Adding short-duration gonadotropin-releasing hormone antagonist and gonadotropin to natural cycle frozen embryo transfer allowed scheduling of transfer day without compromising live birth

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Objective: To determine whether there is an association between the type of natural cycle frozen embryo transfer (FET) (scheduled vs. traditional) and live birth outcomes.
Design: Retrospective cohort of all natural cycle FETs across a single network of fertility clinics in the United States.
Subjects: All natural cycle FETs performed in ovulatory patients between January 2019 and April 2022.
Exposure: Scheduled natural cycle FET cycles that received a short-duration of gonadotropin-releasing hormone antagonist (1 ampule/d) with low-dose gonadotropins (75 IU/d) to delay ovulation to enable more flexible scheduling of the FET were compared with cycles without delay.
Main Outcome Measures: Live birth.
Results: There were a total of 1,087 natural cycle FETs that met the inclusion criteria. The scheduled natural cycle FET protocol was used in 114 (10.5%) of these cycles. The mean age was 35 (interquartile range, 33–38) years. Preimplantation genetic testing for aneuploidy was used in 76.3% (n = 87) of scheduled natural cycle FET cycles and 68.9% (n = 670) of natural cycle FET cycles. The scheduled natural cycle FET group had a significantly higher estradiol level (318 vs. 249 pg/mL) and a lower luteinizing hormone level (5.7 vs. 13.4 mIU/mL) at ovulatory trigger but a comparable peak endometrial thickness (9.4 vs. 9.7 mm) compared with the natural cycle FET group. Overall, there was a significant increase in the rates of positive human chorionic gonadotropin (scheduled natural cycle, 81.6%, vs. natural cycle, 64.3%; relative risk [RR], 1.26 [95% confidence interval {CI}, 1.15–1.38]) and clinical pregnancy (scheduled natural cycle, 68.4%, vs. natural cycle, 57.1%; RR, 1.21 [95% CI, 1.06–1.38]) in the scheduled natural cycle group. There were a higher proportion of live births in the scheduled natural cycle group; however, this did not reach statistical significance (scheduled natural cycle, 57.0%, vs. natural cycle, 49.4%; RR, 1.15 [95% CI, 0.97–1.36]). A subanalysis of preimplantation genetic testing for aneuploidy cycles yielded similar results.
Conclusion: A scheduled natural cycle FET protocol using a short duration of gonadotropin-releasing hormone antagonist along with low-dose gonadotropin add-back did not reduce live birth compared with traditional natural cycle FET cycles. These results suggest that this is an alternative FET protocol that may serve as a viable strategy to provide flexibility in scheduling the day of FET while still allowing a patient to undergo a natural cycle protocol. This protocol modification may enable more clinics to offer natural cycle FET. (Fertil Steril® 2025;124:71–8. ©2025 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Natural cycle, frozen embryo transfer, endometrial preparation, GnRH antagonist, assisted reproductive technology

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Over the past decade, there has been a significant increase in the number of frozen embryo transfers (FETs) (1). In 2021, there were >250,000 FETs performed in the United States alone (2). This trend has been driven by advances in extended culture and cryopreservation techniques. Furthermore, by allowing embryo transfer to take place outside the supraphysiological hormonal milieu of an egg retrieval cycle, FET reduces the risk of ovarian hyperstimulation syndrome and allows embryo selection with preimplantation genetic testing (3, 4). Generally, there are two approaches to preparing the endometrium for FET: programmed and natural cycles (5, 6). Programmed cycles, also known as hormone replacement cycles, use exogenous estradiol and progesterone to prepare the endometrium. The administration of estradiol in the follicular phase suppresses ovulation, and the corpus luteum remains notably absent (4, 5). In contrast, natural cycle FET takes advantage of follicular development, ovulation, and luteinization as a "natural" means of endometrial preparation. The FET is scheduled on the basis of luteinizing hormone (LH) surge or human chorionic gonadotropin (hCG) trigger after follicular and endometrial development (5, 6). Thus, one notable advantage of a programmed cycle is that it facilitates scheduling of the FET compared with natural cycle where timing of the FET is dictated by ovulation.

