Clinical rationale for cryopreservation of entire embryo cohorts in lieu of fresh transfer

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Recent dramatic increases in success rates with frozen–thawed embryo transfer (FET) are encouraging, as are numerous findings of several reduced risks with FET when compared with fresh transfer. These reduced risks include low birth weight and prematurity, among others. However, FET is also associated with increased risks of macrosomia and large for gestational age. There have been reports of greater implantation and pregnancy rates with FET than with fresh autologous embryo transfer, suggesting superior endometrial receptivity in the absence of ovarian stimulation. As cryo-technology evolves, there is potential for further increase in FET success rates, but for now it may be best to follow an individualized approach, balancing fresh transfer and embryo cohort cryopreservation options while considering patient characteristics, cycle parameters, and clinic success rates. (Fertil Steril® 2014;102:3–9. ©2014 by American Society for Reproductive Medicine.)

Key Words: In vitro fertilization, embryo cryopreservation, frozen embryo transfer, ovarian stimulation, perinatal risk

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From 2006 to 2012, the number of autologous frozen–thawed embryo transfers (FET) reported to the Society for Assisted Reproductive Technology (SART) increased 82.5%, whereas fresh cycle starts increased by 3.1%. There was a clear trend toward increased FET usage relative to fresh cycles in that period (Fig. 1). In 2012 SART's member clinics reported 17.3% more FETs and 3.2% fewer fresh cycle starts when compared with 2011, suggesting an accelerating trend toward FET.

This increased use of FET corresponded with a more rapid increase in live birth rates with FET than with fresh transfer. In 2006 the reported live birth rates per transfer were 33.1% with FET and 44.9% with fresh transfer in patients <35 years old, corresponding with a risk ratio (RR) of 0.737 when comparing FET with fresh transfer. By 2012 those respective rates were 42.4% with FET and 47.1% in fresh transfers, so that the RR had increased to 0.900. Over that period, the RR of live birth with FET compared with fresh transfer increased in each SART age group (Fig. 2), and reported birth rates per transfer with FET exceeded those with fresh transfer in four of the five age groups in 2012 (1).

The numbers of live births with FET have therefore also increased more than with fresh transfers (Fig. 3). In 2012, the number of live births with fresh autologous transfer decreased by 2.6% from the prior year, whereas the number of live births from autologous FET increased by 28.0%. Live births from FET were 31.5% of all reported autologous live births in 2012, compared with just 16.9% in 2006 (1).

The increase in FET usage and success rates may have resulted from multiple simultaneous causes. Improved cryopreservation techniques may reduce embryo cryo-damage and therefore increase success rates and confidence in cryopreservation and FET. This might encourage more frequent freezing of entire cohorts rather than freezing "second-best" embryos after the morphologically best embryos are transferred in fresh cycles. Cohort banking is also increasingly routine after the use of a GnRH agonist "trigger" to prevent ovarian hyperstimulation syndrome (OHSS) in high responders. The increased use of genetic screening also increases the use of cryopreservation, because embryos are often frozen while awaiting test results, and transfer of confirmed euploid embryos may contribute to increasing FET success rates. Lastly, the steady

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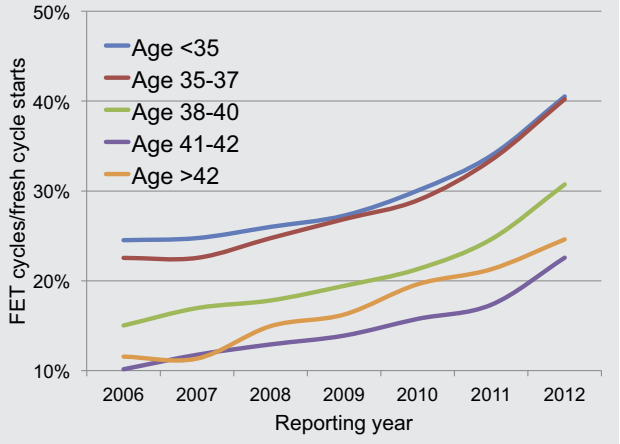
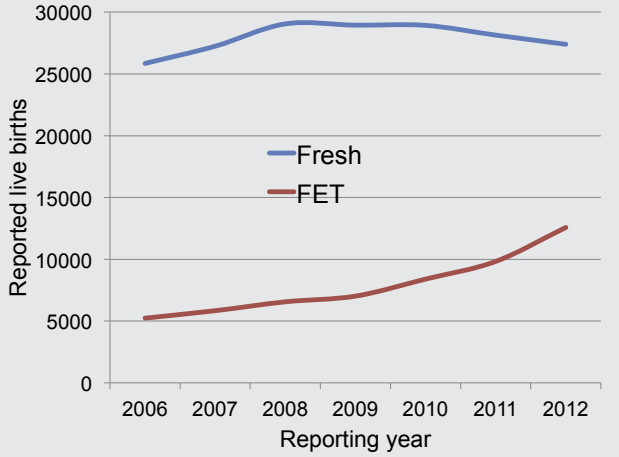
FIGURE 1



