# Impact of follicle size before luteal progesterone supplementation on clinical outcomes of modified natural cycle single frozen embryo transfer

Shahryar K. Kavoussi, M.D., M.P.H., Shu-Hung Chen, M.S., Negar Farzaneh, Ph.D., Arya Farahi, Ph.D., Arya Farahi, Ph.D., Romtin Mehrabani-Farsi, B.S., a Kenneth I. Aston, Ph.D., Justin Chen, B.S.A., and Parviz K. Kavoussi, M.D.

<sup>a</sup> Austin Fertility & Reproductive Medicine/Westlake IVF, Austin, Texas; <sup>b</sup> Department of Emergency Medicine, University of Michigan Medical School, Ann Arbor, Michigan; and <sup>c</sup> Department of Statistics and Data Sciences, The University of Texas at Austin, Austin, Texas

**Objective:** To determine whether follicle size at midcycle transvaginal sonography imaging before luteal progesterone supplementation predicts modified natural cycle single frozen embryo transfer (mNC-SFET) outcomes.

**Design:** Retrospective chart review.

Subjects: Frozen embryo transfer charts were reviewed. After inclusion and exclusion criteria were applied, data were abstracted from cases of mNC-SFET (n = 115).

**Exposure:** For group A, lead follicle measuring < 16 mm on day of trigger or peak + ovulation predictor kit (n = 50), and for group B, lead follicle measuring  $\geq$  16 mm on day of trigger or peak +ovulation predictor kit (n = 65).

Main Outcome Measures: Follicle size analyzed as possible predictor of primary outcome ongoing pregnancy rate (OPR) as well as secondary outcomes implantation rate (IR), clinical pregnancy rate (CPR), and spontaneous abortion (SAB) rate via bivariate associations and multivariate logistic regression analyses.

Results: Bivariate analyses showed no differences between groups in OPR (A, 48.0%, 24/50, and B, 44.6 %, 29/65), IR (A, 64.0%, 32/50, and B, 61.5%, 40/65), CPR (A, 58.0%, 29/50, and B, 52.3%, 34/65), and SAB rates (A, 25.0%, 8/32, and B, 27.5%, 11/40). Multivariate analysis to investigate potential confounding between lead follicle size and outcomes of interest showed no difference in the primary and secondary outcomes. Furthermore, multivariate analyses using lead follicle size as a continuous variable showed no difference in

Conclusion: In normo-ovulatory women undergoing mNC-SFET with natural endometrial preparation with human chorionic gonadotropin trigger or luteinizing hormone surge to time frozen embryo transfer, lead follicle size before luteal phase supplementation does not impact clinical outcomes such as IR, CPR, SAB rate, or OPR. (F S Rep® 2025;6:47-51. ©2024 by American Society for Reproductive Medicine.)

Key Words: Follicle size, follicle, modified natural, FET, frozen embryo transfer

here is a growing trend toward the use of natural cycles (NCs) and modified NCs (mNCs) as effective protocols for frozen embryo transfer (FET). Such approaches to FET minimize the use of medications, essentially eliminating follicular phase endometrial preparation with exogenous estradiol (E2), and emerging data suggest optimal embryo transfer (ET) and obstetric outcomes (1-3). Such NC-FET and mNC-FET protocols can potentially involve several monitoring follicular scans via transvaginal sonog-

thick endometrial lining as well as a large follicle, before luteinizing hormone (LH) surge or human chorionic gonadotropin (hCG) trigger to time the upcoming embryo thaw and transfer. Although an existing study has shown that NC-FET and mNC-FET protocols have similar clinical outcomes (7), there are also data to suggest that mNC-FET outcomes

raphy (TVS) as well as endocrine serum

testing during the follicular phase

(4-6), with the goal of measuring a

Previous publications have indicated that along with endometrial thickness

are more efficacious than NC-FET out-

comes (8, 9).

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Correspondence: Shahryar K. Kavoussi, M.D., M.P.H., Austin Fertility & Reproductive Medicine/Westlake IVF, 300 Beardsley Lane, Bldg B, Suite 200, Austin, Texas 78746 (E-mail: austinfertility@ gmail.com).

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VOL. 6 NO. 1 / MARCH 2025 47 (EMT) monitoring typically to a measurement of  $\geq 7$  mm, natural follicle growth is monitored in the late follicular phase until a dominant follicle reaches a certain size, typically 16–18 mm in diameter, before hCG trigger or LH surge in preparation for potential luteal progesterone (P4) supplementation (LPS) with P4 before the actual FET (4, 6, 8, 10, 11). The monitoring of the dominant follicle has the potential to involve several ultrasound visits, which increase cost and time commitment for patients as well as less predictability in terms of scheduling the upcoming ET for patients and clinicians.