Compared with fresh embryo transfers, pregnancies achieved via FET have been associated with an increased risk of certain adverse obstetric outcomes, including hypertensive disorders of pregnancy (7, 8). However, more recent evidence suggests that this association us limited to programmed FET, where the corpus luteum is notably absent (4, 9). Observational studies have reported decreased risks of preeclampsia, postpartum hemorrhage, and macrosomia in natural cycle compared with programmed FET (10–15). With regard to preeclampsia, a recent meta-analysis found the risk in natural cycle to be half that of programmed FET (16). Overall, these observational studies suggest the potential importance of the corpus luteum in early placentation and vascular remodeling (4, 17). However, given that the data, thus far, are observational, data from experimental studies are still needed before a cause and effect relationship can be established and a randomized trial (NatPro) is currently underway (18). Aside from secreting steroid hormones, the corpus luteum produces a variety of vasoactive substances, including relaxin and vascular endothelial growth factor, that are thought to play a role, not only in placentation but also in cardiovascular and renal adaptions of pregnancy (4, 9, 17, 19).

Despite observational studies suggesting similar live birth and decreased obstetric risk, many clinics either do not offer natural cycle FET or significantly restrict its use (16, 20, 21) due to staffing and scheduling challenges relative to programmed FET cycles, for which transfers can be easily scheduled. A recent survey study of fertility clinics found that "lack of timing predictability for transfer" (81%) and "increased burden on staff/laboratory personnel on holidays and weekends" (54%) comprise the main reasons that most FETs are still performed in programmed cycles (21).

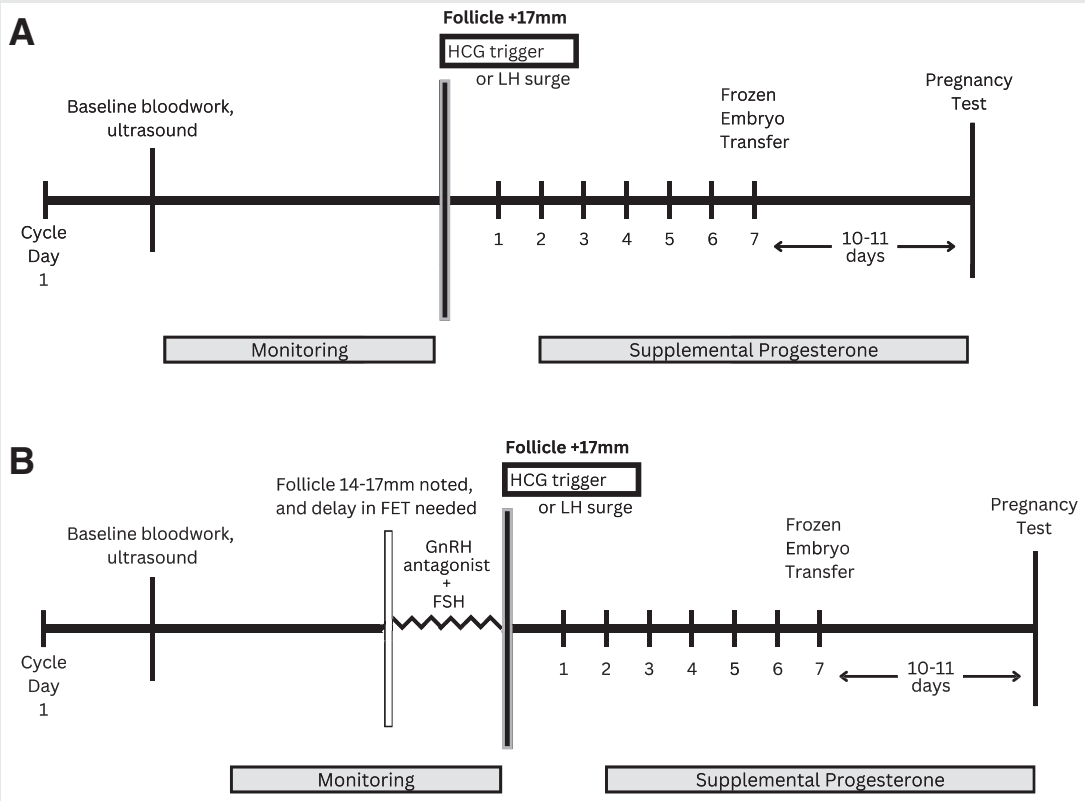
Given that timing of transfer is dictated by ovulation in natural cycle FET, novel strategies that delay the initiation of ovulation would allow for increased flexibility of transfer timing, which may result in increased utilization. In this study, we describe a novel protocol that uses a short duration of gonadotropin-releasing hormone (GnRH) antagonist along with low-dose gonadotropins to delay the development of a dominant follicle to provide more flexibility in timing of FET. Our primary objective was to determine whether the use of a scheduled natural cycle protocol compared with a traditional natural cycle protocol was associated with live birth outcome. We hypothesized that live birth would be similar between cycles that employed the scheduled natural cycle protocol and those that employed the traditional natural cycle protocol that is primarily used at our center.

