TITLE: ALTERNATIVE STRATEGY FOR TRUE NATURAL FROZEN EMBRYO TRANSFERS

AUTHORS: Papri Sarkar, MD[1], Kerry Flannagan PhD[2], Jerry Wang[2], Shayne M Plosker, MD[1,3], Anthony N Imudia MD[1,3]

[1]Department of Obstetrics & Gynecology, University of South Florida, Morsani College of Medicine, Tampa, FL, USA.
[2]Shady Grove Fertility Reproductive Science Center, Rockville, MD, USA.
[3]Shady Grove Fertility of Tampa Bay, Tampa, FL, USA.

BACKGROUND: The window of implantation in a natural cycle frozen embryo transfer (NC-FET) is still unclear. The current practice relies on detecting the luteinizing hormone (LH) surge to time the embryo transfer (ET). However, mistaking a premature LH surge for the true ovulatory surge can lead to suboptimal FET timing, cycle cancellation and/or reduced pregnancy rates. Following ovulation, the corpus luteum produces progesterone (P4), which alters the endometrium, rendering it receptive during a particular time period. We propose an alternative approach to NC-FET based on daily serum P4 measurements post-LH surge to time FET.

OBJECTIVE: To investigate whether NC-FET performed 2 days after the serum P4 level is ≥5ng/mL, post LH-surge, yields equivalent if not superior live birth rates (LBR) compared to conventional FET strategies.

MATERIALS AND METHODS: A retrospective cohort study of patients undergoing autologous single embryo FET at multicentre fertility clinics between 2020 – 2022 was performed. Modified Poisson regression estimated relative risks (RR) with 95% CI of the pregnancy outcomes. The primary outcome was LBR compared between different FET protocols.

1. Group A: NC-FET based on daily P4 measurement (FET 2 days after serum P4 reaches ≥ 5ng/mL post LH-surge).
2. Group B: Estradiol exposure followed by P4 supplementation, and FET performed on the 6th day of P4.
3. Group C: True NC-FET group (FET 6 days post LH-surge).

4. Group D: Modified NC-FET group (FET 7 days post HCG trigger).

RESULTS: The study included 23,211 FET cycles (Group A = 41, Group B = 21,851, Group C = 635, and Group D = 684 cycles). Mean age at egg-retrieval across all groups was 35 years. Most programmed FET cycles were patients' 1st transfer attempt while the NC-FETs were mainly 2nd or 3rd attempt. Across all groups, median endometrial thickness was > 8mm.
LBR per transfer was not significantly different between Group A (48.8%) and B (46.8%); RR 95% CI 1.11 (0.79, 1.56). Similarly, there were no significant differences observed for pregnancy rates 58.5 % vs. 69%; RR 0.87 (0.65, 1.17), and clinical pregnancy rates 48.8% vs. 59.1%; RR 0.86 (0.62, 1.21) between Group A and B cycles. Similar results were observed with euploid only embryos.
In our cohort, when LBR of well-established NC-FET protocols were compared with programmed FET, higher LBR was noted in Group C (48.7% vs. 46.8%, 1.09 (1.01, 1.18) and group D (52.2% vs. 46.8%; 1.19 (1.1, 1.28). However, no difference was noted in LBR when the novel NC-FET protocol was compared with the traditional NC-FET protocols.
Among Group A cycles, the median duration required to attain serum P4 level $\geq$ 5ng/mL post LH-surge was 4 days leading to most of the FETs happening on day 6 post LH-surge, which corroborates with the true NC-FET strategy.

CONCLUSIONS: Monitoring daily P4 levels post-LH surge in NC-FET and scheduling transfer 2 days after serum P4 levels is $\geq$5ng/mL could serve as an alternative strategy with comparable pregnancy outcome to traditional NC-FET. This approach may be of particular interest when LH surge is indeterminate, potentially reducing the risk of cycle cancellation .

FINANCIAL SUPPORT: None