MODIFIED-NATURAL CYCLES (mNC) ARE REIGNING SUPREME: A 5-YEAR RETROSPECTIVE ANALYSIS OF LIVE BIRTHS FOLLOWING SINGLE, EUPLOID, FROZEN EMBRYO TRANSFER (FET) STRATIFIED BY ENDOMETRIAL PREPARATION METHOD

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Background: The number of FETs has grown exponentially within recent years.[1] The choice of endometrial preparation method varies based on several factors including a patient's ovulatory status, preference, clinic scheduling convenience and anecdotal evidence. For patients without a clear indication for a specific protocol, it remains uncertain which method of endometrial preparation leads to the highest live birth rate as current data is conflicting.[2-3] The literature has highlighted the obstetrical benefit to having a corpus luteum in mNC;[4] yet due to the lack of randomized controlled trials, the evidence does not establish a clear treatment hierarchy for FETs.

Objective: To compare live birth outcomes between three different FET endometrial preparation methods: mNC, stimulated, and programmed.

Materials and Methods: A retrospective, multisite, cohort study was performed from January 2019 through December 2023. Patients undergoing their first, autologous, FET cycle using a single blastocyst negative for whole chromosome aneuploidy via PGT-A were included. PGT-M or SR, segmental or mosaic findings, >1 thaw/biopsy procedure, and untested embryos were excluded. The primary outcome was live birth, defined as $\geq$20 weeks gestational age (GA). Secondary outcomes included biochemical (positive bhCG), clinical (cardiac activity present) and ongoing pregnancy (8-9 weeks GA), pregnancy loss (loss of positive hCG or clinical pregnancy), delivery mode, birth weight and GA. Patients were grouped based on endometrial preparation method. Embryo grades were categorized via the SART classification system. ANOVA was performed to analyze differences between groups and Bonferroni correction as applicable for post hoc analyses. Multivariate logistic regression was used to adjust for confounders (oocyte age, BMI, day of blastulation, SART embryo grade class). A p-value < 0.05 was considered statistically significant.

Results: A total of 11,005 patients met criteria (Table 1). 9,205 (83.64%) were programmed, 1,481 (13.46%) were mNC and 319 (2.9 %) were stimulated FETs.

Baseline variables showed no significant differences between programmed and mNC FETs regarding oocyte age, serum FSH, total number and day of blastocysts, or endometrial thickness (mm) prior to progesterone initiation. However, a significant difference was found with mNC and stimulated FETs having a lower mean BMI (kg/m^2). Patients in stimulated FETs were younger, had lower FSH levels, more blastocysts, and thinner linings.

After adjusting for confounders, mNC demonstrated significant increases in biochemical, clinical, and ongoing pregnancy as well as live birth compared to programmed FETs (see Table 2). Furthermore, mNC were associated with a reduction in pregnancy loss (see Table 2). Stimulated and programmed FETs performed similarly across all outcomes. Neonatal outcomes revealed similar birth weights and GA between programmed and mNC FETs, while stimulated FETs had slightly lower birth weights and shorter GA, though these differences are

not clinically significant (Table 3). Finally, mNC FETs were less likely to result in cesarean section (aOR 0.77, CI: 0.67-0.89, p<0.001).

Conclusions: This study demonstrates a 32.6% increase in live birth for those that utilized a mNC FET. These results may have important clinical implications when deciding on type of endometrial preparation method and may encourage clinics to adopt practice models that accommodate mNC FET.

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Table 1. Unadjusted Descriptive Pregnancy and Live Birth Outcomes