MATERIALS AND METHODS

This was a retrospective cohort study across a single network of fertility clinics with natural cycle FET performed at multiple embryology laboratories in the United States. This research was conducted with approval from Advarra Institutional Review Board (R2009.1). All autologous natural cycle vitrified-warmed blastocyst FET cycles performed between January 2019 and April 2022 were included. Natural cycle was defined as FET preparation where at least one dominant follicle developed spontaneously without any exogenous stimulation and ovulation occurred due to hCG administration and/or documented spontaneous LH surge. Patients with oligo-ovulation (or a diagnosis of polycystic ovary syndrome) were excluded given that these patients typically require ovulation induction with either clomiphene citrate, letrozole, or exogenous gonadotropins before the natural development of a dominant follicle. As in many centers, given weekend staffing constraints, FETs are preferentially performed on weekdays in our network, to optimize standardization, quality control, and outcomes (21). Therefore, patients undergoing natural cycle FET are counseled that if their natural follicular progression threatens to result in a weekend FET, adjunctive medications may be used to delay ovulation and ensure weekday FET. Unless they have a contraindication to exogenous estradiol administration, patients are also offered programmed FET preparation.

The referent group (natural cycle FET) consisted of cycles where patients underwent monitoring according to the standard protocol at our clinic (Fig. 1A). Generally, patients presented for natural cycle monitoring approximately 4 days before their expected ovulatory trigger administration on the basis of the length of their natural cycle. Serum hormone levels (estradiol, progesterone, and LH) and transvaginal ultrasound of the uterus and ovaries were performed serially until the endometrial thickness was considered adequate and a dominant follicle measuring >17 mm was measured at which point an hCG ovulatory trigger was administered that evening. Occasionally, hCG trigger was omitted in the setting of a clear LH surge, typically >20 IU/mL, and taking into account baseline LH and increase over time. If any uncertainty regarding the endogenous LH surge, hCG trigger was

FIGURE 1



Schematic of protocols. (**A**) In the standard natural cycle protocol, patients underwent monitoring, and frozen embryo transfer (FET) was performed 6–7 days after human chorionic gonadotropin (hCG) trigger or 5–7 days after luteinizing hormone surge. (**B**) In the scheduled natural cycle protocol, patients underwent monitoring; however, when a follicle measuring ≥14 mm was noted and there was a need to delay FET, gonadotropin-releasing hormone (GnRH) antagonist and low-dose gonadotropin were administered. Subsequently, patients continued as per standard natural cycle protocol. FSH = follicle-stimulating hormone.

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also administered. The FET was performed 7 days after hCG trigger or 6 days after LH surge (5).

The study group (scheduled natural cycle) was initially managed with the same protocol until a follicle was measured between 14 and 17 mm on a Friday (not ready for hCG ovulatory trigger but at risk of an LH surge before Monday evening). At that point, these patients received a GnRH antagonist (0.25 mg, 1 ampule), and gonadotropin (75 IU) add-back (either recombinant follicle-stimulating hormone or human menopausal gonadotropin at provider discretion) was administered daily for typically three nights (median, 3; range, 1–4). These patients then returned for serum hormone levels and transvaginal ultrasound on Monday and received an hCG ovulatory trigger that evening if they met criteria (Fig. 1B). After the ovulatory trigger or LH surge in both groups, supplemental luteal progesterone with micronized vaginal progesterone (200 mg twice daily) was initiated 3–4 days before the FET. No additional bloodwork or ultrasound was performed between ovulatory trigger and pregnancy test other than ultrasound guidance at the time of the embryo transfer.

