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Original Research Article

Endometrial preparation with stimulated versus artificial cycle: a comparative study on frozen embryo transfer outcomes

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ABSTRACT

Background: Successful frozen–thawed embryo transfer (FET) depends on adequate endometrial preparation. Stimulated cycles (SC) may provide a more physiological hormonal milieu by supporting corpus luteum function, whereas artificial cycles (AC) offer flexible scheduling but rely entirely on exogenous hormones. Existing evidence comparing these two approaches remains inconsistent. This study aimed to evaluate reproductive outcomes following FET using stimulated versus artificial cycles.

Methods: This prospective comparative study included 89 women undergoing their first FET between January 2024 and April 2025. Participants were prepared using either a stimulated cycle (n=31) involving letrozole with low-dose gonadotropins or an artificial cycle (n=58) using estrogen–progesterone replacement. Endometrial thickness was monitored and two good-quality day-3 embryos were transferred after adequate progesterone exposure. Outcomes assessed were positive pregnancy test, clinical pregnancy, ongoing pregnancy at 12 weeks and early pregnancy loss. Statistical analysis was performed using Student's t-test, Chi-square test or Fisher's exact test, with $p<0.05$ considered significant.

Results: Baseline characteristics including age, BMI, infertility duration and ovarian reserve were comparable between groups. Pregnancy outcomes were higher in the SC group but did not reach statistical significance: positive pregnancy rate (41.9% vs. 31.0%, p=0.32), clinical pregnancy rate (32.3% vs. 24.1%, p=0.41) and ongoing pregnancy rate (29.0% vs. 19.0%, p=0.27). Early pregnancy loss remained low in both groups (3.2% vs. 5.2%, p=1.00).

Conclusions: Stimulated cycles showed a trend toward improved pregnancy outcomes compared with artificial cycles; however, differences were not statistically significant. Both protocols yielded acceptable clinical results, supporting individualized selection of endometrial preparation based on patient characteristics and clinical judgment.

Keywords: Artificial cycle, Endometrial preparation, Frozen embryo transfer, Pregnancy outcomes, Stimulated cycle

INTRODUCTION

FET has become a cornerstone of assisted reproductive technology (ART), offering several advantages such as optimized embryo selection, reduced risk of ovarian hyperstimulation syndrome (OHSS) and improved cumulative live birth rates.[1,2] With the increasing use of cryopreservation techniques and the "freeze-all" strategy, the number of FET cycles now exceeds that of fresh embryo transfers in many centres worldwide. Successful implantation in FET cycles depends largely on achieving a receptive endometrium synchronized with embryo developmental stage, making endometrial preparation a crucial determinant of success.[3,4] Various protocols have been established for endometrial preparation prior to FET,

primarily categorized as natural cycles (NC), SC, and artificial or hormone replacement cycles (AC).[2,5,6] Artificial cycles, which rely on exogenous estrogen and progesterone, offer convenient scheduling and are particularly suited for anovulatory women. However, recent studies have raised concerns about their association with higher early pregnancy loss and altered placentation due to the absence of corpus luteum derived factors. In contrast, stimulated cycles using low-dose gonadotropins or agents such as letrozole promote endogenous hormone production and maintain corpus luteum function, potentially providing a more physiologic hormonal milieu conducive to implantation and early placental development.[7,8] Despite this theoretical advantage, published data comparing these protocols show inconsistent results regarding pregnancy and live birth outcomes.

While several studies have compared natural and artificial cycles, fewer have focused specifically on stimulated versus artificial cycles for FET. The relative benefits of these two approaches remain unclear, particularly concerning implantation rates, early pregnancy loss and ongoing pregnancy outcomes.[9,10] Moreover, variations in stimulation regimens, patient selection and luteal phase support across studies have led to conflicting conclusions, underscoring the need for further evaluation in real-world clinical settings.

Therefore, the present study aims to compare endometrial preparation using stimulated and artificial cycles and to assess their impact on frozen embryo transfer outcomes in routine clinical practice. By analysing key reproductive outcomes such as implantation, clinical pregnancy and ongoing pregnancy rates, this study seeks to contribute evidence toward optimizing FET protocols for improved reproductive success.

