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# Defining the LH surge in natural cycle frozen-thawed embryo transfer: the role of LH, estradiol, and progesterone

Raoul Orvieto[1,2,3*], Nira Morag[2], Elena Rubin[4] and Ravit Nahum[1,2]

## Abstract

**Objective** Several replacement protocols for frozen-thawed ET (FET) exist, with no advantage of one protocol over the others. In the present retrospective and observational study we aim to evaluate the hormonal changes round the LH surge, for better determination of the LH surge and improving the NC FET outcome.

We reviewed the computerized files of all consecutive women admitted to our IVF Institute, between January 1, 2023 and June 30, 2024, who underwent NC FET cycles in our IVF Institute. The elimination of bias in this selection, for the purposes of this study, was achieved by including only patients who had two consecutive hormonal blood tests and transvaginal ultrasound evaluations prior to ovulation, on two days (D- 2) before and one day before ovulation (D- 1). Data on patient demographics and infertility-treatment-related variables were collected from the files. We studied and compared several variable between patients who conceived and those who did not, including the % changes in LH (D- 1 minus D- 2/D- 2), in estradiol (D- 2 minus D- 1/D- 2) and % change in progesterone (D- 1 minus D- 2/D- 2) levels.

**Results** Six hundreds and sixty-eight NC FET cycles were performed during the study periods. Pregnancy was achieved in 348 patients (pregnancy rate, 52% per cycle). Figure that is not-significantly higher than our previous reported outcome, when the LH surge was defined only by the rise in LH level (46% per cycle). Patients who conceived were significantly younger, with no in-between group differences in LH, E2 and progesterone levels. Moreover, while no differences were observed in the % changes in E2, nor LH levels, the % change in progesterone levels was significantly higher in those who conceived (1.9 + 1.5 vs 1.6 + 1.4, $p < 0.013$), as compared to those who did not.

**Conclusions** Patients undergoing NC FET should be monitored by LH, estradiol and progesterone levels. We suggest that the LH surge should be determined by an increase in LH, concomitant to a drop in estradiol and a three-fold increase in progesterone levels between D- 2 to D- 1. Further large prospective studies are needed to elucidate the aforementioned recommendation prior to its routine implementation.

**Keywords** Cryopreservation, Natural cycle, Frozen-thawed embryo transfer, Luteal support, LH surge, Pregnancy rate, Outcome

*Correspondence:
Raoul Orvieto
raoul.orvieto@sheba.health.gov.il
Full list of author information is available at the end of the article

## Introduction

Single embryo transfer (ET) cycles are commonly employed to reduce the incidence of multiple births [1, 2]. This approach promotes the cryopreservation of surplus embryos for potential future use, contributing to a significant increase in the utilization of frozen embryo transfers (FETs).

Currently, various replacement protocols for frozen-thawed embryo transfer (FET) are in practice [3]. A meta-analysis conducted by Groenewoud et al. in 2017 found no definitive advantage among the different protocols [4], although a trend favouring natural cycle FET (NC-FET) over artificial cycle FET (AC-FET) was noted, with an odds ratio of 1.23 (95% CI: 0.93–1.62) indicating a potentially higher live birth rate (LBR). Wu et al. conducted a meta-analysis showing that NC-FET not only increases the likelihood of LBR [5] but also reduces the risks associated with maternal, obstetrics, and perinatal complications compared to AC-FET [6–8]. A recent analysis of 6682 FET cycles found no significant difference in live birth rates between AC-FET cycles using intramuscular (IM) progesterone or a combination of vaginal progesterone and IM progesterone, when compared to modified natural cycles. However, the relative risk of live birth was lower in AC-FET cycles that exclusively used vaginal progesterone, as compared to modified natural cycles [9].

