Why we should transfer frozen instead of fresh embryos: the translational rationale

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Epidemiologic studies have shown an increased rate of adverse perinatal outcomes, including small for gestational age (SGA) births, in fresh in vitro fertilization (IVF) cycles compared with frozen embryo transfer cycles. This increase is not seen in the donor oocyte population, suggesting that it is the peri-implantation environment created after superovulation that is responsible for these changes. During a fresh IVF cycle, multiple corpora lutea secrete high levels of hormones and other factors that can affect the endometrium and the implanting embryo. In this review, we discuss both animal and human data demonstrating that superovulation has significant effects on the endometrium and embryo. Additionally, potential mechanisms for the adverse effects of gonadotropin stimulation on implantation and placental development are proposed. We think that these data, along with the growing body of epidemiologic evidence, support the proposal that frozen embryo transfer should be considered preferentially, particularly in high responders, as a means to potentially decrease at least some of the adverse perinatal outcomes associated with IVF. (Fertil Steril® 2014;■:■–■. ©2014 by American Society for Reproductive Medicine.)

Key Words: In vitro fertilization, frozen embryo transfer, superovulation, implantation, placentation

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As success rates following assisted reproductive technologies (ART) have improved, attention has increasingly turned to birth outcomes and the long-term health of children born following ART (1, 2). Although the great majority of children born following ART are healthy, epidemiologic studies suggest that ART is associated with an increased risk of adverse perinatal outcomes, including fetal growth restriction, low birth weight, preterm birth, and preeclampsia, even when controlling for multiple gestations (3–5). These outcomes may be associated not only with neonatal morbidity but also with long-term health outcomes, including an increased incidence of metabolic diseases later in life (6, 7). In addition, several rare genetic and epigenetic diseases have been associated with, as yet incompletely identified, aspects of this therapeutic technology (8, 9). Even though the overarching goal must be to minimize these risks for our patients, controversy exists over what aspects of ART are responsible for the observed outcomes (10). One intervention used ubiquitously during in vitro fertilization (IVF) is superovulation with gonadotropins. Superovulation is an integral part of the IVF process, because controlled ovarian hyperstimulation allows the retrieval of multiple oocytes for fertilization and embryo development. However, superovulation results in supraphysiologic levels of multiple hormones and other factors, including E_2, P, and vascular endothelial growth factor (VEGF), both during oocyte development and after embryo transfer. This can have multiple effects, including potential changes to the oocyte, endometrium, and implanting embryo, and the potential contribution of each of these effects on adverse outcomes is not well understood (11).

The negative effects of superovulation may be expressed as a decreased implantation rate, and recent data indeed suggest possible decreased implantation rates in fresh compared with frozen embryo transfers (12–14). However, a large percentage of embryos do implant after fresh IVF transfer. So a question remains: What happens to the developing embryo that does successfully implant in an endometrium exposed to the abnormal hormonal milieu following superovulation? Recent epidemiologic evidence suggests

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that the peri-implantation environment created by superovulation may be contributing to at least some of the adverse perinatal outcomes following ART, and that these effects can be minimized by transferring embryos in a subsequent frozen embryo transfer cycle (4, 5, 15–23). A large retrospective study by Kalra et al. using the Society for Assisted Reproductive Technologies (SART) database demonstrated a significant increase in low-birthweight (LBW) singleton infants (<2,500 g) born after fresh embryo transfers compared with infants born after frozen embryo transfer cycles (odds ratio [OR] 1.46, 95% confidence interval [CI] 1.34–1.58) (5). This difference was even stronger when analyzing pregnancies within a single individual who conceived children after both fresh and frozen embryo transfers (OR for LBW 2.52, 95% CI 1.59–4.00). Importantly, no differences were observed in the rates of LBW between fresh and frozen embryo transfers in donor egg cycles, eliminating the possibility that the freeze-thaw process was responsible for the observed differences. Other studies have confirmed these results, and a growing body of literature supports the observation that fresh embryo transfer leads to increased rates of LBW, preterm delivery, and other adverse pregnancy outcomes compared with frozen embryo transfers (2, 18, 22, 23). In addition, a recent meta-analysis showed that the incidence of LBW was the same following frozen embryo transfer or natural conception (2).

