Reviewer’s report

Title: Live-birth rates and perinatal outcomes when all embryos are frozen compared with conventional fresh- and frozen-embryo transfer: a cohort study of 337,148 in-vitro fertilisation cycles

Version: 0 Date: 23 May 2019

Reviewer: Samuel Santos-Ribeiro

Reviewer's report:

I have read with great interest the manuscript of Smith et al, which focuses on a topic that is of current great interest in the field of Reproductive Medicine. Using registry data, the authors compared the cumulative live birth and perinatal outcomes of complete conventional IVF cycles with those of a so-called "segmentation" approach.

The authors concluded that "segmentation" was associated with lower overall live birth rates and even potentially worse neonatal outcomes in some subgroups as well.

This study includes a large sample set and accounted for many relevant potential confounding factors. However, I unfortunately consider that it currently fails to respond the question it originally sought to answer.

While, following some revision, I consider that this manuscript will deliver valuable information for the physicians who deal with infertility in their daily practice, the fact that it fails, in its current format, to respond the original study question (whether elective segmentation is a good approach or not) limits its current scope of interest.

The reasoning behind my recommendation of major revision of this interesting paper and suggestions for improvement are described further below.

MAIN STRENGTH OF THIS MANUSCRIPT: THE PRAGMATIC APPROACH USING REGISTRY DATA

Contrary to some previous attempts [1, 2], this study uses a registry dataset to assess the cumulative effect of the deferral of the first fresh embryo transfer on the variable that most matters to patients - the cumulative chances of delivering a healthy child - in a general IVF setting. Until now, only one study attempted the same [3] and this study will deliver important validation of these finding.

MAIN WEAKNESS REQUIRING ADDRESSING PRIOR TO PUBLICATION

The study attempts to equate elective embryo cryopreservation to optimize pregnancy outcomes (the actual and relatively recent "segmentation concept" the authors discuss in the introduction)
to a different type of embryo transfer deferral, which was, to my knowledge, the only type of "segmentation" being done in the pre-2012 era: the need to cancel a fresh embryo transfer attempt for specific medical indications.

Moreover, the data used in this study derived from a time period when the cryopreservation technology mostly available was sub-par (slow freezing) and, for this reason, does not reflect that of modern medical practice following the widespread use of vitrification under which the new "segmentation concept" is being put forward.

Elective embryo cryopreservation is a relatively recent concept, which gained most of its traction following the studies of Shapiro et al in 2011 and the review of Devroey, all cited by the authors. Given that the bulk of the data assessed precedes this time, it is probable that these cycles without a fresh transfer were not "elective freeze-only cycles", but rather medically-indicated cancelled fresh embryo transfer cycles.

The most common medical indications for fresh cycle cancellation were then hyper-response, ovarian hyperstimulation syndrome, elevated late-follicular progesterone (in some centres) and a thin endometrial lining.

These were the most likely indications for fresh embryo transfer cancellation before 2011-2012, a time when "freezing because the endometrium may be hindered by the stimulation" was not a widespread concept.

Following these initial studies in 2011-2012, it took time for physicians to take into consideration the "freeze-for-all" theory, a topic that only in the last 4 or 5 years has actually become a widespread issue.

It is problematic to consider that the results of these pre-2012 medically-indicated fresh transfer cancellation results can be extrapolated to what will be true for the more recent segmentation approach. Specifically, many of the medical indications for fresh cycle cancellation are associated with poorer cumulative cycle outcomes already.

For instance, a) OHSS may increase miscarriage [4] and other adverse outcomes [5, 6], b) the bulk of women who have hyper-response - those with polycystic ovaries and PCOS - also have more adverse neonatal outcomes ([7]), c) women with thin endometrium also have poorer live birth rates [8] and neonatal outcomes [9-12] and this event frequently has a compounding effect because sub-optimal endometrial development will frequently recur in subsequent cycles of the women; finally, d) those with elevated progesterone may also have lower cumulative live birth rates [13].