METHODS

Study design

This was a prospective comparative study that included FET cycles performed in the Department of Reproductive Medicine and Surgery, GSL Medical College, between January 2024 and April 2025. The study compared clinical outcomes between SC and AC used for endometrial preparation in women undergoing their first frozen–thawed embryo transfer.

Participants

This study included 89 women undergoing their first FET using their own oocytes and embryos. Eligible participants were women younger than 42 years with a normal uterine cavity on ultrasound and at least three good-quality frozen embryo, in whom fresh embryo transfer was not performed due to an elective freeze-all strategy, risk of OHSS, suboptimal endometrial parameters or patient-requested postponement of fresh transfer and who were able to provide informed consent and comply with study procedures.

Women with uterine abnormalities such as fibroids or intrauterine adhesions, individuals with a history of recurrent pregnancy loss (>2 miscarriages) and those with significant systemic illness were excluded from the study. Patients using surgically retrieved sperm were excluded from the study. Embryos were derived from either conventional in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycles and were vitrified on day 3 after grading according to standard cleavage-stage criteria, including cell number, blastomere symmetry, degree of fragmentation and absence of multinucleation.

Ethical approval was obtained from the Institutional Ethics Committee and informed consent was taken from all participants.

Endometrial preparation protocols

Patients were placed in either the artificial or stimulated cycle group based on the physician's judgment. Endometrial preparation for FET followed one of two protocols shown below:

Stimulated cycle

In the stimulated cycle protocol, a baseline transvaginal ultrasound was performed on Day 1 or 2 of the menstrual cycle. Oral letrozole 5 mg was initiated from Day 2–3 and continued for five days, followed by daily subcutaneous gonadotropin injections (75–150 IU) for three days. The gonadotropin dose was individualized according to body mass index, ovarian reserve and any prior ovarian response to stimulation. Follicular development was monitored with serial transvaginal ultrasound scans from Day 9 onward to assess endometrial thickness and follicular growth and gonadotropin dose adjustment done accordingly.

When endometrial thickness was more than 7 mm, at least one dominant follicle reached ≥17 mm with a corresponding peak plasma estradiol level >200 pg/ml and no LH surge or premature progesterone rise was present, ovulation was triggered with 250 µg recombinant hCG administered subcutaneously. Cycles with endometrial thickness significantly <7 mm by day 20 were cancelled due to poor endometrial response. FET scheduled on hCG+5 day for day-3 embryos.

Oral dydrogesterone 10 mg three times daily and vaginal progesterone 200 mg three times daily were started approximately 36 hours after the hCG trigger, after confirmation of ovulation by ultrasound. progesterone supplementation was continued until 14 days post-transfer when a pregnancy test was performed and continued until 12 weeks' gestation in viable pregnancies and was discontinued immediately in patients with negative pregnancy tests.

Artificial cycle

Endometrial preparation began on day 2-3 of the cycle with oral estradiol valerate (4 mg three times daily) after performing day 2 TVS. Endometrial thickness was monitored on day 9 and 11 and further if needed and dose is adjusted accordingly. Once the endometrium reached ≥7 mm, plasma estradiol level >200 pg/ml and serum progesterone was <1 ng/ml, vaginal progesterone 200 mg three times a day and intramuscular injection of 50 mg progesterone was initiated. If the endometrial thickness was not >7 mm by day 20 then the cycle was cancelled due to inadequate endometrial response despite dose adjustment. FET for Day 3 embryos was scheduled after three days of progesterone administration. Hormonal support was continued until the pregnancy test and maintained up to 12 weeks in viable pregnancies.

Embryo thawing and transfer

After confirming serum progesterone levels greater than 20 ng/ml measured between 10 AM and 12 AM prior to embryo transfer, embryos were thawed using a standardized vitrification–warming protocol and transferred under ultrasound guidance. Only good-quality embryos were selected and two embryos were transferred in accordance with the clinic's embryo transfer policy, taking into consideration the patient's age and embryo quality.