The aim of this study was to determine whether follicle size at midcycle TVS imaging and/or other clinical and embryologic factors are predictive of mNC single FET (mNC-SFET) outcomes. If follicle size before LPS, in combination with a thick endometrial lining, does not impact the outcomes of mNC-FET cycles, then the need for multiple monitoring ultrasounds and endocrine laboratory testing would be minimized, decreasing the number of visit and cost for patients who undergo NC-FET. We hypothesized that follicle size at trigger does not impact mNC-FET outcomes and such an approach would lead to more medically efficient and cost-effective treatment cycles.

#### **MATERIALS AND METHODS**

A retrospective chart review was performed of all FET cycles performed between January 1, 2018, and April 1, 2024 at Austin Fertility & Reproductive Medicine/Westlake IVF. After inclusion and exclusion criteria were applied, clinical and embryology information were abstracted from mNC-SFET cycles (n = 115). The inclusion criteria were normo-ovulatory female subjects between the ages of 18 and 45 years, autologous oocytes for embryo formation, and SFETs with untested or trophectoderm-tested euploid blastocysts for subjects aged <35 years at the time of egg retrieval and with trophectoderm-tested euploid blastocysts for subjects aged  $\geq$  35 years at the time of egg retrieval. The exclusion criteria were donor oocytes for embryo formation, donor embryo cases, double ETs, gestational carrier cases, trophectodermtested aneuploid or mosaic embryos, and mNC-FET cycles that involved the use of any hormonal medications or ovulation induction agent for endometrial preparation. Because of the deidentified nature of the data collected, Institutional review board exemption was obtained from St. David's Healthcare Institutional Review Board. Group A consisted of women who underwent mNC-SFET with lead follicle measuring <16 mm on day of trigger or peak +ovulation predictor kit (n = 50), and group B consisted of women who underwent mNC-SFET with lead follicle measuring  $\geq$  16 mm on day of trigger or peak +ovulation predictor kit FET cycle (n = 65).

All of the patients underwent mNCs with cycle day 10, 11, or 12 initial monitoring with TVS as well as a laboratory draw to check the E2 and P4 levels, with a plan for recombinant hCG (Ovidrel) administration later that night if the EMT was ≥7 mm and if the P4 level (Roche COBAS electrochemiluminescence immunoassay run by Clinical Pathology Laboratories, Austin, TX) was <3 ng/mL, regardless of lead follicle size. Subsequent visit for TVS and serum endocrine testing was needed only if the aforementioned endometrial criteria

were not met at initial day 10, 11, or 12 monitoring TVS. Luteal phase supplementation with either P4 in oil intramuscular injections at a dose of 50 mg once daily or Endometrin 100 mg vaginal inserts 3 times daily was started on the morning after peak LH surge or approximately 36 hours after nighttime hCG injection. Blastocyst thaw and SFET were performed 5-5.5 days after the start of LPS. The timing of blastocyst thaw for FET was scheduled according to either an LH surge or hCG injection for each FET and not with both an LH surge and hCG injection because the previous data have indicated that either LH surge or Ovidrel trigger is optimal for timing of embryo thaw for FET as opposed to the combination of both LH surge and subsequent hCG trigger on the same day, which has been associated with decreased success rates (10, 11). Single FET was performed, via abdominal ultrasound guidance, with a 23-cm Wallace ET catheter. Good-quality blastocysts were considered to be those with a grade of 2BB or higher, in accordance with the Gardner and Schoolcraft grading system for blastocysts (12). A serum quantitative hCG level was checked 9-10 days after ET, and if the hCG level was positive, a second quantitative hCG level was performed 2 days later to assess the trend in level. In the cases of reassuring hCG levels, TVS was performed between 6 and 7 weeks of gestation to evaluate for gestational sac, yolk sac, fetal pole, and fetal cardiac motion.

