# COMPARING CLINICAL EFFICIENCY AND CYCLE CANCELLATION AMONG MODIFIED NATURAL, STIMULATED, AND PROGRAMMED FROZEN EMBRYO TRANSFER PROTOCOLS

Anjali J. Patel, MD[1]; Christine Whitehead[2]; Alejandro Sánchez Martínez[3]; William Spear[2]; Angela Q. Leung, MD[2]

[1]Robert Wood Johnson Medical School, New Brunswick, NJ, USA. [2]IVIRMA New Jersey, Basking Ridge, NJ, USA. [3]IVIRMA Global Research Alliance, IVI Foundation, Instituto de Investigación Sanitaria La Fe (IIS La Fe), Avenida Fernando Abril Martorell, Valencia, Spain.

## BACKGROUND

- Frozen embryo transfer (FET) protocols require endometrial preparation through endogenous or exogenous hormones.

| | Modified Natural (mNC) | Stimulated | Programmed |
|---|---|---|---|
| Def. | spontaneous ovulation or with hCG trigger) | medication-induced follicular development | synthetic hormonal preparation |
| Pros | fewer medications and injections | more natural approach for patients ineligible for mNC | scheduling flexibility |
| Cons | perceived higher cancellation rates due to suboptimal conditions (e.g inadequate endometrial lining/ premature ovulation), perceived higher number of bloodwork and monitoring visits | | increased cost and obstetric/ perinatal risk |

- Current evidence shows no difference in live birth rates (LBR) between modified natural or programmed protocols[1,2].
- Cancelled cycles can impose both psychological and financial cost to the patient[4].

## OBJECTIVE

- To compare clinical efficiency among modified natural (mNC) with hCG trigger, stimulated, and programmed FET cycles, focusing on:
  - cancellation rate,
  - monitoring burden, and
  - time to pregnancy and live birth.

## METHODS

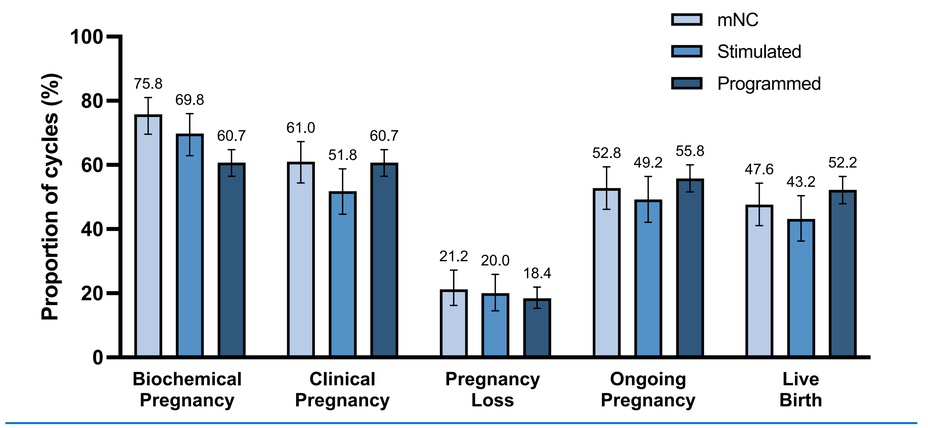
- Retrospective cohort study of patients at a large single center who underwent first single-euploid blastocyst FET from 2017 to 2024 and had ≥1 cancelled FET cycle.
- Exclusion criteria included lack of PGT-A testing, cycle protocol conversion, or prior FET at outside institutions.
- Cycles were categorized as mNC, stimulated, or programmed.
- Primary outcome was overall cancellation rate per protocol.
- Secondary outcomes included pregnancy and live birth rates, number of cycles to achieve pregnancy and live birth, and total monitoring visits.
- Pairwise comparisons between FET protocols were performed using ANOVA with Bonferroni-adjusted post hoc tests as applicable.
- Multivariate logistic regression was used for the primary outcome adjusting for age at time of FET, BMI, diagnosis and FET year and pregnancy outcomes controlling for age at FET, BMI, day of blastulation, SART embryo grade and FET year, with significance set at p<0.05.

| Variable | mNC | Stimulated | Programmed | Total | p-value |
|---|---|---|---|---|---|
| **Characteristics at Oocyte Retrieval** | | | | | |
| | n=171 | n=138 | n=428 | n=737 | |
| Oocyte Age | 36.3 ± 3.8 | 35.3 ± 3.5 | 35.9 ± 4.1 | 35.9 ± 3.9 | 0.067 |
| BMI at VOR | 25.9 ± 5.4 | 25.4 ± 5.3 | 27.0 ± 5.9 | 26.4 ± 5.7 | 0.0062+ |
| Blastocyst Count | 5.4 ± 3.8 | 6.6 ± 5.6 | 6.0 ± 5.3 | 6.0 ± 5.0 | 0.101 |
| **Characteristics of Each Embryo Transfer Cycle** | | | | | |
| Mean Pt Age at ET | n=405 | n=297 | n=1200 | n=1902 | 0.0037+++ |
| | 37.1 ± 3.9 | 36.1 ± 3.7 | 36.5 ± 4.3 | 36.5 ± 4.1 | |
| Mean BMI at ET | n=405 | n=295 | n=1195 | n=1895 | 0.0008++ |
| | 25.7 ± 5.2 | 26.0 ± 5.3 | 26.9 ± 5.8 | 26.5 ± 5.6 | |