Outcome measures

Positive pregnancy was defined as a serum β-hCG level greater than 10 IU/l in the 14 days after cleavage embryo transfer. A transvaginal ultrasound was carried out 2 weeks after the positive test to confirm clinical pregnancy by visualizing a gestational sac, follow up scan done 2 weeks later and again at 12 weeks of gestation to document an ongoing pregnancy (OP) through detection of fetal cardiac activity. Early pregnancy loss was defined as the spontaneous termination of a clinical pregnancy before 12 weeks of gestation.

Statistical analysis

Data were analyzed using version 26 of SPSS program. Continuous variables were presented as mean±standard deviation (SD) and compared using the student's t-test. Categorical variables were compared using the Chi-square or Fisher's exact test. A p value<0.05 was considered statistically significant.

RESULTS

A total of 89 women undergoing their first FET cycle were included in the study, with 31 in the SC group and 58 in the AC group. There were no statistically significant differences between the two groups in terms of female age, body mass index (BMI), infertility duration or antral follicle count (AFC). The mean female age was similar between the SC and AC groups (27.83±5.44 vs. 28.98±5.89 years, p=0.99). Similarly, BMI did not differ significantly (26.50±4.99 vs. 26.24±4.70 kg/m², p = 0.81). The duration of infertility also showed no significant variation (4.68±3.66 vs. 5.09±4.40 years, p=0.99) as shown in Table 1 and Figure 1. The proportion of women with primary infertility was slightly higher in the AC group (67.2%) compared with the SC group (54.8%), but the difference was not statistically significant (p=0.36). Conversely, secondary infertility was more frequent in the SC group (45.2% vs. 32.8%, p=36) as shown in Table 2 and Figure 2.

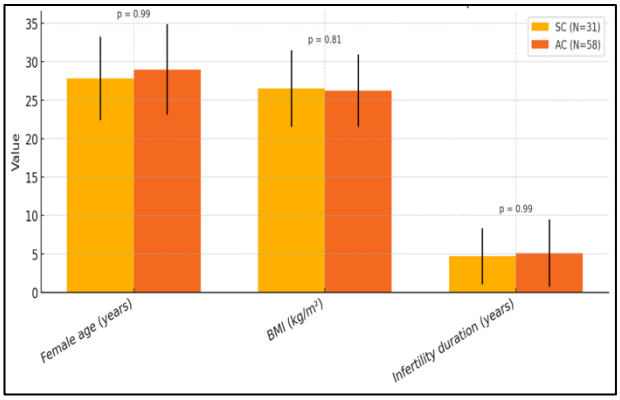

Figure 1: Patient characteristics for SC and AC group.

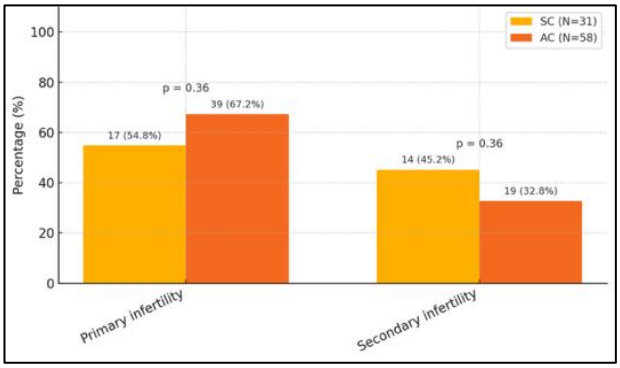

Figure 2: Infertility type distribution in SC and AC group.

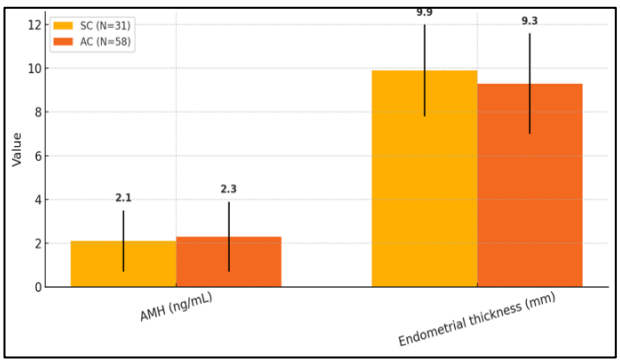

Figure 3: AMH levels and endometrial thickness in SC and AC Group.