A critical factor for successful implantation during NC FET is the synchronization between the endometrium and the developmental stage of the embryo. Therefore, precise detection of the luteinizing hormone (LH) surge and subsequent ovulation is essential for determining the optimal timing of the embryo transfer and achieving favourable outcome. In natural cycle, elevated estrogen levels induce the LH surge at midcycle, while low levels of progesterone act upon the pituitary gland, enhancing the LH response to gonadotropin-releasing hormone (GnRH), and subsequently leading to the midcycle surge of follicle-stimulating hormone (FSH) [10]. During the late follicular phase, estrogen levels rise gradually initially, followed by a rapid increase, peaking approximately 24–36 h before ovulation [11]. The onset of the LH surge coincides with the peak levels of estradiol. Ovulation is reasonably estimated to occur approximately 10–12 h after the LH peak and 24–36 h following the achievement of peak estradiol levels [10, 12].

Despite the significance of predicting ovulation timing, there remains no consensus on the definition of the onset of the LH surge, with varying proposed cut-off levels of >10 to 20 IU/L [13, 14] or an increase in LH concentration of 180% above the most recent serum values that continues to rise thereafter [15]. According to Irani et al. [16], LH surge can be defined as either, the occurrence of LH levels reaching ≥17 IU/L during the follicular phase, followed by a ≥ 30% decrease in estradiol levels the subsequent day, or as the highest LH level observed on the day after reaching ≥17 IU/L, accompanied by a ≥ 30% drop in estradiol levels, which may align more logically with fundamental endocrinological principles.

While the combination of both hormones (LH and estradiol) may offer a more accurate definition of the LH surge, serum progesterone levels have often been overlooked. Given that maturation of the endometrium is induced by progesterone, which starts to rise about 12 h before the start of the LH surge [17], monitoring its levels might be crucial for better synchronization between the endometrium and the embryo. Groenewoud et al. [18] reported that an isolated progesterone level of 4.6 nmol/L or higher was observed in over one-fifth of patients undergoing modified NC FET, without negatively affecting live birth or pregnancy rates. However, others have cancelled modified NC FET cycles if progesterone levels are elevated [19].

In our practice, we offer the NC FET with modified luteal support (Daily vaginal progesterone with two additional injections: one of hCG and the other of GnRH-agonist, administered on ovulation day +3 and 4 days later, respectively) [20]. Patients are monitored with serial blood levels of LH, estradiol and progesterone and ultrasound to assess endometrial thickness and follicular development. Until 2018, the LH surge was determined when the LH level exceeds 180% of the baseline value [21]. Thereafter, following the publication of Irani et al. [16], LH surge was defined as LH level exceeding 180% of the baseline value either, accompanied by a drop in estradiol levels, indicating the day prior to ovulation/oocyte pick up (OPU).

Prompted by the aforementioned observations, we aimed to evaluate our NC FET outcome following the change in LH surge definition and in relation to the hormonal changes surrounding the LH surge, with the goal to redefine the LH surge and optimize the predictive markers for NC FET outcomes.

## Patients and Methods

We reviewed the computerized files of all consecutive women admitted to our IVF Institute, between January 1, 2023 and June 30, 2024, who underwent NC FET cycles. The elimination of bias in this selection, for the purposes of this study, was achieved by including only patients who had two consecutive hormonal blood tests and transvaginal ultrasound evaluations prior to ovulation, conducted on two days: two days before ovulation (D- 2) and one day before ovulation (D- 1). Those without these two consecutive measurements were excluded (about third of our cohort). The study was approved by the Institutional

Research Ethics Board of our Medical Centre (SMC-D-1856–25). No patients consent was required.

Our NC FET preparation protocol followed these steps [20]: After spontaneous menstruation, patients were monitored with serial ultrasound to assess endometrial thickness, follicular development, and blood levels of LH, estradiol, and progesterone until a rise in LH level was observed [when the LH level exceeds 180% of the baseline value [21]], accompanied by a drop in estradiol levels [16], indicating the day of peak LH. This day corresponded to one day prior to OPU/ovulation. On the following day, progesterone luteal support was initiated, along with two additional injections: one of recombinant hCG (Ovitrelle, Merck Serono, Herzliya, Israel; s.c. 250 mcg) and the other of GnRH-agonist (Triptorelin, Ferring Lapidot, Netanya, Israel; s.c. 0.1 mg), administered on ovulation day + 3 and 4 days later, respectively [20].