### TABLE 1. Baseline Characteristics

*Reported as mean ±SD or proportion [95% CI]. After post hoc analysis: +not significant, ++significant between mNC and programmed, +++significant between mNC and stimulated and mNC and programmed*

| Cycle Type | mNC | Stimulated | Programmed |
|---|---|---|---|
| Cancellation rate (p<0.001) | 7.0% | 21.2% | 5.0% |

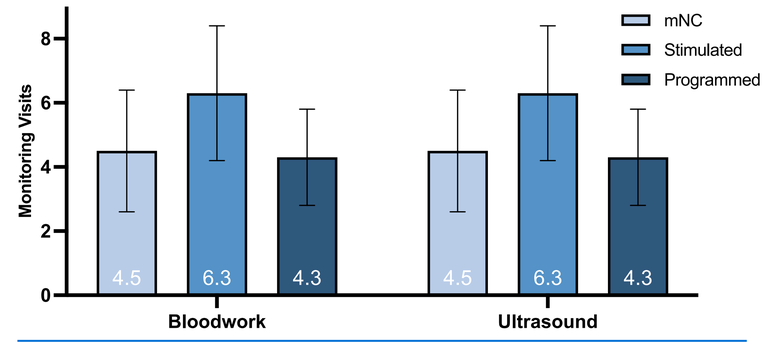



### FIGURE 3. Adjusted Pregnancy and Live Birth Outcomes

*Reported as % with error bars showing 95% CI.*

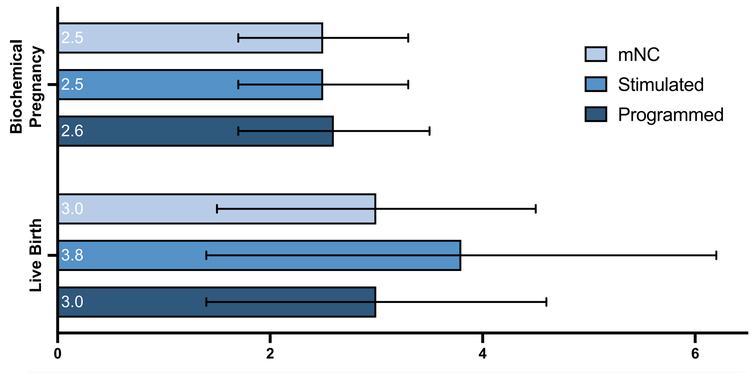
## RESULTS

- 728 patients met inclusion criteria, representing 1,902 FET attempts: 405 cycles (21.3%) were mNC, 297 (15.6%) stimulated, and 1,200 (63.1%) programmed.
- Overall, 922 cycles were cancelled. Cancellation rate was 21.2% for stimulated, 7.0% for natural, and 5.0% for programmed cycles (p<0.001).
- Following cycle cancellation, the protocol was changed in the subsequent cycle in 106 (40.6%) of natural cycles, 167 (63.0%) of stimulated cycles, and 110 (17.0%) of programmed cycles (p<0.0001).
- Pregnancy outcomes, including biochemical, clinical, and ongoing pregnancy, pregnancy loss, and live birth were similar (Figure 3). mNC cycles showed slightly higher clinical pregnancy rate compared with stimulated cycles, but live birth rates were comparable.
- Controlling for confounders, stimulated cycles required significantly more monitoring visits compared with mNC and programmed cycles (Figure 1). Stimulated cycles also required significantly more attempts to achieve chemical pregnancy/live birth (Figure 2).




### FIGURE 1. Number of Monitoring Visits

*Mean ±SD. P value <0.0001 between all groups for bloodwork, P value <0.0001 between stimulated and mNC/stimulated and programmed for ultrasound visits.*




### FIGURE 2. Number of Cycle Attempts

*Reported as mean ±SD. P value <0.0001 between stimulated and mNC and stimulated and programmed for both outcomes.*

## CONCLUSIONS

- **Stimulated FET cycles were associated with higher cancellation rates, increased monitoring visits, and a higher likelihood of protocol changes before successful transfer.**
- **mNC and programmed cycles demonstrated comparable efficiency.**
- **Pregnancy and live birth outcomes were similar across all cycle types.**
- **These findings challenge the previously held notion that natural FET cycles are more susceptible to cancellation.**

## REFERENCES

1. 2. 3. 4.