OPINION

Elective frozen replacement cycles for all: ready for prime time?

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ABSTRACT: Conventionally, most in vitro fertilization (IVF) embryos are transferred in fresh treatment cycles with freezing reserved for spare ones. Improvement in cryopreservation facilities over time has encouraged the greater use of this technology with the success rate of frozen replacement cycles approaching that associated with fresh embryo transfer. Data from observational studies suggest that obstetric and perinatal outcomes are better in pregnancies resulting from frozen replacement cycles. In the interests of promoting feto-maternal safety is it therefore time to avoid fresh embryo transfers in IVF, freeze all available embryos and replace them in subsequent cycles? In this article we explore the biological plausibility of this concept, appraise the evidence underpinning it and consider the implications of adopting such a strategy in routine clinical practice. The outcomes of existing randomized trials appear to favour a strategy of frozen embryo transfer, but larger trials are needed before a major change in clinical practice can be considered.

Key words: IVF / ICSI / perinatal outcomes / obstetric outcomes / frozen embryo transfer

Introduction

Since the birth of Louise Brown in 1978, over 3.5 million babies have been born as a result of in vitro fertilization (IVF) and, more recently, intracytoplasmic sperm injection (ICSI). While the demand for these procedures continues to grow, obstetric and perinatal outcomes in pregnancies conceived through IVF and ICSI have been shown to be consistently poorer in comparison those occurring spontaneously (Helmerhorst et al., 2004; McGovern et al., 2004; Pandey et al., 2012). As fertility practitioners, our focus has begun to shift from live birth rates as a sole measure of treatment success towards outcomes which also reflect feto-maternal safety (Christensen et al., 2011; Turan et al., 2012). This is evident from the media hype following the publication of a recent article on birth defects (Davies et al., 2012) following IVF and ICSI.

Conventionally, most IVF embryos are transferred in a fresh treatment cycle; any spare embryos are frozen and stored for use when no pregnancy results from the fresh transfer or when couples wish to try for a possible second child. Although the first live birth after transfer of a thawed cryopreserved embryo was reported in 1984 (Zeilmaker et al., 1984), the use of frozen—thawed IVF embryos has consistently lagged behind fresh embryo transfer. With refinement of technology in recent years, the numbers of frozen embryo transfers (FETs) have increased (De Mouzon et al., 2010) as have pregnancy rates associated with them, to the extent that it has been suggested that selection of embryos may become less relevant in future as a means of increasing success rates in IVF/ICSI, as almost all embryos will survive the freezing—thawing processes (Mastenbroek et al., 2011). The pregnancy rates of frozen–thawed embryo transfers, according to some authors, are on par with, or superior to those associated with fresh embryo transfer (Aflatoonian et al., 2010; Shapiro et al., 2011; Zhu et al., 2011). Follow-up data from children conceived through FET have been reassuring (Kansal Kalra et al., 2011) and a recent systematic review and meta-analysis (Maheshwari et al., 2012) of observational studies has shown that singleton pregnancies following frozen—thawed embryo transfer have better perinatal outcomes when compared with pregnancies after fresh embryo transfer.

Thus, pregnancy rates associated with frozen—thawed embryos would appear to be comparable with those after fresh embryo transfers, with potentially better obstetric and perinatal outcomes. Is it therefore time to eschew fresh embryo transfers in IVF, freeze all available embryos and replace them in subsequent cycles? In this article, we appraise the evidence underpinning it, explore the biological plausibility of this concept and consider the implications of adopting such a strategy in routine clinical practice.

Pregnancy rates following elective frozen replacement cycles: evidence from randomized trials

Two randomized controlled trials (RCTs) have compared fertility outcomes in women randomized to elective fresh versus frozen—thawed
embryo transfers. Both show higher clinical pregnancy rates in the frozen replacement cycle group (84 versus 54.7% (Shapiro et al., 2011); 39 versus 27.8% (Aflatoonian et al., 2010)). Aflatoonian et al. (2010) included women under 38 in whom ovarian response was anticipated to be vigorous (n = 374) while Shapiro et al. (2011) included women under 41 expected to have a normal response to gonadotrophins (n = 137). The trial by Shapiro et al. (2011) was underpowered (required sample size = 411), involved co-interventions such as dual trigger for final oocyte maturation and led to pregnancy rates (84%) which were far higher than those reported from European or American registries.