	Group			
Outcome	**Programmed**	**mNC**	**Stimulated**	**p-value**
Biochemical Pregnancy	N (proportion) 95% CI	N (proportion) 95% CI	N (proportion) 95% CI	0.01
No	1935 (21.02%) (20.19-21.87)	265 (17.89%) (15.97-19.94)	75 (23.51%) (18.97-28.56)	
Yes	7270 (78.98%) (78.13-79.81)	1216 (82.11%) (80.06-84.03)	244 (76.49%)(71.44-81.03)	
Clinical Pregnancy				<0.001
No	3183 (34.58%) (33.61-35.56)	428 (28.90%) (26.60-31.28)	122 (38.24%) (32.89-43.82)	
Yes	6022 (65.42%) (64.44-66.39)	1053 (71.10%) (68.72-73.40)	197 (61.76%) (56.18-67.11)	
Ectopic Pregnancy				0.681
No	9169 (99.61%) (99.46-99.73)	1473 (99.46%) (98.94-99.77)	318 (99.69%) (98.27-99.99)	
Yes	36 (0.39%) (0.27-0.54)	8 (0.54%) (0.23-1.06)	1 (0.31%) (0.01-1.73)	
Pregnancy Loss				<0.001
No	5602 (77.06%) (76.07-78.02)	1005 (82.65%) (80.40-84.74)	186 (76.23%) (70.38-81.43)	
Yes	1668 (22.94%) (21.98-23.93)	211 (17.35%) (15.26-19.60)	58 (23.77%) (18.57-29.62)	
Ongoing Pregnancy				<0.001
No	3429 (37.25%) (36.26-38.25)	448 (30.25%) (27.92-32.66)	130 (40.75%) (35.31-46.37)	
Yes	5776 (62.75%) (61.75-63.74)	1033 (69.75%) (67.34-72.08)	189 (59.25%) (53.63-64.69)	
Live Birth				<0.001
No	3666 (39.87%)	486 (32.82%)	135 (42.32%)	

	Group			
	(38.87-40.88)	(30.43-35.27)	(36.83-47.95)	
Yes	5528 (60.13%) (59.12-61.13)	995 (67.18%) (64.73-69.57)	184 (57.68%) (52.05-63.17)	

Table 2. Adjusted Pregnancy and Live Birth Outcomes Compared to Programmed FET

Outcome	Group compared to programmed	aOR	95% CI	p-value	Change (%)
Biochemical Pregnancy	mNC	1.194	1.033 - 1.380	0.02	+19.4%
	Stimulated	0.857	0.656 - 1.121	0.26	N/A
Clinical Pregnancy	mNC	1.281	1.132 - 1.448	<0.001	+28.1%
	Stimulated	0.856	0.677 - 1.082	0.19	N/A
Ongoing Pregnancy	mNC	1.343	1.189 - 1.516	<0.001	+34.3%
	Stimulated	0.868	0.689 - 1.094	0.23	N/A
Pregnancy Loss	mNC	0.717	0.610 - 0.841	<0.001	-28.3%
	Stimulated	1.030	0.761 - 1.395	0.848	N/A
Live Birth	mNC	1.326	1.177 - 1.493	<0.001	+32.6%
	Stimulated	0.910	0.723 - 1.146	0.424	N/A

Table 3. Unadjusted Descriptive Delivery and Neonatal Outcomes

	Group			
Variable	**Programmed**	**mNC**	**Stimulated**	**p-value**
Birth Weight (grams)				0.002
Mean (SD) (95% CI)	3321.53 (576.19) (3306.32-3336.73)	3286.54 (576.44) (3250.68-3322.40)	3185.42 (628.59) (3093.74-3277.10)	
Gestational Age (weeks)				0.074
Mean (SD) (95% CI)	39.13 (2.05) (39.08-39.18)	39.17 (1.83) (39.05-39.28)	38.80 (2.44) (38.44-39.15)	
Delivery Mode				<0.001
Cesarean N (proportion), (95% CI)	2801 (51.48%) (50.14-52.82)	424 (43.44%) (40.31-46.62)	62 (34.64%) (27.70-42.10)	
Vaginal, N	2640 (48.52%) (47.18-49.86)	552 (56.56%)(53.38-59.69)	117 (65.36%) (57.90-72.30)	

	Group			
(proportion), (95% CI)				
Live Birth Count				0.009
Singletons N (proportion), (95% CI)	5473 (99.01%) (98.71-99.25)	974 (97.89%) (96.79-98.69)	181 (98.37%) (95.31-99.66)	
Twins N (proportion), (95% CI)	55 (0.99%) (0.75-1.29)	21 (2.11%) (1.31-3.21)	3 (1.63%) (0.34-4.69)	

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