The cause-effect relationship between the peri-implantation environment and perinatal outcomes is supported by several studies demonstrating that the adverse effects of the peri-implantation environment are most significant in those patients with vigorous responses to ovarian stimulation (24–26). A recent pilot study by Imudia et al. showed that when patients at high risk of ovarian hyperstimulation syndrome (OHSS) chose elective cryopreservation of all embryos, their rates of preeclampsia and SGA, defined as <10% for gestational age, were lower than patients who chose to proceed with a fresh embryo transfer (26). That group has also found higher rates of preeclampsia and SGA in patients with E_2 levels greater than the 90th percentile for their institution, suggesting that vigorous response to superovulation may be associated with a greater risk of adverse pregnancy outcomes (OR for SGA 9.40, 95% CI 3.22–27.46; OR for preeclampsia 4.79, 95% CI 1.55–14.84) (27).

Taken together, these studies suggest that the abnormal hormonal milieu following superovulation contributes, directly or indirectly, to the adverse outcomes seen in pregnancies conceived with the use ART. Although there is minimal direct evidence linking the superovulation-related hormonal milieu to adverse perinatal outcomes, in this review we will discuss both human and animal data showing that ovarian hyperstimulation with gonadotropins has effects on the endometrium and early embryo that may affect early implantation and placentation. We think that these data, along with compelling recent epidemiologic observations, support the preferential transfer of cryopreserved embryos in a more physiologic hormonal milieu over the transfer of fresh embryos immediately following ovarian hyperstimulation.

EFFECTS ON THE ENDOMETRIUM

Endometrial Receptivity

Evidence from human and animal studies suggests that superovulation leads to histologic changes in the endometrium at the time of implantation. In animal models, superovulation has been shown to affect the depth of the surface epithelium, the number and length of microvilli, and the mitotic activity in the surface epithelium and stromal cells (28, 29). Both human and animal studies have found that superovulation lowers the expression of specific integrins associated with the window of implantation (30, 31). Evidence also suggests that superovulation may affect the timing of the "window of receptivity," the time period during which the endometrium is receptive to embryo implantation. In humans, implantation normally occurs 8–10 days after ovulation (32). Histologically, this is represented by glandular changes in the endometrium, which exhibits subnuclear vacuoles, as well as the appearance of pinopodes on the luminal surface of the epithelium (33). In superovulated cycles, these cellular changes occur earlier than in nonsuperovulated cycles. Studies of endometrial biopsies taken on the day of oocyte retrieval in IVF cycles show endometrial advancement in a majority of samples, with a more significant increase in this advancement in younger patients and those who had a larger number of oocytes retrieved (34, 35). The histologic advancement seen with superovulation has also been confirmed with an earlier appearance of endometrial nucleolar channel systems, a marker of endometrial maturation, after superovulation (36). This shift in the window of endometrial receptivity can affect implantation; endometrial advancement of >3 days has been associated with failed implantation (35). The shift in the window of implantation may also affect the development of an embryo once it successfully implants; mouse studies suggest that embryos that implant beyond the normal window of receptivity are more likely to show defects in placental formation and fetal growth (37).

Endometrial receptivity may be most affected in those patients with an exaggerated response to ovarian stimulation. This may be due to the fact that these patients have the greatest rise in both estrogen and progesterone during and after superovulation. Clinical studies indicate that higher E_2 levels are correlated with earlier rises in P, even before administration of the hCG ovulation trigger (38–41). Elevated P levels (particularly >1.5 ng/mL) have been associated with histologic endometrial advancement and decreased pregnancy rates after fresh IVF transfers (42). In a retrospective study of 4,032 fresh IVF/intracytoplasmic sperm injection cycles performed by Bosch et al., patients who had a P level >1.5 ng/mL on the day of hCG ovulation trigger had an ongoing pregnancy rate of 19% compared with 31% in patients with a $P<1.5$ ng/mL ($P<.001$; OR 0.53, 95% CI 0.38–0.72) (38). Pregnancy rates were not decreased when these embryos were transferred in a subsequent frozen cycle, demonstrating that the detrimental effect of the elevated P is on the endometrium, not the embryo (43, 44).

The effects of superovulation on endometrial receptivity may therefore affect both the rate and the quality of