The primary outcome was ongoing pregnancy rate (OPR), defined as the number of ongoing pregnancies divided by the number of ETs per group. The secondary outcome measures were implantation rate (IR), clinical pregnancy rate (CPR), and spontaneous abortion (SAB) rate. IR was defined as the number of gestational sacs visible at TVS between 6 and 7 weeks of gestation divided by the number of ETs per group. CPR was defined as the number of gestational sacs visible at TVS between 6 and 7 weeks of gestation, with fetal pole and fetal cardiac motion, divided by the number of ETs per group. The SAB rate was defined as the number of pregnant patients who experienced miscarriage, before 20 weeks of gestation, divided by the number of pregnancies in each group. Statistical analyses were performed with t-tests for means of continuous variables, and the Pearson chi-square test was used for categorical variables. We used the Pearson chi-square test, with Yates correction where appropriate, to examine initial bivariate associations between group and each of the binary indicators, indicating a descriptive comparison of the rates of interest. We also employed a logistic regression model to conduct 8 multivariate analyses aimed at examining the relationship between lead follicle size and 4 critical outcomes: OPR, IR, CPR, and SAB rate. The logistic regression model included the following inputs: patient's age; height; weight; body mass index (BMI); gravity; parity; EMT; lead follicle size; and levels of antimüllerian hormone (AMH), E2, and P4. We used lead follicle size twice in each analysis, first as a binary variable, where we divided the participants into 2 groups: group A with a lead follicle size of <6 mm and group B with a lead follicle size of  $\geq$  16 mm and then as a continuous variable measured in millimeters. This approach allowed us to comprehensively investigate the potential impact of lead follicle size on the outcomes of interest, aiming to capture any nuanced relationships between the

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# TABLE 1

Characteristics and pregnancy outcomes of group A (women who underwent modified natural cycle frozen embryo transfer with lead follicle measuring <16 mm on day of trigger or peak +ovulation predictor kit) vs. group B (women who underwent modified natural cycle frozen embryo transfer with lead follicle measuring ≥16 mm on day of trigger or peak +ovulation predictor kit).

Characteristics	Group A (n = 50)	(n = 65)	P value
Female age (y)	35.8	35.9	.49
Parity	0.7	0.7	.47
BMI	25.0	27.0	.03
AMH level (ng/mL)	3.1	3.1	.44
PIO injections	24	33	.92
Endometrin vaginal inserts	26	32	
Trigger	44	51	.28
LH surge	6	14	
Day of trigger/LH surge	12.1	12.4	.24
Lead follicle size (mm)	12.9	19.5	.00
Endometrial thickness (mm)	8.8	9.0	.22
Midcycle E2 (pg/mL)	130.2 (n = 49)	226.5	.00
Midcycle P4 (ng/mL)	0.4	0.6	.01
PGT-A	36	40	.33
No PGT-A	14	25	0.5
Ongoing pregnancy rate	24/50 (48.0%)	29/65 (44.6%)	.86
Implantation rate	32/50 (64.0%)	40/65 (61.5%)	.94
Miscarriage rate	8/32 (25.0%)	11/40 (27.5%)	.98
Clinical pregnancy rate	29/50 (58.0%)	34/65 (52.3%)	.68

Note: The means for continuous variables were assessed via t-test. In bivariate analyses, P values were assessed via the Pearson chi-square test. AMH = antimüllerian hormone; BMI = body mass index; E2 = estradiol; FET = frozen embryo transfer; LH = luteinizing hormone; PGT-A = preimplantation genetic testing for aneuploidy; PIO = progesterone in oil; P4 = progesterone.

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predictor and outcome variables. P values of <.05 were considered statistically significant.

#### **RESULTS**

Characteristics and in vitro fertilization outcomes of women in groups A and B are shown in Table 1. There were no differences in mean female age, parity, antimüllerian hormone levels, mean day of trigger/LH surge, or EMT between groups. There was no difference in frequency of trigger or LH surge before LPS among groups. The mean BMI was higher in group B (27.0) than in group A (25.0, P=.03). The mean midcycle E2 and P4 levels were significantly higher in group B than in group A. Lead follicle size in group B (19.5 mm) was significantly higher than that in group A (12.9 mm; P<.0001).

In terms of the primary outcome, there was no difference in OPR for groups A and B-48.0% (24/50) and 44.6 % (29/65), respectively (P=.86). In terms of the secondary outcome measures, there were no differences between groups in terms of IR (A, 64.0%, 32/50, and B, 61.5%, 40/65; P=.94), CPR (A, 58.0%, 29/50, and B, 52.3%, 34/65; P=.68), and SAB rates (A, 25.0%, 8/32, and B, 27.5%, 11/40; P=.98).

The different etiologies of infertility in groups A and B are listed in Table 2. The sample sizes were small; therefore, this table's data are descriptive.

After observing a statistically significant difference in covariates BMI, E2 level, and P4 level between groups A and B, we conducted a multivariate analysis to investigate whether these variables were confounding the relationship between lead follicle size and the outcomes of interest. The E2 variable was missing for 1 patient; therefore, there were complete data for 114 cases for OPR, IR, and CPR and complete data for 71 cases for SAB rate. Despite accounting for these variables, our

results remained unchanged. Specifically, we found no significant difference in OPR between groups A and B (P=.95), indicating that lead follicle size was not a significant predictor of this outcome. Similarly, we observed no significant differences between the groups in terms of IR (P=.72), CPR (P=.97), or SAB rates (P=.56) (Table 3). These findings suggest that lead follicle size does not play a significant role in determining mNC-SFET outcomes in this patient population.