Data on patient demographics and infertility-treatment-related variables were collected from the records. Based on published data, we also studied and compared various variables between patients who conceived and those who did not, including the changes rate (%Δ) in LH (D- 1 minus D- 2/D- 2), in estradiol (D- 2 minus D- 1/D- 2) and %Δ change in progesterone(D- 1 minus D- 2/D- 2) levels.

Clinical pregnancy was defined as visualization of a gestational sac and fetal cardiac activity on transvaginal ultrasound.

Data were analyzed with IBM SPSS statistics software version 29.0. (SPSS Inc. Headquarters, 233 S. Wacker Drive, 11 th floor Chicago, Illinois 60606, USA).

*P*-values were two-sided, and the significance levels were set at 0.05. Baseline characteristic were presented as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. Chi-square tests and independent t-tests were performed to compare conceptus versus non-conceptus for categorical and continuous variables, respectively.

Logistic regression models performed multivariate analysis for pregnancy prediction, including odds ratios with 95% confidence Intervals. The analyses included independent variables/covariates that were statistically significant in the univariate analyses. The goodness of fit of the model to the observed events rates was evaluated by the Hosmer–Lemeshow statistic.

## Results

Six hundreds and sixty-eight NC FET cycles were performed during the study periods. Women age and body mass index were 35.2 ± 4.8 yrs and 23.6 ± 4.7 kg/m2, respectively. The study group NC FET cycle characteristics and the clinical outcome are shown in Table 1. Pregnancy was achieved in 348 patients (pregnancy rate, 52% per cycle). This figure is not-significantly ($p = 0.34$) higher than our previous reported outcome [19], when the LH surge was defined only by the rise in LH level (27/59, 46% per cycle).

**Table 1** Patients and NC FET cycle characteristics

| Characteristics | |
|---|---|
| Basal FSH (IU/L) | 7.0 + 2.4 |
| Basal LH (IU/L) | 5.3 + 2.5 |
| Ovulation minus 2 days (D- 2) | |
| LH (IU/L) | 26.6 + 15.9 |
| Estradiol (pmol/L) | 1143 + 494 |
| Progesterone (nmol/L) | 1.6 + 1.0 |
| Dominant follicle size (mm) | 19.1 + 2.8 |
| Ovulation minus 1 day (D- 1) | |
| LH (IU/L) | 40.6 + 25.5 |
| Estradiol (pmol/L) | 784 + 436 |
| Progesterone (nmol/L) | 3.7 + 1.7 |
| Endometrial tickness (mm) | 9.3 + 1.6 |
| Dominant follicle size (mm) | 17.5 + 5.1 |
| Number of embryos transferred | 1.2 + 0.4 |
| Clinical pregnancy rate | 52% |

Patients who conceived were significantly younger (Table 2), with no in-between group differences in LH, E2 and progesterone levels on D- 2 nor D- 1. Moreover, while no differences were observed in the %Δ change in LH, nor %Δ change in estradiol levels, the %Δ change in progesterone (D- 1 minus D2/D- 2) levels was significantly higher in those who conceived (1.9 ± 1.5 vs 1.6 ± 1.4, $p = 0.013$), as compared to those who did not (Fig. 1).

While examining pregnancy rate in the different %Δ change progesterone tertiles, a progressive sharp increase was observed in pregnancy rate that continued consistently in %Δ change above 2.08, correspendoing to tripling the progesterone levels on D- 1 compared to D- 2 (Fig. 2). Pregnancy rate in patients with %Δ change in progesterone level above 2.08 was 56.8% (126/222), which is not-significaty higher than the figure published in our previous study [19] (56.8% vs 46% per cycle, $p = 0.13$).