The primary outcome was live birth, defined as a live born infant at 22 weeks of gestation or beyond. The secondary outcomes included positive β-hCG, clinical pregnancy (presence of an intrauterine gestational sac), and spontaneous abortion.

Continuous variables were expressed as medians with interquartile ranges (IQRs), and categorical variables were expressed as counts with percentages. *P* values comparing distributions of covariates by cycle type were obtained using regression models fitted with generalized estimating equations to account for cycle repeats per patient. The outcome of these models was a given covariate, and cycle type was entered as a single predictor. The models were linear, log-linear, logistic, or ordinal multinomial logistic depending on the distribution of the outcome. The *P* value was obtained from a Wald test of the model parameter for the cycle type predictor. Generalized estimating equation modeling of the cycle and pregnancy outcomes was performed to control for potential confounding variables, selected a priori on the basis of biologically plausible association with the exposure and primary outcome. Variables in the model included the following: female age at time of transfer (years); female age at time of embryo creation (years); body mass index at transfer (kg/m^2); number of prior failed transfers; number of

embryos transferred; endometrial thickness (mm) ; notated diagnosis of "uterine factor" infertility; and preimplantation genetic testing for aneuploidy (PGT-A) utilization. Because untriggered cycles were eligible to be included in both the referent and study groups and the choice to trigger or not occurred after the choice to convert a patient's cycle to a scheduled natural cycle, we chose not to adjust for trigger vs. surge in the models. These models were fitted with an exchangeable correlation structure and were weighted by the inverse of the number of cycles contributed by a patient, to account for informative cluster sizing in which patients who successfully become pregnant are likely to contribute fewer cycles to the analysis (22). A subgroup analysis was performed, limited to PGT-A cycles. A *P* value of >.05 was considered statistically significant.

It is possible that the rate of cycle cancellation may differ between the study and referent groups, creating possible selection bias. To assess this, we compared the probability of cycle cancellation among scheduled natural cycles vs. among natural cycles in which at least one follicle reached a size of 14 mm (i.e., the group of natural cycles that would have been eligible to become scheduled natural cycles, if the large follicle was observed on a Friday). These probabilities were 3.6% (N = 10) and 8.1% (N = 36) among scheduled natural cycles and natural cycles, respectively (*P*=.02). We, therefore, conducted a sensitivity analysis accounting for potential selection bias using inverse probability of selection weighting. Stabilized weights were constructed using a logistic regression model with noncancellation as the outcome and predictors including cycle protocol (scheduled natural vs. natural), patient age, maximum observed follicle size, and primary diagnosis. These weights were applied to the same generalized estimating equation models as in the main analysis.

RESULTS

Data from 1,087 natural cycles (scheduled natural cycle, n = 114; natural cycle, n = 973) among 795 patients were analyzed. The median age at the time of ovarian stimulation was 35 (IQR, 33–38) years, and most patients had at least one prior failed embryo transfer (Table 1). Those in the scheduled natural cycle group had a small but statistically significantly lower body mass index (scheduled natural cycle, 23.7 [IQR, 21.5–26.8] kg/m^2, vs. natural cycle, 24.7 [IQR, 21.8–28.1] kg/m^2; *P*=.001) and were more likely to have unexplained infertility (scheduled natural cycle, 35.1%, vs. natural cycle, 25.4%; *P*=.029). Otherwise, there were no significant differences in patient characteristics assessed between groups.

Regarding cycle characteristics, the groups were comparable in terms of utilization of a single embryo transfer (scheduled natural cycle, 96.5%, vs. natural cycle, 92%; *P*=.090), and there was no significant difference in the proportion of cycles with PGT-A (scheduled natural cycle,

TABLE 1

Patient and cycle characteristics.