Trends in the ratio of the numbers of reported frozen–thawed embryo transfers to reported fresh cycle starts in each SART age group.

Shapiro. Cryopreservation of embryo cohorts. Fertil Steril 2014.

FIGURE 3



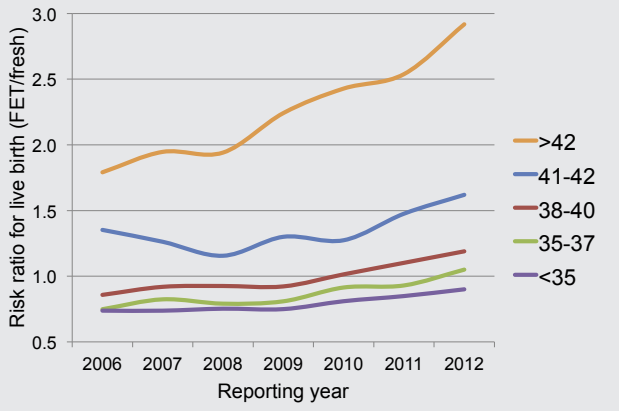
Trends in estimated numbers of live births with fresh transfer and FET. These estimates were calculated by multiplying the reported numbers of cycles and the respective birth rates on SART's national report, and summing across age groups.

Shapiro. Cryopreservation of embryo cohorts. Fertil Steril 2014.

decrease in national average numbers of embryos used in each transfer should have left more embryos for potential cryopreservation and FET.

The increasing use of FET and the increasing numbers of resulting births compel continuing scrutiny of risks associated with FET, including risk comparisons with the alternative of fresh transfer. Comparisons between FET and fresh transfer are also comparisons of their respective uterine environments, and many have suggested that the reported outcome and risk differences are due to negative effects of controlled ovarian stimulation (COS) on the uterine environment in fresh transfers. This review will therefore start by examining the effects of COS on the uterine environment.

FIGURE 2



Trends in RR for live birth per transfer in FET vs. fresh transfer by SART age group. An RR exceeding 1.0 indicates greater birth rate with FET. By 2012 the birth rate per transfer with FET exceeded that for fresh transfer in the four oldest age groups.

Shapiro. Cryopreservation of embryo cohorts. Fertil Steril 2014.

EFFECT OF COS ON ENDOMETRIAL DEVELOPMENT AND RECEPTIVITY

Controlled ovarian stimulation with exogenous gonadotropins is routinely used to promote follicular development so that many oocytes may be obtained for cycles of IVF. The developing follicles are typically far more numerous than in natural menstrual cycles and collectively produce supraphysiologic levels of E_2, P, and other hormones. Estradiol and P are closely linked to endometrial development and maturation.

Two frequently observed features of endometria after COS are advanced histology (2–4) and advanced down-regulation of the P receptor (3, 4), each a suspected indicator of an advanced receptive phase. The degree of histologic advancement correlates with premature P elevation and with implantation failure through an effect of embryo–endometrium asynchrony (2, 5, 6). Nucleolar channel system formation is also advanced after COS (7).

Implantation patterns in cycles with and without COS have shown greater implantation rates of day-5 blastocysts when compared with day-6 blastocysts in cycles with COS exposure, but not in cycles without COS exposure (8, 9), and greater implantation rates of day-6 blastocysts in freeze–thaw cycles than in fresh transfer after COS (9–11). One randomized trial found greater pregnancy and implantation rates with frozen–thawed embryos than with fresh embryos transferred into endometria exposed to COS (12). A comparison of embryos in a shared oocyte donation program found reduced pregnancy rates in donors exposed to COS when compared with recipients without COS exposure using oocytes from the same retrievals (13). Collectively, these findings suggest reduced endometrial receptivity after COS exposure, perhaps through a selection bias against implantation of embryos