In a multivariate logistic regression, including age, endo, follicle size, %delta of R2, LH and progesterone, only age and the rise in progesterone levles were significantly related to pregnancy. Hosmer-Lmeshow chi-square = 8.730, $P = 0.366$.

## Discussion

Elective FET might increase LBRs compared to fresh ET in hyper responders, but not in normo-responders, with comparable cumulative LBR in the overall population and lower risk of moderate/severe OHSS [22, 23].

**Table 2** Comparison between conceptus and non-conceptus cycles

| Characteristics | Conceptus | non- conceptus | *p* valus |
|---|---|---|---|
| Number of cycles | 348 | 320 | |
| Patients' age | 34.7 ± 4.6 | 35.7 ± 5.1 | 0.013 |
| BMI (kg/m2) | 23.3 ± 4.6 | 23.8 ± 4.8 | 0.202 |
| Ovulation minus 2 days (D- 2) | | | |
| LH (IU/L) | 26.9 ± 17.3 | 26.4 ± 14.4 | 0.719 |
| Estradiol (pmol/L) | 1140 ± 497 | 1147 ± 491 | 0.849 |
| Progesterone (nmol/L) | 1.57 ± 0.98 | 1.74 ± 1.12 | 0.030 |
| Dominant follicle size (mm) | 19.32 ± 2.85 | 19.0 ± 2.9 | 0.151 |
| Ovulation minus 1 day (D- 1) | | | |
| LH (IU/L) | 41.95 ± 25.8 | 39.2 ± 25.3 | 0.160 |
| Estradiol (pmol/L) | 799.8 ± 463 | 766.8 ± 405 | 0.326 |
| Progesterone (nmol/L) | 3.78 ± 1.8 | 3.4 ± 1.7 | 0.801 |
| Endometrial tickness (mm) | 9.40 ± 1.6 | 9.22 ± 1.6 | 0.143 |
| Dominant follicle size (mm) | 17.39 ± 5.2 | 17.7 ± 5.0 | 0.475 |
| %Δ change in estradiol | 0.27 ± 0.33 | 0.29 ± 0.31 | 0.470 |
| %Δ change in LH | 1.36 ± 2.3 | 1.29 ± 3.2 | 0.772 |
| %Δ change in progesterone | 1.92 ± 1.5 | 1.64 ± 1.39 | 0.013 |
| Number of transfers with day 2–4 embryos | 177 (51%) | 181 (57%) | * |
| Number of transfers with day 5–6 embryos | 171 (49%) | 139 (43%) | 0.140 |
| Number of embryos transferred | 1.20 ± 0.44 | 1.15 ± 0.37 | 0.122 |

* Both lines complement each other and therefore both have only one *p* value

Change rate (%Δ) in estradiol levels = (D- 2 minus D- 1/D- 2)

%Δ change in LH levels = (D- 1 minus D- 2/D- 2)

%Δ change in progesterone levels = (D- 1 minus D- 2/D- 2)