Last, we performed multivariate analyses using lead follicle size as a continuous variable, which allowed us to explore the potential relationship between incremental changes in lead follicle size and in vitro fertilization

#### TABLE 2

Etiology of infertility for group A (women who underwent modified natural cycle frozen embryo transfer with lead follicle measuring <16 mm on day of trigger or peak +ovulation predictor kit) vs. group B (women who underwent modified natural cycle frozen embryo transfer with lead follicle measuring  $\ge$ 16 mm on day of trigger or peak +ovulation predictor kit).

Etiology of infertility	Group A (n = 50)	Group B (n = 65)			
Oligo-ovulation/anovulation	0	1			
Diminished ovarian reserve	2	3			
Endometriosis	1	1			
Male factor	5	15			
Tubal factor	3	2			
Uterine	1	1			
Unexplained	3	1			
Recurrent pregnancy loss	4	5			
Multiple factors	30	32			
Other	1	4			
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# TABLE 3

Logistic regression analysis of factors differentiating ongoing pregnancy rate-positive, implantation rate-positive, clinical pregnancy rate-positive, and spontaneous abortion-positive vs. ongoing pregnancy rate-negative, implantation rate-negative, clinical pregnancy rate-negative, and spontaneous abortion-negative patients, using lead follicle size as a binary variable (threshold, 16 mm).

	OPR	IR	CPR	SAB
Sample size	114	114	114	71
Intercept	-0.5000 (0.97)	-8.2966 (0.48)	-8.7345 (0.46)	-26.4481 (0.44)
Age	0.0364 (0.53)	-0.0087 (0.89)	0.0348 (0.56)	-0.0650 (0.47)
Height (inches)	-0.0344 (0.85)	0.1184 (0.52)	0.0985 (0.59)	0.4397 (0.41)
Weight (pounds)	-0.0112 (0.75)	-0.0211 (0.55)	-0.0219 (0.54)	-0.0508(0.62)
BMI	0.0459 (0.82)	0.1016 (0.62)	0.0905 (0.66)	0.3064 (0.62)
Gravity	0.0929 (0.56)	0.2108 (0.22)	0.2333 (0.16)	0.1080 (0.66)
Parity	0.1107 (0.72)	0.3601 (0.32)	0.0091 (0.98)	0.1626 (0.69)
Endometrial thickness (mm)	0.1609 (0.16)	0.1903 (0.13)	0.1965 (0.10)	-0.0870 (0.63)
Lead follicle size	-0.0287 (0.95)	0.1746 (0.72)	-0.0206 (0.97)	0.4008 (0.56)
(≥16 mm or not)				
AMH (ng/mL)	0.0823 (0.37)	0.0472 (0.66)	0.1325 (0.20)	-0.1027 (0.42)
E2 (pg/mL)	-0.0007 (0.73)	-0.0014 (0.49)	-0.0013 (0.54)	-0.0007 (0.84)
P4 (ng/mL)	-0.0311 (0.96)	-0.3772 (0.54)	-0.0279 (0.96)	-0.4257 (0.66)

Note: Numbers outside of parentheses indicate linear regression coefficients, and numbers in parentheses indicate P values. AMH = antimüllerian hormone; BMI = body mass index; CPR = clinical pregnancy rate; E2 = estradiol; IR = implantation rate; OPR = ongoing pregnancy rate; P4 = progesterone; SAB = spontaneous abortion.

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outcomes. Again, in these analyses, we found no significant association between lead follicle size and any of the outcomes of interest (Table 4). These results provide further evidence that lead follicle size may not be a significant predictor of FET outcomes in this patient population, regardless of whether it is analyzed as a binary or continuous variable.