Variable	Scheduled natural cycle (N = 114)	Natural cycle (N = 973)	*P* value[a]
Patient characteristics			
Age at freeze, y	35 (33–37.8)	35 (33–38)	.44
Age at transfer, y	36 (34–39)	36 (34–39)	.85
BMI, kg/m^2	23.7 (21.5–26.8)	24.7 (21.8–28.1)	.001
Gravidity	2 (1–2.8)	1 (1–3)	.95
Parity	0 (0–1)	0 (0–1)	.29
Spontaneous abortions	0 (0–1)	0 (0–1)	.60
No. of prior failed transfers	1 (0–2)	1 (1–2)	.67
Primary diagnosis, n (%)			<.0001
DOR	9 (7.9)	95 (9.8)	
Tubal factor	9 (7.9)	82 (8.4)	
Uterine factor	4 (3.5)	33 (3.4)	
Endometriosis	3 (2.6)	38 (3.9)	
Male factor infertility	24 (21.1)	232 (23.8)	
Unexplained	40 (35.1)	247 (25.4)	
Other	25 (21.9)	246 (25.3)	
Cycle characteristics			
PGT-A, n (%)	87 (76.3)	670 (68.9)	.11
SET, n (%)	110 (96.5)	895 (92.0)	.09
E2, pg/mL[b]	318 (208–433)	249 (182–326)	.0002
P4, ng/mL[b]	0.48 (0.32–0.66)	0.54 (0.37–0.99)	.003
LH, mIU/mL[b]	5.7 (3.1–10.1)	13.4 (7.3–28.1)	<.0001
Maximum follicle diameter, mm	19.8 (17.8–21.1)	18.8 (17.5–20.4)	.03
Maximum endometrial thickness, mm	9.4 (8.3–10.9)	9.7 (8.5–11.2)	.06

Note: Data presented as medians (interquartile ranges) or counts (percentages). BMI = body mass index; DOR = diminished ovarian reserve; E2 = estradiol; hCG = human chorionic gonadotropin; LH = luteinizing hormone; P4 = progesterone; PGT-A = preimplantation genetic testing for aneuploidy; SET = single embryo transfer.

[a] Unadjusted *P* value.

[b] Serum levels at time of trigger or surge.

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76.3%, vs. natural cycle, 68.9%; $P=.11$). The dominant follicle exhibited a small but statistically significant larger mean diameter at the time of trigger in the scheduled natural cycle group (scheduled natural cycle, 19.8 [IQR, 17.8–21.1] mm, vs. natural cycle, 18.8 [IQR, 17.5–20.4] mm; $P=.030$), and the peak serum estradiol level was also significantly higher in the scheduled natural cycle group (scheduled natural cycle, 318 [IQR, 208–433] pg/mL, vs. natural cycle, 249 [IQR, 182–326] pg/mL; $P=.0002$). There was no significant difference in peak endometrial thickness or serum progesterone level on the day of ovulatory trigger between the groups. However, the peak serum LH level measured on the ovulatory trigger day was significantly lower in the scheduled natural cycle group (scheduled natural cycle, 5.7 [IQR, 3.1–10.1] mIU/mL, vs. natural, 13.4 [IQR, 7.3–28.1] mIU/mL; $P<.0001$).

The pregnancy outcomes from the primary analysis are shown in Table 2. The positive hCG (scheduled natural cycle, 81.6%, vs. natural cycle, 64.3%; relative risk [RR], 1.26 [95% confidence interval {CI}, 1.15–1.38]) and clinical pregnancy rates significantly increased in the scheduled natural cycle group (scheduled natural cycle, 68.4%, vs. natural cycle, 57.1%; RR, 1.21 [95% CI, 1.06–1.38]). Although there were a higher proportion of live births in the scheduled natural cycle group, this difference did not reach statistical significance (scheduled natural cycle, 57.0%, vs. natural cycle, 49.4%; RR, 1.15 [95% CI, 0.97–1.36]). Furthermore, there was no significant difference in spontaneous abortion between groups (scheduled natural cycle, 11.8%, vs. 9.7%; RR, 1.27 [95% CI, 0.65–2.46]).

