation. The risk of preterm preeclampsia (presenting before 37 weeks of gestation), term preeclampsia (presenting at or after 37 weeks of gestation) and gestational hypertension are presented as unadjusted and adjusted odds ratio (OR).
Results: Frozen embryo transfer have similar risk for developing preterm preeclampsia compared to fresh embryo transfer, with an OR of 1.95 (CI 95% 0.72, 5.26, p = 0.18), as well as term preeclampsia (OR 0.3, 95%CI 0.04, 2.35, p = 0.25), and gestational hypertension (OR 1.45, 95% CI 0.75, 2.81, P = 0.27).
Conclusions: Despite a high prevalence of preeclampsia in pregnancies achieved by oocyte donation, the freezing-thawing process does not confer more risk than the fresh embryo transfers in preterm preeclampsia, term preeclampsia or gestational hypertension.

Introduction

The use of frozen-thawed embryo transfer (frozen ET) is increasing worldwide, in part due to the growing trend towards single embryo transfer, and the implantation of freeze all policies when there is a risk of lower endometrial receptivity or OHSS. The ICMART registry reported a 27.6% increase of non-donor frozen ET between 2008–2010, with a pregnancy rate of 29.1% and a delivery rate of 20.7% in 2010 [1]

Several authors suggest that the supraphysiological hormonal levels reached during controlled ovarian stimulation have deleterious effects on the endometrium, causing placental dysfunction and alterations, thus likely affecting the pregnancy course [2–4]. When compared to fresh embryo transfers (fresh ET), frozen ET have been associated with lower rate of low birth weight singletons [1–9], less preterm birth; [6,8], and ectopic pregnancy [10,11]. Moreover, while we find higher rates of large for gestational age singletons in frozen ET compared to fresh ET [5–8,12], data are still inconsistent about the perinatal mortality of frozen ET babies: while in some papers the risk is higher compared to fresh ET(5, 6), others do not find differences [8], or even report less risk [13].

The effect of frozen ET on the occurrence of placental alteration has been less studied so far: the rate of placenta previa seems either lower [5], or not different [7], while the occurrence of placenta accreta seems higher after frozen ET [7].

Of note, it seems that an increase in preeclampsia (PE) is the only reported maternal effect increased in frozen ET vs fresh ET [5,7,14–16], even though some authors found that the elective cryopreservation of embryos in IVF cycles at risk of ovarian hyperstimulation syndrome reduces the odds of PE [9].

A common bias in all the studies so far is the comparison of treatments when the patient's own oocytes are used in all transfers. While this is very relevant for the counselling of patients, it does not allow to understand more in detail the source of the

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hypothetical effects of frozen ET, since in fresh ET the endometrium has been affected by the controlled ovarian stimulation, and in frozen ET by hormonal preparation of the endometrium for embryo reception. In this sense, oocyte donation offers a model to isolate the effect of the frozen ET, since all endometrium are prepared, and no ovarian stimulation is performed.

On the other hand, PE incidence has been reported to be higher in OD pregnancies compared to pregnancy achieved with a woman own oocytes (Blazquez, JARG, 2016). The embryo in OD pregnancies is allogeneic to the mother, as both alleles of the HLA expressed by the trophoblastic cells non self. The HLA is the ligand for the KIR, the receptor in the uterine NK (uNK) for the HLA. The function of uNK cells is to modulate proangiogenic and endothelial factors that leads to the proper perfusion of the placenta and the fetus. The immunological theory is based on the dysfunctional response of these uNK that takes place when the HLA is less recognizable for the mother, as it is after an oocyte donation, leading to a hypoperfusion of the placenta and finally to PE.

The aim of our study is therefore to assess whether there is an increased risk of PE in patients recipients of embryos from oocyte donation (OD) undergoing frozen ET compared to recipients undergoing fresh ET, in order to analyze the effect of the freezing-thawing of the embryo and without the bias of the ovarian stimulation.

Material and methods

Study design

This is a retrospective cohort study of 433 consecutive patients that have achieved a pregnancy by IVF/ICSI with donated oocytes and partner's sperm, either after a fresh or a frozen ET, between March 2013 and April 2016 in a large fertility center. Data were obtained through a questionnaire emailed to the patients and filled-in with the help of their physician. This questionnaire was sent automatically as a part of the clinic follow-up protocol to all patients achieving the 20th week of gestation. If patients did not reply, the questionnaire was sent up to three times.

