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Commentary Open Access

Is the freeze-all strategy for all?

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Commentary

In the past few years, the freeze-all strategy has emerged as an alternative to fresh embryo transfer (ET) during in vitro fertilization (IVF) cycles. Although fresh ET is the norm during assisted reproductive therapies (ART), there are many concerns about the possible adverse effects of controlled ovarian stimulation (COS) over the endometrium [1]. COS is necessary to the development and maturation of many follicles and oocytes, therefore, it increases the chance of positive outcomes and cumulative pregnancy rates during ART [2]. However, the supra-physiologic hormonal levels that occur during a conventional COS are associated with modifications in the peri-implantation endometrium that may be related to decrease in pregnancy rates [3,4], and poorer obstetric and perinatal outcomes [5-7] when comparing fresh to frozen-thawed embryo transfers.

There is scientific evidence showing that COS may be related to an endometrial advancement, that can be observed during histological evaluation during a fresh cycle, and when this advancement is over 3 days no pregnancies are achieved [8,9]. There are also changes in gene expression profiles in the endometrium of patients submitted to ovarian stimulation [10]. These changes may be associated with progesterone (P) levels. Labarta et al., found differences in endometrial gene expression between patients with elevated P on the day of final oocyte maturation compared with patients with normal P levels [11]. These studies suggested that hyper-stimulation might be detrimental to implantation by altering genes that are crucial for the endometrium-embryo interaction.

In the freeze-all strategy, the entire cohort of embryos is cryopreserved (not just the "second best"), and the best embryos are transferred in a posterior cycle with a more physiologic endometrium. By performing delayed frozen-thawed ET (FET), the deleterious effects of COS over endometrium would be avoided and better outcomes would be expected [12]. A recent meta-analysis showed an increase in 32% in the ongoing pregnancy rate when the freeze-all strategy was performed when compared to fresh ET [4]. However, there were only three studies included in this meta-analysis [3,13,14] and one of them [13] was retracted due to methodological problems when performing the study. More randomized clinical trials (RCT) evaluating this strategy are necessary, and not only in normal and high responders. Until now, there are no studies evaluating this strategy in poor responders.

There are some registered RCT aiming to evaluate this strategy (NCT00823121, NCT01841528, NCT02148393, NCT02471573, NTR3187, ACTRN12612000422820), and we will probably have a more robust evidence favoring or not the elective frozen-thawed ET when these studies are concluded.

When elective FET was implemented, the main idea was to improve IVF outcomes. However, it is important to evaluate not only the effectiveness of ART, but also its safety. One of the major complications observed during COS in IVF cycles is ovarian hyper-stimulation syndrome (OHSS). It is an iatrogenic, potentially lethal and occurs in approximately 1%-14% of ART cycles [15]. Nowadays, it is fundamental to prevent the development of OHSS. When the final oocyte maturation with GnRH agonist is performed in patients with an antagonist protocol and all oocytes/embryos are cryopreserved, the onset of early and late OHSS is virtually eliminated [16,17]. Moreover, there is a reduction in the risk of ectopic pregnancy [18,19], lower risk of low birth weight and pre-term birth [7,20,21] after FET when comparing to fresh ET. However, the FET cycles are associated with a higher incidence of large for gestational age [22,23].

Potential Advantages	Potential Disadvantages
↓ OHSS	↑ macrosomia
↑ endometrial receptivity	↑ hypertensive disorders
↑ implantation rates	↑ placenta accreta
↓ ectopic pregnancy	↑ costs
↓ placenta previa	Few RCTs
↓ pre-term birth	No data on poor responders
↓ small for gestational age	
↓ perinatal mortality	

Table 1: Potential advantages and disadvantages of freeze-all strategy.

Although there are many potential advantages in performing a freeze-all cycle over a fresh ET, it seems that the freeze-all strategy is not designed for all of IVF patients. There is a large amount of patients that get pregnant and don't have any obstetrical/perinatal complication even after fresh ET. Moreover, there is a need for studies comparing the costs and cumulative pregnancy rates between the two strategies. There is a need to develop a non-invasive clinical tool to evaluate the endometrial receptivity during a fresh cycle that will allow the selection of patients that would benefit from this strategy. Nowadays, it is reasonable to perform elective cryopreservation of all oocytes/embryos in cases with a risk of OHSS development and in patients with supra-physiologic hormonal levels during follicular phase of COS. All other cases should be discussed with the patients, evaluating the pros and cons (Table 1), including the potential costs, the delay in treatment, and also potential risks of this strategy.

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