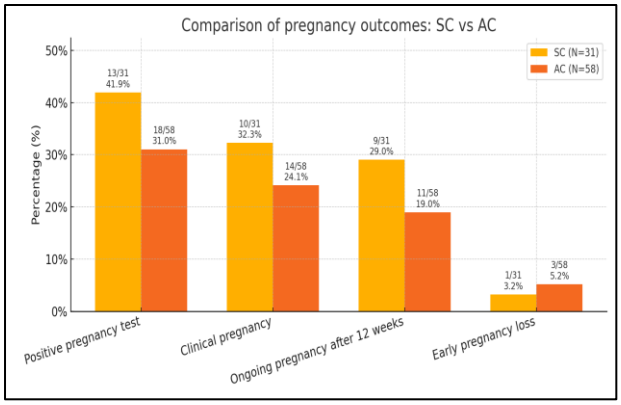

Figure 4: Reproductive outcomes for ET after SC and AC group.

Ovarian reserve as assessed by AMH levels was similar between SC and AC groups (2.1±1.4 vs. 2.3±1.6 ng/ml, p=0.54). Mean endometrial thickness measured prior to progesterone initiation did not differ significantly between groups (9.9±2.1 vs. 9.3±2.3 mm, p=0.22) as shown in Table 3 and Figure 3. Overall, baseline clinical and demographic characteristics were comparable between the SC and AC groups. The reproductive outcomes following embryo transfer in the SC and AC groups are summarized in Table 4 and Figure 4. The SC group demonstrated slightly higher values across most pregnancy outcomes. Positive pregnancy tests were more frequent in the SC group (41.9%) compared with the AC group (31.0%, p=0.32). A similar pattern was noted for clinical pregnancy rates, which were 32.3% in the SC group and 24.1% in the AC group (p=0.41). Ongoing pregnancy rates beyond 12 weeks were also somewhat higher in the SC group (29.0%) than in the AC group (19.0%, p=0.27). Early pregnancy loss remained low in both groups, occurring in 3.2% of SC cycles and 5.2% of AC cycles (p=1.00). Importantly, no ectopic pregnancies were observed in either group throughout the study period. Overall, the rates of positive pregnancy, clinical pregnancy, ongoing pregnancy and early pregnancy loss were similar between the two groups, with no statistically significant differences observed.

Table 1: Patient characteristics for SC and AC group.

Variables	SC (n=31)	AC (n=58)	P value
Female age (in years)	27.83±5.44	28.98±5.89	0.99
BMI (kg/m²)	26.50±4.99	26.24±4.70	0.81
Infertility duration (in years)	4.68±3.66	5.09±4.40	0.99

Table 2: Infertility type distribution in SC and AC group.

Variables	SC (n=31)	AC (n=58)	P value
Primary infertility (%)	17 (54.8)	39 (67.2)	0.36
Secondary infertility (%)	14 (45.2)	19 (32.8)	0.36

Table 3: AMH levels and endometrial thickness in SC and AC group.

Variables	SC (n=31)	AC (n=58)	P value
AMH (ng/ml)	2.1±1.4	2.3±1.6	0.54
Endometrial thickness (mm)	9.9±2.1	9.3±2.3	0.22

Table 4: Reproductive outcomes for ET after SC and AC group.

