Significantly lower ectopic pregnancy rates after frozen embryo transfer: implications toward segmentation of in vitro fertilization treatment

Ectopic pregnancy rates have not declined over the last 15 years in the United States, and a long-term population-based study supports an increasing trend, with an annual age-adjusted rate of 21.1 ectopic pregnancies per 10,000 woman-years between 2005 and 2007 (1). This trend may be attributed to the significant increase of assisted reproductive technologies (ART) over the last decades and the fact that ectopic pregnancy is twice as frequent in ART cycles compared with natural conception.

In a well-conducted retrospective cohort study, Shapiro et al. (2) describe significantly lower ectopic pregnancy risk in frozen–thawed embryo transfers compared with fresh ones (0 vs. 1.5%). However, a critical question is this: why are ectopic pregnancies significantly lower in frozen replacement cycles?

Shapiro et al. (2) suggest that the most reasonable mechanism is the negative effect of ovarian stimulation on endometrial receptivity. Such a hypothesis seems to be valid because a detrimental effect of ovarian stimulation on the endometrium may affect implantation rates and lead to an increase in ectopic pregnancy and a decrease in viable intrauterine pregnancy rates. This is in accordance with a randomized trial, conducted by the same group (3), which strongly suggests decreased pregnancy rates in fresh stimulated cycles compared with frozen–thawed cycles in normal ovarian responders.

However, can this be the only mechanism explaining this reduced incidence of ectopic pregnancies after frozen–thawed embryo transfers? If so, why is this not reflected in the miscarriage rates, which in the present study are comparable between fresh and frozen embryo transfers (2)? We believe that another synergic mechanism exists behind this observation, and this is the diverse uterine contractility in stimulated compared with nonstimulated cycles. A previous prospective study has shown that uterine contractility after stimulated cycles is considerable up to 4 days after hCG administration. This contractility, although reduced, still exists even 7 days after hCG administration (1.5 contractions per minute), contrary to nonstimulated cycles, in which endometrial wavelike activity is not increased after ovulation (4). As successfully described by Shapiro et al. (2), "The high implantation potential that is protective against ectopic pregnancy requires favourable endometrial receptivity and endometrial receptivity can be compromised by ovarian stimulation." This, in synergy with increased uterine contractility after a stimulated cycle, may explain why the high implantation potential of a blastocyst may result in significantly higher ectopic pregnancy rates in a fresh stimulated cycle, compared with the replacement of a frozen–thawed embryo in a nonstimulated cycle.

Nonetheless, despite the underlying mechanisms behind this lower ectopic pregnancy rate, the crucial question to be answered is this: what is the clinical importance of the present study, and may this lead toward a change in existing clinical practice?

Shapiro et al. (2) confirm the results of a recent Japanese nationally based registry analysis, suggesting reduced ectopic pregnancy rates after replacement of frozen–thawed blastocysts (5). One may argue that a reduction of approximately 1% in ectopic pregnancy rates may be considered of limited clinical significance, in view of the low incidence of ectopic pregnancy in ART cycles. However, these studies, in combination with a previous randomized trial (3), highlight a more favorable outcome in nonstimulated frozen–thawed cycles compared with stimulated fresh embryo transfers. In this regard, such an observation may indeed be of high clinical importance, if we consider that it provides an insight into the implantation potential after stimulated and nonstimulated cycles and may be the onset of a novel management of infertile patients undergoing assisted reproduction.

The concept of segmentation of IVF treatment and frozen–thawed embryo replacement in a receptive, nonstimulated endometrium has been described as the most optimal management towards an "OHSS [ovarian hyperstimulation syndrome]-free clinic" (6). The present study by Shapiro et al. (2) provides reassuring evidence that segmentation of IVF treatment may not only be safer owing to the eradication of OHSS, but may also result in significantly lower ectopic pregnancy and higher live birth rates.

In conclusion, the data provided by Shapiro et al. (2) in favor of a lower ectopic pregnancy rate in frozen–thawed embryo transfers highlight a new strategy toward an improved outcome in ART. This new strategy of segmentation of IVF treatment can provide a safe outcome in different aspects: elimination of OHSS, increase in ongoing pregnancies after frozen embryo replacement, reduction of multiple pregnancies, and a significant decrease of ectopic pregnancies.

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