In other words, the main issue of is the study is that one is unable in the current version of the manuscript to disentangle the indication for the cancelled fresh cycle in this pre-2012 era from its repercussion on the overall IVF success and hence, one cannot state that this can be extrapolated
to those who currently perform elective segmentation, which is indeed the clinical question of interest for a general audience such as the one of BMC Medicine.

Most importantly, presenting a direct extrapolation of medically-indicated cancelled fresh cycles to elective segmentation may inadvertently fuel patients to demand for a fresh embryo transfer "at all costs" and disarm physicians from using elective cryopreservation due to clear safety and efficiency concerns such as OHSS prevention and late-follicular elevated progesterone, a fact mentioned by the authors.

That said, can the authors present valid arguments for why these cycles can be considered as a valid surrogate for the "elective segmentation" concept currently in vogue as they discuss in the introduction?

THE ISSUE OF CONSIDERING "YEAR OF TREATMENT" AS A SURROGATE MARKER OF "SLOW FREEZING USE"

Slow freezing has been progressively replaced by vitrification due to the lower embryo survival rates associated with this method. The authors try to account for this defining arbitrarily that 2011 marks a transition phase after which clinics changed their cryopreservation technologies. However, it is not adequate in my view to affirm that vitrification had been adopted completely by then.

To that extent, just as an example, I present a meta-analysis which demonstrates that vitrification was still a relatively new and discussed concept in 2011, with RCTs being performed after 2013 as well [14]. If the authors can prove further that vitrification was widespread after 2011, then they should present evidence for such. Contacting the clinics could, for instance, be an easy solution for this problem.

ANOTHER POSSIBLE JUSTIFICATION FOR THEIR FINDING

If is very notable in figure 2 how a very simple confounder adjustment (age, cycle number and the number of oocytes retrieved) inverted the relationship between segmentation and the probability of a live birth. This may indicate the presence of unmeasured confounding or an effect-modification associated with one of these variables.

The variable which one may be most concerned with is the number of oocytes retrieved. In other words, patients with a low number of oocytes retrieved (i.e. small amount of embryos produced) will have a larger negative effect on their chances of conception with segmentation due to the fact that the few embryos they produced need to go through the extra self-selection procedure of cryopreservation.

Meanwhile, those with a normal and high response may not have this effect and may even be the ones benefiting from segmentation. It would be interesting to see the results divided by ovarian response to see this assumption is verifiable. If so, then the bulk of results may possibly be
explained by this factor, a fact that would be very interesting to know. As food for thought, a brief overview of preceding literature shows that this rationale may indeed be the justification for the results found [1, 3].

MINOR ISSUES

- Blastocysts may survive cryopreservation better than cleavage stage embryos, potentially providing better cumulative live birth rates [15]. The HFEA database has this variable recorded. Why do the authors not account for it?

- The HFEA dataset has a more subdivided categorization of female age, but the authors chose to merge some subgroups? Why? I am especially concerned with group with 35-37 year-old and 38-39 year-old subgroups being merged, as this is the moment of crucial importance for IVF success, with a stark decrease in pregnancy outcomes. I believe this merging may unnecessarily cause unmeasured confounding.

- Z-scores are the preferred method to assess differences in birth-weight. I understand that the authors do not have this variable recorded in the dataset, however they must mention this in the limitations of their study. The authors should also mention, in the limitations section that, since 2009, the HFEA data inclusion for research has been subject to patient consent and that the acceptance has been relatively low.

- HFEA did not collect this data prospectively for this study. In fact, a number of key variables for the studied outcomes are missing (e.g. female smoking, overall parity instead of IVF parity, previous episodes of premature delivery), variables that would likely not be missing if this was a prospective study as mentioned in the abstract. That said, would this study not be better classified as being retrospective?

- While indeed severe OHSS with hospitalization is a fortunately rare event, hyper-response and fresh cycle cancellation due to moderate OHSS can occur in up to third of all cycles performed in high-risk patients. To say that this was likely not a main criteria for medically-indicated segmentation (as mentioned in the discussion) in a time when mostly hCG was used for triggering after hyper-response may be a bit too optimistic. I suggest moderating this section in the discussion

REFERENCES


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