It's all about timing: Is the window of implantation different for day 5 and 6 blastocysts?

The frozen-thawed ET (FET) cycle is becoming the most common type of assisted reproductive technology. Between 2008 and 2016, the number of frozen nondonor cycles reported to the United States Centers for Disease Control (CDC) increased more than threefold, from 25,261 to 86,266. In contrast, during this time period, the number of fresh nondonor in vitro fertilization (IVF) cycles reported to the CDC decreased yearly from 104,673 in 2008 to 86,237 in 2016 (1). In the most recent CDC report from 2016, for the first time, the number of FET cycles surpassed the number of fresh cycles (1). The increased use of FET is the result of several factors, including use of GnRH trigger to prevent ovarian hyperstimulation syndrome, use of preimplantation genetic testing, and increased use of elective single ET, which leaves an increased number of supernumerary embryos for cryopreservation (2).

It is likely that the increased use of FET will continue, particularly since these cycles are becoming more successful. From 2008 to 2016, the live birth rate after FET increased by 50% (30.6% in 2008 and 45.9% in 2016), while the live birth rate remained stable for fresh cycles (36.7% in 2008 and 36.3% in 2016) (1). Advances in embryo cryopreservation techniques, using vitrification, along with improvements in preimplantation genetic testing for aneuploidy, have led to better results after FET (2). The success of FET has led some clinicians to consider planned cryopreservation of embryos rather than fresh transfer (2).

Despite the increasing success of FET, live birth rates remain less than 50%. Given the increasing popularity of FET, further improvements have the potential to significantly impact the success of assisted reproduction. The success of FET relies on synchronization between the embryo and endometrium so that the endometrium is optimally receptive for the embryo to implant (3). The timing of P administration is critical for establishing the window of implantation (WOI), the time during which the endometrium becomes receptive for embryo implantation. Initiation of P will open the WOI a few days later (3). Initially, data from the early days of IVF suggested the WOI was rather wide since embryo implantation has been demonstrated over a 5 day period, but more recent studies indicate that the optimal WOI is narrow, likely not more than two days in duration (3). It has been suggested that some women have displaced WOI, which can be diagnosed using molecular markers of endometrial receptivity. For these women, an adjustment of P initiation in relation to the ET would better synchronize the endometrium (3).

The optimal duration of P administration before FET has yet to be determined. In this current issue, Roelens and colleagues seek to address this uncertainty and investigate clinical outcomes in FET cycles of blastocyst embryos performed on the sixth or seventh day of P administration (4). The authors examined data from 619 women who underwent FET of previously vitrified blastocyst embryos, between December 2015 and December 2017. They found comparable rates of miscarriage and live birth between the groups (4). Interestingly, when they performed subgroup analysis to compare outcomes of the P regimens for day 5 and day 6 blastocysts, they found better clinical outcomes when day 6 blastocysts had a longer period of P exposure. A significantly higher miscarriage rate was seen when ET of day 6 blastocysts was performed on the sixth day of P (50%) compared with the seventh day (21.4%). There was also a tendency toward lower live birth rates for day 6 blastocysts transferred on the sixth day of P (21.5%) compared with 7 days of P (35.5%). These data would suggest that the slower growing embryos are intrinsically different and require a longer duration of P exposure for optimal synchronization with the endometrium.

Numerous studies have tried to determine whether embryos that develop into blastocysts on the sixth day after fertilization are fundamentally different from those that become blastocysts by the fifth day after fertilization. Studies performed to determine whether clinical outcomes differed after transfer of day 5 and day 6 blastocysts have conflicting results, particularly in FET cycles (5), which may, in part, be due to differences in the cryopreservation technique that was used. In older studies, embryo cryopreservation was performed by a slow freezing technique, while the more successful vitrification technique was typically used in the more recent studies (5).

In 2019, Bourdon and colleagues published a systematic review examining the clinical outcomes of fresh and frozen cycles after transfer of blastocysts that developed on day 5 compared with those that developed on day 6 (5). Their review included data from 29 studies, published between 2005 and 2018, and differentiated between results of slow freezing and vitrification techniques. This meta-analysis found significantly higher clinical pregnancy rates and live birth rates after ET of day 5 blastocysts when compared with day 6 blastocysts in both fresh IVF cycles and FET cycles with previously vitrified embryos (5). There was a significantly higher rate of miscarriage after ET of day 6 blastocysts compared with day 5 blastocysts in both fresh cycles and FET cycles using embryos that had previously undergone vitrification.

The unanswered question is whether the superior outcomes seen with transfer of a day 5 blastocyst were due to an intrinsically better-quality embryo with superior implantation potential or due to better synchronization with the endometrium. In fresh cycles, the decreased implantation rate seen with transfer of the day 6 blastocysts has been attributed to suboptimal synchronization between the embryo and the endometrium rather than to an inherent defect in the day 6 embryo. Controlled ovarian stimulation results in advanced endometrial development with earlier WOI, which would not be optimal for the slow developing day 6 blastocyst (2, 3). Consistent with this finding, older studies found that day 6 blastocysts have higher implantation and ongoing pregnancy rates when synchronized in a FET cycle compared with fresh ET (2, 3).

In this meta-analysis, better clinical outcomes were also seen in FET cycles after transfer of day 5 blastocysts compared

with day 6 blastocysts, which would argue against suboptimal endometrial synchronization as the sole cause of inferior clinical outcomes after transfer of day 6 blastocysts (5). The fact that superior outcomes were noted in the day 5 blastocysts would be consistent with the hypothesis that late blastulating embryos have lower implantation potential, perhaps due to metabolic or epigenetic differences (5). The findings of Roelens and colleagues, however, would suggest that slower developing day 6 blastocysts have the potential to implant but may have a different and possibly narrower WOI compared with day 5 embryos. With vitrified-warmed day 5 blastocyst embryos, similar clinical outcomes were seen when ET took place on the sixth or seventh day of P, but with day 6 blastocysts better results were seen with the longer period of P exposure (4).

This study by Roelens et al. represents another advance in the quest to improve ET and IVF outcomes. The study suggests that some patients do not conceive after ET due to suboptimal timing rather than a pathologic issue. Generally, the duration of P exposure before ET has been considered equal for day 5 and 6 embryos, but that might not be the case. By considering the developmental stage of the blastocyst and tailoring endometrial preparation optimally, patients may experience higher live birth rates and lower miscarriage rates. Although not statistically significant, in this study, one additional day of P treatment led to an increase in the live birth rate for the slower developing blastocyst embryos (4). If the findings of their retrospective study are confirmed in a larger prospective trial, a simple alteration in P regimen may lead to significant improvement in IVF outcomes.

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