Both trials recruited a high proportion of eligible couples [100 and 95%, respectively, in Shapiro et al. (2011) and Aflatoonian et al. (2010)] and all randomized women received the allocated intervention (except where cycles were cancelled on medical grounds). No losses to follow-up or difficulty in recruitment were reported. Women were recruited after egg collection and embryos were frozen on Day 2 using vitrification (Aflatoonian et al. 2010) and slow freezing (Shapiro et al., 2011). Frozen–thawed Day 2 embryos were cultured till Day 3 (Aflatoonian et al., 2010) or blastocysts (Shapiro et al., 2011) and replaced in hormonally mediated cycles.

The data from these trials are very encouraging, but the results have limited external validity. None of these RCTs are able to provide live birth rates or data on cost-effectiveness and acceptability. The total number of women (511) fall short of a projected total number of 918 (459 in each group) to show a difference in live birth rates of 10% (between 25 and 35%) with 90% power and 95% confidence (epi info version 3.5.3; http://www.cdc.gov/epiinfo/html/downloads.htm).

**Obstetric and perinatal outcomes after frozen–thawed versus fresh embryo transfer**

Eleven observational studies have reported on obstetric and perinatal outcomes in pregnancies subsequent to frozen—thawed versus fresh embryo transfer. The denominator in each of these studies was the number of women with ongoing pregnancies after either fresh or FET. A recent meta-analysis (Maheshwari et al., 2012) showed that in women carrying singleton pregnancies following IVF, the relative risks (95% Confidence intervals) of small for gestational age [0.45 (0.30–0.66)], preterm birth [0.84 (0.78–0.90)], low birth weight [0.69 (0.62–0.76)], perinatal mortality [0.68 (0.48–0.96)] and antepartum haemorrhage [0.67 (0.55–0.81)] were lower in those who received frozen, as opposed to fresh embryos. However, this meta-analysis of aggregated data was unable to adjust for confounders such as age, smoking, parity duration of infertility and pre-existing medical illness. There was significant heterogeneity in terms of the population sampled, design of studies, regimens used for freezing, thawing and replacement of embryos. Thus, while the results favour FET, there is an urgent need to provide data on reproductive outcomes from more robust experimental studies.

**Mechanism of action: is there a biological plausibility?**

Controlled ovarian hyper stimulation in IVF produces multi-follicular ovulation with the aim of retrieving a number of oocytes. While there is a practical advantage in having a choice of oocytes to take on to the next stage, i.e. fertilization, the supra-physiological levels of estrogens produced by the growing follicles can have a potentially negative impact on endometrial angiogenesis and implantation (Amor et al., 2009; Healy et al., 2010; Kansal Kalra et al., 2011). Haozui et al. (2009) demonstrated that gonadotrophin treatment in stimulated cycles led to disruption of the transcriptional activation of genes involved in endometrial receptivity.

Normally, the human embryo develops within the Fallopian tube, entering the endometrial cavity 5 days after fertilization. Replacing embryos on the second or third day after fertilization in a fresh IVF cycle involves a degree of asynchrony between the phase of development of the embryo and endometrium (Shapiro et al., 2011). This can be circumvented by transferring embryos on Day 5 (blastocyst stage), but for embryos to survive prolonged in vitro culture is only feasible in 20% of IVF cycles (Khalafer et al., 2008); however, in good prognosis patients, this proportion could be much higher (Glujovsky et al., 2012).

