COULD SUBLINGUAL PROGESTERONE BE A VIABLE ALTERNATIVE TO INTRAMUSCULAR PROGESTERONE IN OIL FOR PROGRAMMED FROZEN EMBRYO TRANSFER CYCLES?

RS Mandelbaum[1,2], N Raj-Derouin[3], K Erickson[4], I Sriprasert[1], JZ Guner[1,2], MM Quinn[2], B Kolb[2], JG Wilcox[2], RJ Paulson[1,2]

1) Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Southern California Keck School of Medicine, Los Angeles, CA, USA
2) HRC Fertility, an affiliate of Keck School of Medicine at USC, Pasadena, CA, USA
3) Department of Obstetrics and Gynecology, Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA
4) Keck School of Medicine, University of Southern California, Los Angeles, CA

BACKGROUND: Programmed frozen embryo transfers (pFET) are reliant on exogenous progesterone for endometrial preparation and to support implantation and early pregnancy given the absence of a corpus luteum. Because oral progesterone has poor absorption and bioavailability due to hepatic first-pass effect, pFET protocols typically involve intramuscular (IM) and/or vaginal routes of administration. A recent study found that IM progesterone in oil led to significantly superior live birth rates compared to vaginal administration alone in pFET cycles, yet IM injections are painful and lead to poorer patient satisfaction. [1] Progesterone can also be administered via the sublingual (SL) route, which may be an option to also bypass first-pass effect and achieve high serum progesterone levels while obviating the need for frequent IM injection, but pregnancy and birth outcomes have not been previously evaluated.

OBJECTIVE: To compare pregnancy outcomes following single euploid pFETs in women who took SL progesterone as compared to IM progesterone injections.

MATERIALS AND METHODS: This is a retrospective analysis of patients who underwent single euploid pFETs at a single center between 1/2018 and 4/2023. Exclusion criteria included lack of PGT-A, multiple embryo transfer, or use of a gestational carrier or donor gametes. Patients either received compounded progesterone lozenges containing 200mg three times per day (MDR Pharmacy) or 50mg of IM progesterone in oil daily. Both groups also received vaginal progesterone supplementation. Primary outcomes included clinical pregnancy rate (bhCG $\geq$ 5 mIU/mL), ongoing pregnancy rate (pregnancy progressing past 8 weeks), live birth rate, and miscarriage rate, all assessed with multivariate logistic regression accounting for age, endometrial thickness, and physician performing the transfer. Secondary outcomes included progesterone levels at or one day prior to embryo transfer and at the time of the first pregnancy test as well as birth weight, all assessed with student's t-test.

RESULTS: Of 1,951 pFETs included, 921 (47.2%) were in the SL progesterone group and 1,030 (52.8%) were in the IM progesterone group. Patients in the SL group were on average one year younger than those in the IM group (37.2 ($\pm$ 4.9) vs. 36.2 ($\pm$ 4.9) (P<0.01)). There was no difference in pregnancy and birth outcomes between the two groups (P=NS, all) (Table 1). In the IM progesterone group, mean serum progesterone levels were higher at the time of embryo transfer (41.61 $\pm$ 10.90 vs. 30.47 $\pm$ 15.73 ng/mL, P<0.01) and at first bhCG measurement (36.5 $\pm$ 11.50 vs. 29.4 $\pm$ 14.97 ng/mL, P<0.01) as compared to the SL group, however as aforementioned, this did not translate to any differences in pregnancy outcomes. Mean birth

weight among live births did not differ between the IM and SL progesterone groups (7.12 ± 1.15 lbs vs. 7.01 ± 1.01 lbs, P=NS, respectively).

Table 1: Pregnancy and Birth Outcomes of Single Euploid Frozen Embryo Transfers

	Sublingual progesterone n = 921 (47.2%)	**Intramuscular progesterone** n = 1,030 (52.8%)	OR (95% CI), P-value
Clinical pregnancy rate (positive hCG per transfer)	74.4%	69.5%	1.12 (0.80-1.56) P= 0.52
Ongoing pregnancy rate (pregnancy ≥ 8 weeks per transfer)	61.1%	56.1%	1.25 (0.92-1.69) P=0.15
Live birth rate (per transfer, excluding currently ongoing pregnancies)	57%	50.9%	1.34 (0.96-1.87) P=0.09
Biochemical pregnancy loss (per positive hCG)	11.5%	12.8%	0.86 (0.58-1.27) P=0.45
Clinical pregnancy loss (per positive hCG)	12.4%	11.5%	0.96 (0.65-1.43) P=0.85
Overall pregnancy loss (per positive hCG)	24.1%	25.2%	0.87 (0.65-1.17) P=0.35

CONCLUSIONS: SL progesterone is a viable alternative to IM progesterone for pFET that can minimize injection burden and likely improve patient satisfaction without compromising pregnancy outcomes. Progesterone levels, while slightly lower than the IM route, are in an acceptable range for luteal support.

FINANCIAL SUPPORT: none

REFERENCES:

1. Devine K, Richter KS, Jahandideh S, Widra EA, McKeeby JL. Intramuscular progesterone optimizes live birth from programmed frozen embryo transfer: a randomized clinical trial. Fertil Steril. 2021 Sep;116(3):633-643.