Similar results were observed in a subanalysis of the FET cycles using PGT-A (Table 2). Again, the positive hCG rate significantly increased in the scheduled natural cycle group (scheduled natural cycle, 82.8%, vs. natural cycle, 66.3%; RR, 1.24 [95% CI, 1.11–1.37]). There were a higher proportion of clinical pregnancies in the scheduled natural cycle group; however, this difference did not reach statistical significance (scheduled natural cycle, 67.8%, vs. natural cycle, 58.8%; RR, 1.16 [95% CI, 0.999–1.36]). Notably, the primary outcome of live birth was similar between the two groups (scheduled natural cycle, 55.2%, vs. natural cycle, 52.4%; RR, 1.03 [95% CI, 0.84–1.26]). There was no significant difference in spontaneous abortion (scheduled natural cycle, 12.5%, vs. natural cycle, 7.9%; RR, 1.93 [95% CI, 0.90–4.13]). All results were similar after accounting for differential cancellation rates using inverse probability of selection weighting (Supplemental Table 1, available online).

DISCUSSION

A growing body of evidence suggests that endometrial preparation via the natural cycle approach, which allows for FET in the presence of a corpus luteum, results in similar or improved live birth outcomes while possibly reducing obstetric risk compared with programmed FET cycles (16, 20). Although demand for natural cycle FET is expected to increase, a major barrier to its uptake is that scheduling of transfer is dictated by the ovulatory cycle and, thus, has potential to fall on a date precluded by patient or clinic availability (21). In this study, we described a novel natural cycle FET protocol that allows more flexibility in scheduling the day of embryo transfer without compromising clinical outcomes.

A recent survey of fertility clinics in the United States found that 17% of clinics do not offer natural cycle FET and 81% of those reported not doing so due to "lack of timing predictability for transfer" (21). Notably, these clinics tended to be smaller practices located in less population dense areas. These data highlight the barrier that scheduling challenges pose to implementation of natural cycle FET. Scheduling challenges are multifactorial including expertise level, chain of custody minimums, and economics. Therefore, strategies that allow for more control over the timing of FET may serve to reduce geographic disparities and improve accessibility to natural cycle FET.

Our protocol used GnRH antagonist along with low-dose gonadotropins for a short duration to allow for an adjustable delay in ovulation and corresponding shift in timing of transfer. There was no significant difference in live birth among cycles using this protocol compared with the referent group of natural FET cycles. The positive hCG and clinical pregnancy rates increased in the scheduled natural cycle group, whereas the live birth rate was not statistically different between the two groups. These results were consistent across

TABLE 2

Reproductive outcomes.

Variable	Scheduled natural cycle	Natural cycle	Unadjusted *P* value	RR (95% CI), scheduled natural vs. natural cycle	Adjusted *P* value
Overall	114	973			
Positive hCG	93 (81.6)	626 (64.3)	<.0001	1.26 (1.15–1.38)	<.0001
Clinical pregnancy	78 (68.4)	556 (57.1)	.005	1.21 (1.06–1.38)	.004
Spontaneous abortion	11 (11.8)	61 (9.7)	.457	1.27 (0.65–2.46)	.483
Live birth	65 (57)	481 (49.4)	.093	1.15 (0.97–1.36)	.097
PGT-A cycles	87	670			
Positive hCG	72 (82.8)	444 (66.3)	.0001	1.24 (1.11–1.37)	<.0001
Clinical pregnancy	59 (67.8)	394 (58.8)	.044	1.16 (0.999–1.36)	.052
Spontaneous abortion	9 (12.5)	35 (7.9)	.100	1.93 (0.90–4.13)	.089
Live birth	48 (55.2)	351 (52.4)	.690	1.03 (0.84–1.26)	.757

Note: Data presented as counts (percentages) unless otherwise stated. CI = confidence interval; hCG = human chorionic gonadotropin; PGT-A = preimplantation genetic testing for aneuploidy; RR = relative risk.

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univariate and multivariate analyses. Furthermore, similar results were observed in a subgroup analysis limited to PGT-A cycles. These data suggest that delaying ovulation in natural cycle FET did not negatively impact FET outcome.