It has been suggested that transfer of frozen—thawed embryos in a non-stimulated cycle is more conducive to early placentation and embryogenesis (Amor et al., 2009; Healy et al., 2010; Kansal Kalra et al., 2011) when compared with fresh IVF cycles where supra-physiological doses of gonadotrophins are administered (Aflatoonian et al., 2010; Shapiro et al., 2011). This is true even when thawed embryos are replaced in artificial cycles where the endometrium is prepared by means of physiological doses of estrogen and progesterones. This argument is further strengthened by the findings of Healy et al. (2010) who showed that in pregnancies arising from fresh embryo transfers, the risk of antepartum haemorrhage was correlated with the numbers of oocytes retrieved and the accompanying rise in serum estradiol levels. A second explanation for improved outcomes in pregnancies resulting from FET could be that the physical effects of freezing and thawing embryos may filter out those of borderline quality (Shih et al., 2008). This would allow the more robust embryos to survive and develop, resulting in more optimal fetal growth. Thus, there are a number of potential reasons to support the thesis that pregnancies resulting from frozen—thawed embryo transfer cycles have better outcomes.

**Interpretation of the available evidence**

Pooled observational data indicate that ongoing pregnancies associated with frozen—thawed embryos are associated with fewer obstetric and perinatal risks compared with those which occur after the transfer of fresh embryos. A limited amount of data from randomized trials suggests that, in selected groups of women, a strategy of elective cryopreservation of all fresh embryos with subsequent transfer in a new replacement cycle could offer pregnancy rates similar to fresh transfer. It can, therefore, be argued that, in women with a good prognosis, one could freeze all embryos and replace them in a non-stimulation cycle to achieve an optimum outcomes following IVF/ICSI. This represents a major paradigm change in assisted reproduction, and one which could satisfy the twin demands of optimizing safety and success. However, the existing data have a number of limitations which need to be addressed in the context of further research before this strategy can be rolled out into routine clinical practice. The initial step must be to provide robust evidence to demonstrate that elective freezing of
embryos and can increase the chances of having a healthy baby. This is best performed in the context of an adequately powered randomized controlled trial alongside a large observational study to determine effectiveness as well as side effects.

**Evaluation of a strategy of elective freezing: designing a randomized, controlled trial**

Designing any trial in infertility and assisted reproduction presents a number of methodological challenges (Vail and Gardener, 2003). The rather restrictive eligibility criteria of existing trials have tended to impair the generalizability of their findings. A definitive trial with the potential to change practice must have a more flexible approach towards its target population such that the results are relevant to the majority of women undergoing IVF.

The intervention, i.e. elective cryopreservation of all embryos followed by frozen—thawed embryo transfer in a subsequent cycle, needs to be clarified. A critical issue for all trials involving cryopreservation is the time a participant spends within it, i.e. duration of intervention. While the ideal would be to evaluate outcomes over a number of FET in both groups (elective cryopreservation as well as fresh transfer) following a single episode of oocyte retrieval, this may not be feasible due to logistic reasons and an alternative would be to have a fixed time horizon.

It is necessary to be clear about whether all available embryos should be frozen, or whether this should only be done in embryos of appropriate quality. Alfatoonian et al. (2010) advocated a ‘freeze all’ policy only in patients who have adequate number of good quality embryos—again a subjective assessment with criteria which can vary across different IVF clinics. There is also likely to be some debate about the optimal method (slow freezing or vitrification) and time (pronucleate, cleavage or blastocyst stage) of cryopreservation. There will also be controversy about the best way of dealing with embryos which could be transferred fresh but deemed to be not good enough to freeze, hence denying couples the chances of a potential pregnancy with fresh embryo transfer. It can be argued that these issues are not insurmountable in the context of a pragmatic trial, with stratification for individual centres which use different protocols (Bhattacharya and Mollison, 2004).