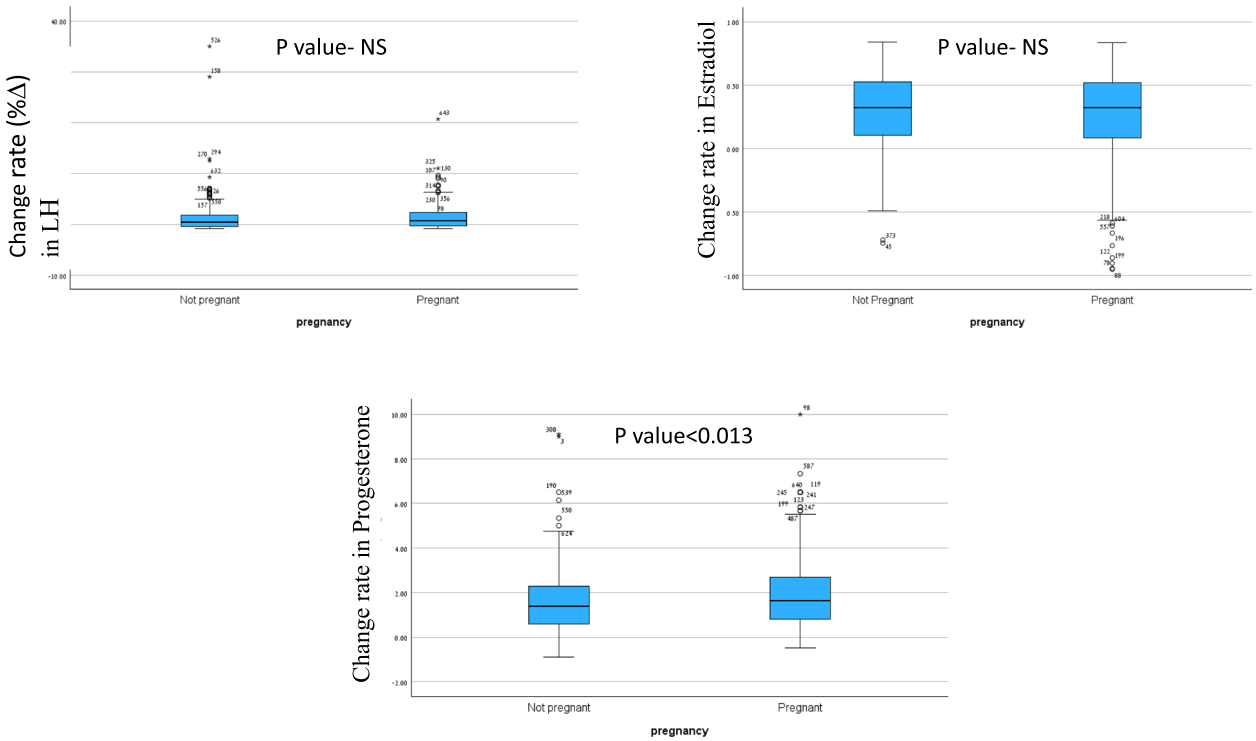


**Fig. 1** Change rate (%Δ) in LH, %Δ change in estradiol levels, and the %Δ change in progesterone (D- 1 minus D2/D- 2) levels