Ethical approval

Permission to conduct the study was obtained from the local Ethical Committee for Clinical Research of the center.

Recipient population

The two study groups were: recipients of oocyte donations with pregnancies achieved through either fresh ET (fresh embryos) or frozen ET (vitrified-warmed embryos). Pregnancies must be ongoing at 20th week to be included in the study.

The primary outcome of this study was the number of PE, defined as gestational hypertension (systolic blood pressure $\geq$ 140 or diastolic blood pressure $\geq$ 90 mmHg) associated with proteinuria ($\geq$ 300 mg/24 h) at or after 20 weeks of gestation. PE is classified in two subclasses, preterm and term PE [17], categories of clinical relevance as the consequences of the syndrome are more severe in preterm PE [18,19]. Preterm PE was defined as requiring delivery before 37 weeks of pregnancy, while term PE delivery occurred at or after 37 weeks. The secondary outcome was the number of gestational hypertension (GH) reported by the patients in the questionnaires. GH is defined by hypertension at or after 20 weeks of gestation.

Endometrial preparation for embryo reception

Endometrial preparation of the patients started with oral contraceptives for 21 days if they had irregular menstrual cycles, with an injection of GnRH agonist (GnRHa; Decapeptyl, Ipsen Pharma, Spain) depot on the 17th day of the oral contraceptive. Recipients with regular menstrual cycles were administered a GnRHa depot in the mesoluteal phase of the cycle. At the first day of menstruation of the cycle immediately following, the estrogen preparation was initiated, with either patches (150 mg/3 days; Estradot, Novartis Pharma, Spain or Vivelledot, Novartis Pharma, Spain) or pills (6 mg/day; Progynova, Bayer Health Care, Spain or Provames, Sanofi-Aventis, France). Vaginal progesterone (400 mg/12 h; Crinone, Merck S. L., Spain) was initiated on the same night as the donor ovum retrieval. In cases in which endometrial thickness did not achieve 6 mm, patients added a higher dose of vaginal estrogens until the endometrium reached at least 6 mm.

Statistical analysis

The risk of preterm PE, term PE and GH in frozen ET compared to fresh ET is presented as odds ratio (OR), with the associated confidence interval (95% CI) and p-value tested by 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 $\leq$0.05 was set as statistically significant.

Results

Demographic characteristics

A total of 1538 patients were sent the questionnaire, and 433 returned it completed, resulting in a response rate of 28.15%. Demographic characteristics and risk factors for PE between responders and non-responders show no significant differences (Supplementary Table 1). Of the 433 patients included, 353 become pregnant after fresh ET and 80 after frozen ET. The mean maternal age was 41.8 and primigravity represented 55.2% of cases. None of the demographic characteristics analyzed differed significantly between groups (Table 1).

Cycle characteristics and pregnancy outcomes

The majority of donor oocytes were inseminated with frozen sperm (85.7%), and most of the embryo transfers were performed on day 2–3 of development (90.8%). The rate of multiple gestations was 22.6%, and 64.6% of deliveries were by C- section.

No significant differences were observed between study groups (Table 2), except for the number of embryos transferred; while in 322 (91.2%) of the fresh ET group two embryos were transferred, in the frozen ET group, 54 cases were double embryo transfer (67.5%), 12 (15%) were single embryo transfers and 14 (17%) triple embryo transfer.

Table 1
Demographic characteristics overall and by study group.

	Overall (n = 433)	Frozen (n = 80)	Fresh (n = 353)	p-value
Age, Mean (SD)	41.86 (4.56)	42.5 (4.2)	41.7 (4.6)	0.15[a]
BMI, Mean (SD)	23.2 (3.9)	23.2 (3.9)	23.2 (3.9)	1.00[a]
Primigravity, n (%)	239 (55.2)	45 (56.3)	194 (55.0)	0.83[b]
Offspring				
- no, n (%)	359 (82.9)	67 (83.8)	292 (82.7)	0.71[b]
- yes, n (%)	46 (10.6)	9 (11.3)	37 (10.5)	

[a] Student's *t*-test.
[b] Pearson's Chi^2.