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Subcutaneous progesterone: a more patient friendly approach for programmed frozen embryo transfers.

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Subcutaneous progesterone: a more patient friendly approach for programmed frozen embryo transfers.

Patient convenience and autonomy have moved front and center to our discussion of how best to assist patients in conceiving through ART. Buzz-words such as “minimal stimulation”, “needle-less IVF” and “time to conception” have taken over the discourse around infertility treatment. Embryo cryopreservation has become an integral part of the ART process to improve the probability of live birth following a single cycle of stimulation. Limiting the number of embryos transferred to a single embryo and cryopreserving excess embryos has been the most successful means of limiting multiple gestations. Replacing cryopreserved embryos requires either identifying the natural cycle LH surge to synchronize the embryo stage with uterine development or utilizing hormone replacement to prepare a synchronized endometrium with embryo development. While estradiol replacement can be either oral or transdermal with similar efficacy, progesterone replacement has proved more challenging. Intramuscular (IM) progesterone, which has been the gold standard for many years yields higher pregnancy rates and lower miscarriage rates when compared to vaginal progesterone replacement in hormonally prepared cycles (1). This hormone replacement treatment must be continued until approximately 10 weeks of gestational age until the luteo-placental shift is complete. Even though programmed FET’s have been associated with a twofold higher probability of hypertensive disorders of pregnancy (adjusted OR 2.39; 95% CI, 1.37-4.17) and overall maternal complications (adjusted OR 2.21; 95% CI, 1.51-3.22) compared to embryo replacement based on natural LH surge timing (2), this form of embryo transfer appears to be the predominant approach in most ART clinics.

The # of cycles in which all embryos are frozen thereby requiring a subsequent transfer of a frozen embryo appears to now have surpassed the number of patients undergoing fresh embryo transfer 3-5 days following retrieval of oocytes in the USA. The latest available SART report in 2019 (3), there were more frozen embryo transfers (FET) performed (72,373 FET's) as the first transfer than the transfer of fresh embryos (54,527 fresh embryo transfers).

In this issue , Boynukalin et al report on their prospective, non-randomized study to evaluate the efficacy of an aqueous SQ progesterone (not available yet in many countries) to IM progesterone for hormone replacement in artificially programmed frozen embryo transfer cycles (4). A total of 224 patients ≤35 years of age were included and the choice of progesterone was left to the patient and the provider based on proximity to the hospital for the daily IM injections. Only the first frozen embryo transfer cycle was included after a freeze all cycle. Exclusion criteria included use of embryos that were PGT-A tested and other factors associated with reduced implantation rates like uterine pathology and hydrosalpinx as well as any additional vaginal progesterone use. All other parameters were similar between the 2 groups (age, BMI, P4 levels both on day of first administration and day of ET, embryo quality and endometrial thickness). There were no significant differences in the implantation rate (64.7% vs. 62.6%), miscarriage rate (24.4% vs. 17.5%) or ongoing pregnancy rate (48.9% vs. 51.6%) between the SQ P4 and IM P4 groups respectively. Interestingly, patients in the lowest quartile of P4 levels on the day of ET in both groups had the lowest pregnancy rates compared to all of the other quartiles. As long as P4 levels were > 15.2 ng/ml in the SQ and 16.5

ng/ml in the IM P4 groups respectively, outcomes were similar. The only parameter that impacted these outcomes in this group of young patients was, as expected embryo quality.

Since most IVF clinics prefer to schedule their frozen embryo transfers using hormone replacement, this study reinforces reports in the literature that parenteral P4 given via the SQ route provides equivalent outcomes with regard to live birth rates when compared to IM route of administration. We should not forget, however that frozen embryo transfers can be performed during a natural or induced ovulatory cycle with equivalent or better pregnancy outcomes compared to artificially programmed hormone replacement cycles without the need for parenteral administration of progesterone (5). Despite this knowledge, many programs continue to exclusively utilize artificial cycles to time frozen embryo transfers mostly for the convenience of the patient and the clinic.

IVF has evolved into a more “patient-friendly” and effective treatment with random start stimulation, progesterone or GnRH antagonists to prevent an unwanted LH surge, GnRH agonists to induce an LH surge and avoid ovarian hyperstimulation in at risk patients. These strategies also include vitrification of embryos and embryo transfer in a subsequent cycle to attempt pregnancy. Our ability to vitrify embryos without apparent reduction in the viability of the embryo has improved overall cumulative live birth rates following a single cycle of ovarian stimulation. For patients requiring artificial hormone replacement for their FET, SQ aqueous progesterone appears to provide equivalent outcomes to IM administration of P4 in oil. It allows for patients to more easily administer the injections by themselves and not need to rely on a partner or friend which continues to improve the patient

experience while undergoing stressful treatments in the quest to have a child. Hopefully in the near future SQ progesterone will be available universally for all patients undergoing programmed frozen embryo transfers.

1) Devine K, Richter KS, Widra EA, McKeeby JL. Vitrified blastocyst transfe cycles with theuse of only vaginal progesterone replacement with endometrin have inferior ongoing pregnancy rates: results from the planned interim analysis of a three-arm randomized controlled non-inferiority trial. Fertil Steril 2018;109:266-75.

2) Makhijani R, Bartels C, Godiwala P, et al Maternal and perinatal outcomes in programmed versus natural vitrified-warmed blastocyst transfer cycles. RBMO 2020;41(2):300-308

3) SART data available at: https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reportingYear=2019

4) Boynukalin FK, Abali R, Gultomruk M, et al. Does subcutaneous progesterone provide similar ongoing pregnancy rate compared to intramuscular progesterone in hormone replacement therapy frozen embryo transfer cycles? 2023

5) Melnick AM, Setton R, Stone L et al. Replacing single frozen-thawed euploid embryos in a natural cycle in ovulatory women may increase live birth rates compared to medicated cycles in anovulatory women. J Assist Reprod Genet 2017;34:1325-1331