Notably, the scheduled natural cycle protocol was associated with significant changes to the late follicular phase as evidenced by larger follicle size, higher serum estradiol level, and lower serum LH level. One potential advantage of the scheduled natural cycle protocol is the suppression of LH until ovulatory trigger is administered. This may have allowed for greater precision for the time interval between ovulation and embryo transfer than the natural cycle protocol in which some patients may experience an initial LH increase before the ovulatory trigger administration. However, ultimately, the live birth was comparable between the two groups suggesting that patients managed with a scheduled natural cycle FET will have comparable outcomes to patients managed with a traditional natural cycle FET. It is interesting that the scheduled natural cycle FET group had a significant increase in the positive hCG and clinical pregnancy rates, and it is possible that the greater precision from time to ovulatory trigger to FET in the scheduled natural cycle protocol resulted in improved accuracy with regard to FET timing with the window of implantation. Furthermore, the larger follicular diameters and higher serum estradiol levels may correspond to a generally more developed follicle, which may have resulted in more robust endogenous luteinization in the scheduled natural cycle FET group. However, it should also be noted that this secondary outcome may have occurred due to either random chance or confounding by prognosis if patients with a better prognosis were more likely to have undergone a scheduled natural cycle FET. Ultimately, the increased clinical pregnancy rate did not result in a statistically significant difference in live birth between the two groups, particularly in PGT-A cycles.

This study was strengthened by use of live birth as the primary outcome, which was high in both cohorts. Additionally, the data were derived across a multicenter in vitro fertilization network with multiple embryology laboratories enhancing generalizability of the results. Furthermore, the high rates of PGT-A utilization and single embryo transfers reflect contemporary US practice. This study also has several limitations to acknowledge. First, this study was limited by minor heterogeneity in natural cycle FET protocols inherent in a retrospective study design including small variations in the timing of FET relative to LH surge/trigger. We did not perform separate analysis of true natural cycle because the omission of ovulation trigger was relatively rare, and therefore, this may limit the generalizability of these results to natural cycle FET cycles that do not receive an ovulatory trigger. However, randomized controlled trials have concluded that pregnancy outcomes are comparable between natural cycle with surge and natural cycle with ovulatory trigger protocols, which is reassuring (23, 24). Furthermore, the potential for selection bias in terms of which patients underwent a scheduled natural cycle compared with a traditional natural cycle exists given the lack of randomization and standardized criteria for selecting candidates for scheduled natural cycle FET. Overall, the findings of the current study justify further prospective studies comparing scheduled natural cycle FET with traditional natural cycle and/or programmed FET protocols to confirm the findings of this study.

CONCLUSION

We describe a novel natural cycle FET protocol that allows for more flexibility in scheduling the day of transfer. In this protocol, ovulation was delayed with short-duration GnRH antagonist along with low-dose gonadotropin add-back, resulting in a corresponding shift in day of transfer. This protocol maintained comparable pregnancy outcomes compared with patients undergoing the traditional natural cycle FET. Although the positive hCG and clinical pregnancy rates were statistically higher in those who used the scheduled protocol, these data should be interpreted with caution given limitations of sample size in this cohort and ultimately did not result in difference in live birth, particularly among PGT-A cycles. The study findings may enable more clinics and their patients to undertake FET in the setting of a corpus luteum, which may be preferred by patients and has been hypothesized to result in improved maternal-fetal outcomes. These data may become particularly valuable if forthcoming randomized controlled trial data confirm decreased rates of hypertensive disorders of pregnancy after natural cycle FET cycles compared with those after programmed FET cycles (18).

CRediT Authorship Contribution Statement

Ali Borazjani: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis. **Kerry S.J. Flannagan:** Formal analysis. **Jeanne E. O'Brien:** Writing – review & editing. **Phillip A. Romanski:** Writing – review & editing. **Micah Hill:** Writing – review & editing. **Kate Devine:** Writing – review & editing, Project administration, Conceptualization.