Variables	SC (n=31)	AC (n=58)	P value
Positive pregnancy test (%)	13 (41.9)	18 (31.0)	0.32
Clinical pregnancy (%)	10 (32.3)	14 (24.1)	0.41
Ongoing pregnancy after 12 weeks (%)	9 (29.)	11 (19.0)	0.27
Early pregnancy loss (%)	1 (3.2)	3 (5.2)	1.00

DISCUSSION

This study compared reproductive outcomes between SC using letrozole with low-dose gonadotropins and artificial hormone replacement cycles AC for endometrial preparation before FET. Although the SC group showed numerically higher rates of positive pregnancy, clinical pregnancy and ongoing pregnancy, these differences were not statistically significant. Early pregnancy loss rates were low and similar between the two groups. These findings contribute to the ongoing discussions about the most appropriate endometrial preparation method for FET and highlight the challenge of translating theoretical physiological advantages into clear clinical benefits. A proposed advantage of stimulated cycles is the presence of a functional corpus luteum, which secretes progesterone,

relaxin and vasoactive substances that support early placentation and maternal cardiovascular adaptation.[11,12] Artificial cycles lack corpus luteum derived factors and several studies have linked AC protocols with higher risks of hypertensive disorders and abnormal placentation.[13,14] The results are comparable to the findings of Li et al and Hosseini-Najarkolaei et al both of whom reported no significant differences in implantation, pregnancy rates or miscarriage when comparing stimulated and artificial cycles.[15,16] However, several observational studies have reported potential benefits of ovulatory protocol. Zhang et al compared letrozole plus HMG versus GnRH agonist-suppressed HRT in patients with endometriosis and observed similar live birth and clinical pregnancy rates but a lower miscarriage trend and significantly fewer hypertensive disorders of pregnancy in the stimulated group.[17] Although the difference was not statistically significant, the trend favouring stimulated cycles in our study is similar to what many other studies have reported.

Early pregnancy loss remains a critical outcome measure in FET cycles, yet the literature presents conflicting evidence regarding the impact of endometrial preparation protocols on miscarriage rates. In the study, early pregnancy loss was low in both groups (3.2% in SC vs. 5.2% in AC), with no significant difference. Similar findings were reported by Li et al and Hosseini-Najarkolaei et al.[15,16] Other studies, such as Zhang et al have shown lower miscarriage rates in ovulatory or modified natural protocols.[18] Overall, evidence remains inconsistent and differences across studies may reflect variations in patient characteristics and protocol design. This study was prospectively designed with clear inclusion and exclusion criteria, reducing selection bias. Baseline characteristics were well matched between groups and standardized protocols were used for both SC and AC cycles. All embryo transfers were performed by experienced clinicians, minimizing technical variation.

However, the study has several limitations. The sample size was relatively small, limiting the ability to detect modest differences. Another limitation is the lack of randomization, as treatment choice was based on physician judgment, which may introduce selection bias even though baseline characteristics were comparable. As a single-center study, the findings may also have limited generalizability. Further limitations include the use of only day-3 embryos, lack of long-term follow-up and missing data on corpus luteum function, endometrial receptivity markers and patient-reported outcomes.

Current evidence supports an individualized approach to endometrial preparation. Stimulated cycles may be beneficial in women with regular ovulatory cycles, adequate ovarian reserve, PCOS or prior artificial-cycle failures.[19-22] Artificial hormone replacement cycles remain an important option, especially for women with anovulation, irregular cycles or scheduling constraints and for patients who prefer fixed-cycle planning or fewer monitoring visits.[23] Ultimately, protocol selection should consider patient preference, prior treatment response, cost considerations and clinic-specific experience. Shared decision-making is essential, as both protocols yield acceptable pregnancy outcomes.

Future research should focus on large, multicentre randomized trials to clarify whether stimulated cycles offer true clinical advantages over artificial cycles and to evaluate their impact on obstetric and neonatal outcomes. Mechanistic studies investigating corpus luteum function, endometrial receptivity and placental development are also needed. Standardized reporting and the identification of patient subgroups may further refine protocol selection and improve clinical outcomes.

CONCLUSION

This study found that stimulated cycles showed higher but not statistically significant pregnancy outcomes compared with artificial cycles. These results reflect existing evidence suggesting possible but inconsistent advantages of ovulatory-based protocols. As no clear superiority is established, both approaches remain appropriate and protocol selection should be individualized based on patient characteristics and preferences. Larger randomized trials and mechanistic studies are needed to clarify whether stimulated cycles offer meaningful clinical benefits.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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