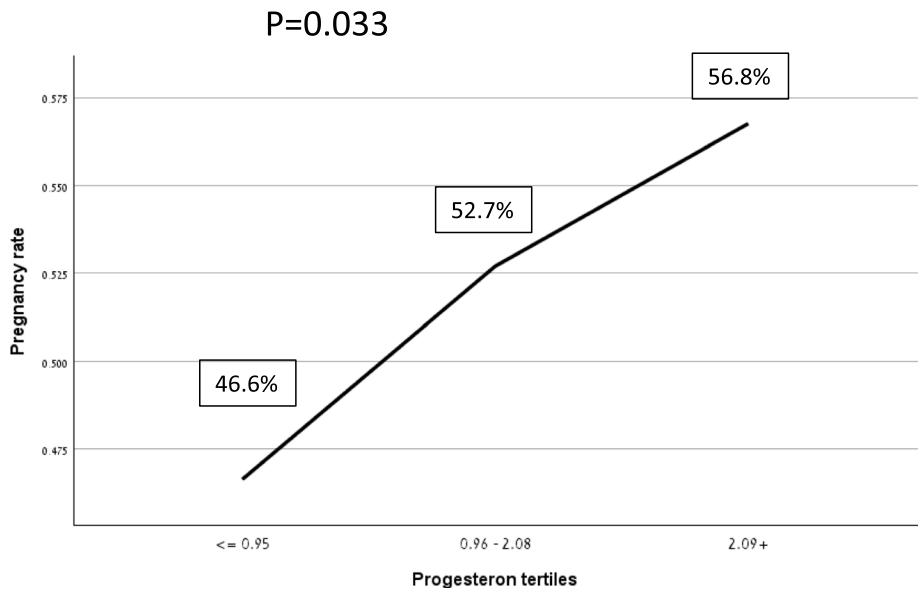


**Fig. 2** Pregnancy rate in the different change rate (%Δ) in progesterone tertiles

Moreover, FET was associated with lower risk of prematurity and LBW and increased risk of LGA and/or macrosomic in singletons, when compared with fresh ET. The relative risk of hypertensive disorders in pregnancy, as well as perinatal mortality were also demonstrated to be increased in FET compared with singletons from fresh ET and NC [6–8]. Studies have related the aforementioned pregnancy complications to programmed FET rather than those following natural and stimulated cycles, supporting the link between absence of corpus luteum in artificial cycle and adverse maternal outcomes [24]. The closer alignment with the natural physiology, lower risk of complications, better success rates in certain patients, and cost-effectiveness have led

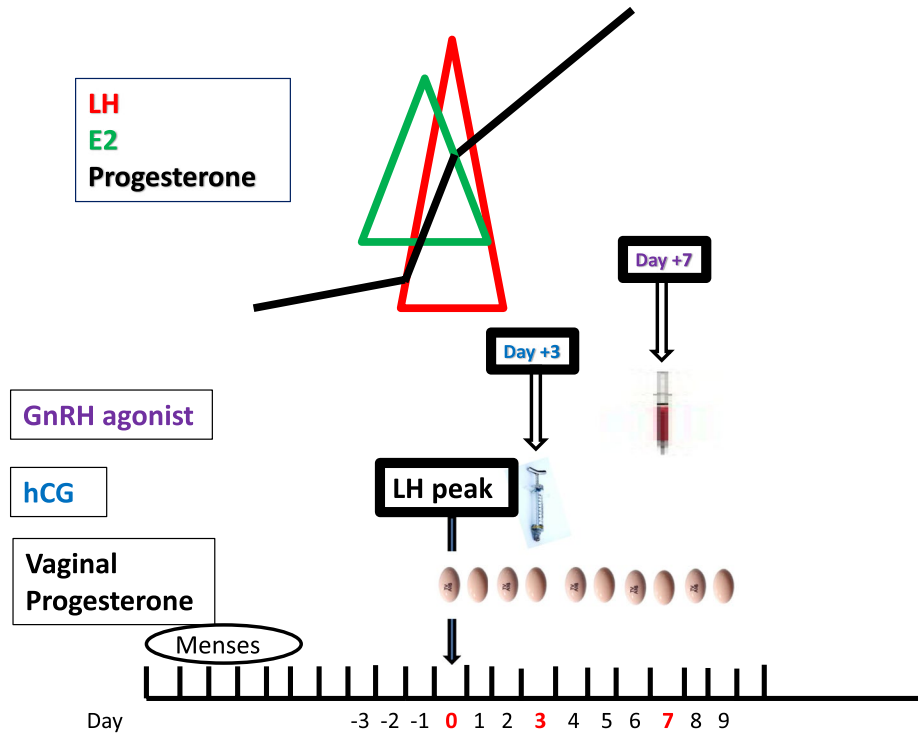


**Fig. 3** A practical approach to NC FET

to a shift towards NC-FET, with NC FET being the preferred choice for many patients and fertility clinics.

In the present study of patients undergoing NC FET with modified luteal support [20], pregnancy was achieved in 52% of the cycles and even higher (56.8%) when the LH surge was defined as a rise in LH level exceeding 180% of the baseline value, accompanied by a drop in estradiol levels and a threefold increase in progesterone levels on D- 1 compared to D- 2.