Declaration of Interests

A.B. reports patents US20220225961A1 (imaging probe adapter), WO2016176632A1 (wearable maternal device for use during sleep), US20170265980A1 (smart surgical spacer for tissue-implant interface), WO2023184022A1 (devices systems and methods for vaginal therapeutics), EP4274482A1 (methods and systems for vaginal therapeutic device fitting), and US20140275841A1 (insertable probe); President and Founder of Global Innovations for Reproductive Health and Life; and stock options from Cosm Medical Corp., outside the submitted work. K.S.J.F. is employed by US Fertility so time as a statistician on this manuscript was paid for by them. J.E.O. has nothing to disclose. P.A.R. has nothing to disclose. M.H. reports stock options from Research Advisor, Thread Robotics, unrelated to publication. K.D. reports consulting fees from BluDiagnostics and Medscape; honoraria from the University of California San Diego and Primary Care Respiratory Society; travel support from the American Society for Reproductive Medicine, Society for Assisted Reproductive Technology, and US Fertility; advisory boards of Medscape, BluDiagnostics, Future Fertility, and Life Whisperer; Society for Reproductive Endocrinology and Infertility Research Chair; Society for Assisted Reproductive Technology Quality Assurance Chair; and Medical Director and Chief Research Officer of US Fertility, outside the submitted work.

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La adición de un antagonista de la hormona liberadora de gonadotropina (GOH) de corta duración y gonadotropina a la transferencia de embriones congelados en ciclo natural permitió programar la fecha de transferencia sin comprometer la probabilidad de nacimiento vivo.

Objetivo: Determinar si existe una asociación entre el tipo de transferencia de embriones congelados (TEF) en ciclo natural (programada vs. tradicional) y los resultados de nacimiento vivo.

Diseño: Cohorte retrospectiva de todas las TEF en ciclo natural en una única red de clínicas de fertilidad en Estados Unidos.

Sujetos: Todas las TEF en ciclo natural realizadas a pacientes ovulatorias entre enero de 2019 y abril de 2022.

Exposición: Se compararon ciclos de TEF en un ciclo natural programado que recibieron un antagonista de la GOH de corta duración (1 ampolla/día) con gonadotropinas a dosis bajas (75 UI/día) para retrasar la ovulación y permitir una programación más flexible de la TEF, sin retrasar los ciclos.

Principales medidas de resultado: Nacido vivo.

Resultados: Hubo un total de 1087 TEF de ciclo natural que cumplieron los criterios de inclusión. El protocolo de TEF de ciclo natural programado se utilizó en 114 (10,5 %) de estos ciclos. La edad media fue de 35 años (rango intercuartil, 33-38). Se utilizaron pruebas genéticas preimplantacionales para aneuploidía en el 76,3 % (n = 87) de los ciclos de TEF de ciclo natural programados y en el 68,9 % (n = 670) de los ciclos de TEF de ciclo natural. El grupo de TEF de ciclo natural programado tuvo un nivel de estradiol significativamente mayor (318 frente a 249 pg/ml) y un nivel de hormona luteinizante menor (5,7 frente a 13,4 mUI/ml) en el momento desencadenante de la ovulación, pero un grosor endometrial máximo comparable (9,4 frente a 9,7 mm) en comparación con el grupo de TEF de ciclo natural. En general, hubo un aumento significativo en las tasas de gonadotropina coriónica humana positiva (ciclo natural programado, 81,6 %, frente a ciclo natural, 64,3 %; riesgo relativo [RR], 1,26 [intervalo de confianza {IC} del 95 %, 1,15-1,38]) y embarazo clínico (ciclo natural programado, 68,4 %, frente a ciclo natural, 57,1 %; RR, 1,21 [IC del 95 %, 1,06-1,38]) en el grupo de ciclo natural programado. Hubo una mayor proporción de nacidos vivos en el grupo de ciclo natural programado; sin embargo, esto no alcanzó a tener significación estadística (ciclo natural programado, 57,0 %, frente a ciclo natural, 49,4 %; RR, 1,15 [IC del 95 %, 0,97-1,36]). Un subanálisis de las pruebas genéticas preimplantacionales para ciclos de aneuploidía arrojó resultados similares.

Conclusión: Un protocolo de TEF programada en ciclo natural, que utiliza un antagonista de la hormona liberadora de gonadotropina (GOH) de corta duración junto con una dosis baja de gonadotropina como tratamiento de reemplazo, no redujo la tasa de nacidos vivos en comparación con los ciclos de TEF tradicionales en ciclo natural. Estos resultados sugieren que este protocolo de TEF alternativo puede ser una estrategia viable para brindar flexibilidad en la programación del día de la TEF, permitiendo a la paciente seguir un protocolo de ciclo natural. Esta modificación del protocolo podría permitir que más clínicas ofrezcan TEF en ciclo natural.