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IVF/ICSI frozen replacement cycles; every cycle? Opinion expressed after a systematic review of the literature

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Summary

Objective: To determine whether in vitro fertilization (IVF), frozen replacement cycles offer better outcomes than fresh cycles in order to support, or not, a possible shift towards total replacement of fresh IVF/intracytoplasmic sperm injection (ICSI) cycles from frozen elective transfers (FETs). *Study design:* Systematic review; opinion paper. *Results:* Initial results seem to support a shift in current practice towards frozen cycles. *Conclusion:* Initial results may support replacement all fresh IVF/ICSI cycles with FETs, as this could be a safer and equally effective strategy. However, robust evidence from randomized controlled trials is needed if this will be generally applied.

Key words: In vitro fertilization (IVF); Intracytoplasmic sperm injection (ICSI); Frozen elective transfers (FET).

Introduction

Assisted reproduction technology (ART), through in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), has offered a happy family to million of couples since its first implementation in the 1970's [1]. Close to the increased demand for ART, nowadays lies the need for fetal and maternal safety [2-5].

Worldwide, the majority of IVF/ICSI cycles are "fresh" treatment cycles; any embryos left from them, remain frozen in storage for future use.

The first ever live birth after transfer of a thawed cryopreserved embryo took place in 1984 [6]. Since then, freezing-thawing technology has advanced greatly; so have number of frozen embryo transfers (FETs) and live births associated with them [7]. While having already accepted FET safety, in terms of offspring health [8] and obstetric outcome [9], it seems that efficacy in terms of live birth, is also comparable [10-12].

With the present study, the authors attempted to summarize currently available evidence examining FETs in order to support, or not, a possible shift towards total replacement of fresh IVF/ICSI cycles from FETs.

Methodology

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews were followed. A systematic literature search was conducted using two standard electronic databases (Pubmed and Embase) plus Cochrane database of Systematic Reviews. All computerized searches were performed using the following medical subject heading terms: 'frozen embryo transfer', 'IVF', 'perinatal', 'obstetric', ' outcome', 'fresh'. Publication type was either 'randomized controlled trial' or ' systematic review'. There was no language restriction.

The search was performed between December 1, 2012 and January 31, 2013 for all available papers that had to be written in English. All papers' reference lists were checked in order to identify additional studies. From this search the authors identified two RCTs examining fertility outcomes in women undergoing either fresh or elective frozen embryo transfers [10-11]. Moreover, they report the outcomes of a meta-analysis of observational studies examining obstetric and perinatal outcomes of either frozen or fresh embryo transfers [9].

Pregnancy rates after fresh cycles and FETs: is there a biological mechanism behind these?

Results of the two randomized controlled trials are presented in Table 1. They both present much higher clinical pregnancy rates in the FET group: 39 *vs.* 27.8% [10] and 84 *vs.* 54.7% [11], respectively. Aflatoonian *et al.* included 374 women aged under 38 years while Shapiro *et al.* included 137 women under 41 years old with an expected normal response to ovarian stimulation.

The biological mechanism behind these differences in not clearly defined. Several researchers have suggested better endometrial receptivity and higher embryonic-endometrial synchronization in FET cycles [13-16].

Hormonal profile in fresh cycles [very high E2 levels in proliferative phase causes upregulation of endometrial progesterone receptors [15], as well (along with high prog-

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Table 1. — *Fertility outcomes after fresh cycles and FETs.*

Search	Type	Population	Intervention	Comparison	Outcome	Result
Aflatoonian [10]	RCT	374 women <38 years old	Elective FETs	Fresh embryo transfer	Clinical pregnancy	Higher pregnancy rates in FETs (39% *vs.* 27.8%)
Shapiro [11]	RCT	137 women <41 years old, with expected normal ovarian response	Elective FETs embryo transfer	Fresh pregnancy	Clinical	Higher pregnancy rates in FETs (84% *vs.* 54.7%)

Table 2. — *Obstetric outcomes following fresh IVF cycles and FETs. Relative risk, 95% confidence interval, FET vs. fresh embryo transfer.*

Study	Small for gestational age	Preterm birth	Low birth weight	Perinatal mortality	Antepartum hemorrhage
Maheswari [9]	0.45 (0.30–0.66)	0.84 (0.78–0.90)	0.69 (0.62–0.76)	0.68 (0.48–0.96)	0.67 (0.55–0.81)

esterone) as alteration in endometrial gene expression profiles[16]) is considered responsible for that decreased receptivity.

Molecular pathways responsible involve the complement, the transforming growth factor beta (TGFβ) signaling pathway, the "coagulation cascade" and the leukocyte transendothelial migration [10]. Thus, as progesterone's role is recognized, in FET cycles, embryonic and endometrial synchronization can be achieved better by timing progesterone administration [10]. Therefore, the proposed "freeze-all embryos" cryopreservation and their transfer in a subsequent cycle, may increase endometrial receptivity and, therefore, implantation rate and live-birth outcome. Thus, it provides clinical benefits, including the increase of cumulative pregnancy and reducing the risk of ovarian hyperstimulation syndrome (OHSS [10].

Close to the increased endometrial receptivity, Shapiro *et al.* [11] suggested a different mechanism for the better results of the cryopreservation group. They suggested that the freeze–thaw procedure preferentially "selects" and rules outlawed embryos. Therefore, it results in a greater proportion of better quality, viable blastocysts being transferred in the cryopreservation group, and thus pregnancy rates are indirectly increased.

Results of both studies are encouraging. Nevertheless, both trials have some methodological limitations. Shapiro *et al.* [11] study was underpowered (required sample size 411) [17], with co-interventions (such as dual trigger for final oocyte maturation) and its pregnancy rates (84% *vs.* 54.7%) were far higher than those reported in worldwide available registries.

None of these RCTs provide live birth rates or cost-effectiveness and patients' acceptability data [17]. Different types of freezing (Aflatoonian *et al.* [10]: vitrification / Shapiro *et al.* [11]: slow freezing) had been used and embryos were replaced in hormonally mediated cycles on Day-3 (Aflatoonian *et al.* [10]) or at blastocyst-stage (Shapiro *et al.* [11]).

The total number of 511 women remains far from the projected total number of 918 (459 in each group) to show a difference of 10% in pregnancy rates (between 25 and 35%) with 90% power and 95% as Maheswari and Bhattacharya reports [17].

Obstetric – perinatal results after fresh IVF cycles and FETs

The most reliable available meta-analysis [9] showed that in pregnant women after IVF, the relative risks of preterm birth, small for gestational age, low birth weight, perinatal mortality, and antepartum hemorrhage were significantly lower in those after FET than in those getting a fresh embryo transfer. Nevertheless, this meta-analysis has a number of limitations. Firstly, it examines only singleton pregnancies. Moreover, aggregated data cannot be adjusted for confounders (such as age, smoking, etc) whereas significant statistical heterogeneity (population, design of studies, and freezing-thawing protocols) exists.

Clinical implications

From the initial available results, it seems that the strategy of elective cryopreservation of all fresh embryos achieved in a fresh IVF/ICSI cycle and their transfer in a subsequent frozen (perhaps downregulated) cycle could offer pregnancy rates close to those of fresh embryo transfer. If we add evidence that show better results regarding obstetric safety, then a shift to ART practice may become a reality. Nevertheless, proper, robust randomized trials that will eliminate the flaws of those currently available, need to take place in order to boost that change in everyday clinical practice in ART.

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