The rationale behind choosing the aforementioned approach is based on the following observations: Supplementation with progesterone in NC FET improved the number of live births [25]; The administration of hCG injection on day of transfer was chosen based on the ability of hCG to further improve the function of the corpus luteum [26]; and the administration of GnRH-agonist relied on the previous observed higher pregnancy rate in patients who received a mid-luteal injection of a GnRH-agonist [27, 28]. These latter effects were explained by a putative direct or indirect effect of the GnRH direct effect on the endometrium and/or corpus luteum. Moreover, the increase in LH levels following GnRH administration precedes several pathways, which result in the secretion of growth factors, cytokines, angiogenic and adhesion molecules, all involved in the implantation process [27].

The most notable finding in the present study was the significant difference in the %Δ change in progesterone levels between patients who conceived and those who did not. Patients who conceived exhibited a significantly higher %Δ change in progesterone levels from Day − 2 to Day − 1 (1.9 ± 1.5) compared to those who did not conceive (1.6 ± 1.4, $p < 0.013$). This suggests that a more pronounced increase in progesterone (at least threefold) on the day of LH surge may be an important factor for successful implantation, potentially indicating better endometrial preparation for embryo implantation. This observation is in line with the observation that endometrial maturation is induced by progesterone, which starts to rise about 12 h before the start of the LH surge [17].

Equally important is understanding the required hormonal changes surrounding the LH surge, which are necessary to define the LH surge more precisely, leading to optimal outcomes. Following our observation, we suggest that the LH surge should be determined when the LH level exceeds 180% of the baseline value [21], accompanied by a drop in estradiol levels [16], and tripling the progesterone levels compared to D- 2. This day corresponds to one day prior to ovulation/OPU.

A limitation of our study is its retrospective design and the lack of data on live birth rates. However, this limitation is partially mitigated by the large study sample and the fact that all women who participated in our study underwent the same NC FET preparation protocol at the same institute, with two consecutive hormonal measurements taken two and one day prior to ovulation.

## Conclusions

The choice of endometrial preparation protocol for frozen-thawed ET cycle depends on the individual woman's ovarian function and convenience of the method, as well as the experience of the clinical team with the chosen approach. When natural cycle FET is utilized, our data suggest that the precise timing of the LH surge should be determined by a simultaneous increase in LH, decrease in estradiol and a tripling of progesterone levels between D- 2 and D- 1. Moreover, adding two injections of recombinant hCG and GnRH-agonist, on ovulation day + 3 and 4 days later, respectively, might optimized NC FET outcomes (Fig. 3).

Further large prospective studies are needed to validate the aforementioned recommendation before their routine implementation, including the use of progesterone monitoring that may benefit from further investigation. Moreover, an additional prospective trial (before clinical implementation) is a need to investigate whether starting vaginal progesterone supplementation on day of LH peak, rather than day of ovulation, will improve outcome in patients with %Δ change in progesterone levels from Day − 2 to Day − 1 of < 2.

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**Authors' contributions**
R.O. Designed the study, analyzed the data, wrote the first paper draft, edited it, proof read the paper and took part in discussions regarding the results. N.M. Analyzed the data, proof read the paper and took part in discussions regarding the results. E.R. and R.N. Retrieved the Data, proof read the paper and took part in discussions regarding the results.

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**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
The study was approved by our institutional (Sheba Medical Center) review board (SMC-D- 1856–25).

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

**Author details**
[1]Department of Obstetrics and Gynecology, Chaim Sheba Medical Center (Tel Hashomer), Ramat Gan 52621, Israel. [2]Faculty of Medical and Health Science, Tel Aviv University, Tel Aviv, Israel. [3]The Tarnesby-Tarnowski Chair for Family Planning and Fertility Regulation, at the Faculty of Medical and Health Science,

Tel Aviv University, Tel Aviv, Israel. [4]Department of Obstetrics and Gynecology, Mayanei Hayeshua Medical Center, Bnei Brak, Israel.

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## Publisher's Note