Choice of an appropriate outcome measure is crucial. In the context of IVF, suggestions have ranged from pregnancy rate per transfer to birth of term singleton live birth per initiated cycle (Messinis and Domali, 2004; Min et al., 2004). The most popular outcome, favoured by most national registries (HFEA, SART), i.e. live birth per fresh IVF cycle, is not free from bias (Abdalla et al., 2010) and unsuitable for a trial on elective embryo cryopreservation. An outcome measure which incorporates effectiveness and safety is healthy singleton live birth, although the definition of healthy is open to interpretation and some might want to capture the health state of the child beyond birth, up to 1 year or even beyond. Calculating health utility values such as quality-adjusted life years for fertility outcomes is controversial and complicated. The primary economic outcomes could include costs to the health service and incremental cost per healthy singleton live birth for a strategy of elective cryopreservation versus fresh embryo transfer.

Another challenge will be the number of patients that need to be recruited to adequately power a trial: if the fresh and frozen strategies have similar effectiveness in terms of live birth rates, than one would need to demonstrate increased safety (‘health of babies born’). Although pregnancies derived from frozen embryos might indeed be healthier; in general the vast majority (>95%) of children born from fresh or frozen embryos is healthy. Thus it will be difficult to conduct a trial demonstrating increased safety of the frozen embryo strategy as this would require thousands of patients.

**Stakeholder views**

Any proposed research on evaluation of healthcare interventions needs to be sensitive to consumer opinion. Currently, there are no studies in the literature on consumers’ views on freezing all the embryos with a view to transfer at a later date. Although the two published trials (Alfatoonian et al., 2010; Shapiro et al., 2011) have not encountered any difficulty in recruitment, the literature on the acceptability of elective single-embryo transfer provides a degree of insight into how challenging it is for patients to contemplate major changes in treatment strategy (Maheshwari et al., 2010) be it in the context of a clinical trial or a reform of policy based on data from trials. In addition, clinical equipoise on the part of health professionals is critical for recruitment to a trial, and previous work has revealed the wide variation in attitudes amongst health care providers to proposed trials of alternative strategies of embryo transfer (Hartshorne and Lilford, 2002). Hence, there is a need to explore the perceptions of couples and those looking after them towards the proposed intervention, gauge their willingness to participate in the randomization process and assess their support for a change in practice based on the outcome of a definitive trial.

**Logistic and funding implications**

The disarticulation of ovarian stimulation and embryo transfer may appear to be radical, but could provide a number of potential benefits. For example, a policy of freezing all IVF embryos obtained has been identified as a means of reducing the risk of ovarian hyper-stimulation syndrome (Devroey et al., 2011) as a GnRHa-agonist can be used as an ovulatory trigger instead of HCG (Humaidan et al., 2011; Papanikolaou et al., 2011). In addition, there will be reduced need for a 7-day clinical and laboratory service with consequent benefits in terms of safety and economic savings. However, it is unlikely that in the immediate future this strategy will be the norm for all patients. As long as conventional management based on fresh embryo transfers continues alongside it, no cost savings are envisaged. Instead, there may be additional expenses for additional personnel and storage capacity due to the increased demand for cryopreservation.

The way in which IVF is priced will need to change radically if all embryos are to be frozen. A radical change in strategy will need to accommodate freezing, thawing and replacement of embryos within the same financial package. Adopting a ‘freeze all’ policy will require a change in the definition of what constitutes an IVF/ICSI cycle, i.e. one episode of egg collection followed by all embryo transfers accruing from it. This will have implications in countries, such as the UK, where State-funded treatment is rationed and one IVF/ICSI cycle is synonymous with one fresh embryo transfer in many areas.
Conclusions

Avoiding fresh embryo transfer and freezing all embryos destined for transfer could improve the safety and effectiveness of IVF and ICSI. The prospect of improved feto-maternal outcomes is particularly relevant given the increasing uptake of IVF across the world. The available evidence does not justify a change in practice at present but strongly supports the need for a large multicentre, randomized trial to evaluate the clinical and cost-effectiveness as well as acceptability of elective cryopreservation versus fresh embryo transfer. The nature of the proposed strategy poses major logistic challenges, both in terms of mounting a definitive trial, as well as implementing any policy changes that emerge from it.

References


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