#### **DISCUSSION**

Our data have shown that in mNC-SFET, defined in our practice as cycles with either LH surge or hCG trigger injection with LPS for FET, provided that EMT is  $\geq 7$  mm and the P4 level is <3.0 ng/mL before LPS, lead follicle size on day of hCG trigger or within the day of LH surge does not impact downstream FET outcomes such as IR, CPR, SAB rate, and OPR. Our standard protocol for mNC-FET in normo-

ovulatory women, with natural endometrial preparation, the use of hCG trigger if no LH surge by the day of trigger, and prescribing LPS is one way to approach such treatment cycles, which has been shown to improve NC-FET outcomes in existing literature (13). The investigators of a systematic review and meta-analysis concluded that P4 administration for LPS is beneficial in NC-FET cycles because of higher CPR and higher live birth rate (14). Although the same publication showed no evidence to support the use of hCG trigger for these cases (14), a retrospective study showed that compared with NC-FET (n = 378), mNC-FET (n = 650), which involved the use of hCG trigger and no LPS, was associated with significantly higher positive hCG rates, IR, CPR, and live birth rate (8). In addition, previous data have demonstrated an adverse effect of luteinized unruptured follicles on mNC-FET outcomes (15).

# **TABLE 4**

Logistic regression analysis of factors differentiating ongoing pregnancy rate-positive, implantation rate-positive, clinical pregnancy rate-positive, and spontaneous abortion-positive vs. ongoing pregnancy rate-negative, implantation rate-negative, clinical pregnancy rate-negative, and spontaneous abortion-negative patients, using lead follicle size as a *continuous* variable.

	OPR	IR	CPR	SAB
Sample size	114	114	114	71
Intercept	0.4568 (0.97)	-8.2966 (0.48)	-8.3246 (0.48)	-18.2844 (0.60)
Age	0.0403 (0.50)	-0.0087 (0.89)	0.0374 (0.53)	-0.0695 (0.45)
Height (inches)	-0.0423 (0.81)	0.1184 (0.52)	0.0951 (0.60)	0.2941 (0.58)
Weight (pounds)	-0.0071 (0.84)	-0.0211 (0.55)	-0.0202 (0.56)	-0.0249 (0.81)
BMI	0.0313 (0.88)	0.1016 (0.62)	0.0847 (0.68)	0.1436 (0.82)
Gravity	0.0574 (0.72)	0.2108 (0.22)	0.2171 (0.20)	0.1677 (0.50)
Parity	0.1643 (0.60)	0.3601 (0.32)	0.0318 (0.92)	0.1226 (0.77)
Endometrial thickness (mm)	0.1589 (0.17)	0.1903 (0.13)	0.1924 (0.11)	-0.1009 (0.59)
Lead follicle size (mm)	-0.0698 (0.26)	0.1746 (0.72)	-0.0323 (0.60)	0.1426 (0.14)
AMH (ng/mL)	0.0948 (0.31)	0.0472 (0.66)	0.1409 (0.18)	-0.1118 (0.40)
E2 (pg/mL)	0.0005 (0.82)	-0.0014 (0.49)	-0.0008 (0.72)	-0.0026 (0.51)
P4 (ng/mL)	0.1654 (0.78)	-0.3772 (0.54)	0.0594 (0.92)	-0.8083 (0.45)

Note: Numbers outside of parentheses indicate linear regression coefficients, and numbers in parentheses indicate P values. AMH = antimüllerian hormone; BMI = body mass index; CPR = clinical pregnancy rate; E2 = estradiol; IR = implantation rate; OPR = ongoing pregnancy rate; P4 = progesterone; SAB = spontaneous abortion.

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The strengths of our study include the inclusion of FET with a single blastocyst as well as vitrified-thawed blastocysts only. Another strength of our study is that the mNC-SFET that were included in this analysis were relatively homogeneous as cycles with endometrial preparation via exogenous hormones and/or ovulation induction agents were excluded, which led to the main limitation of our study, which was the small sample sizes in each group. The limitations of our study were the biases inherent to retrospective study design as well as the small sample sizes in the control and study groups.

### **CONCLUSION**

In normo-ovulatory women undergoing mNC-SFET with natural endometrial preparation and the use of either hCG trigger or LH surge to time FET, lead follicle size before LPS does not seem to impact clinical outcomes such as IR, CPR, SAB rate, or OPR. These findings may be useful to decrease the number of visits and cost associated with each treatment cycle. Further studies are necessary to confirm these findings with larger sample sizes.

# **CRediT Authorship Contribution Statement**

Shahryar K. Kavoussi: Conceptualization, Writing – original draft. Shu-Hung Chen: Methodology, Writing – review & editing. Negar Farzaneh: Formal analysis, Writing – review & editing. Arya Farahi: Formal analysis, Writing – review & editing. Romtin Mehrabani-Farsi: Data curation. Kenneth I. Aston: Formal analysis, Writing – review & editing. Justin Chen: Methodology, Writing – review & editing. Parviz K. Kavoussi: Formal analysis, Writing – review & editing.

#### **Declaration of Interests**

S.K.K. is a consultant for Medtronic and reports honoraria from Medtronic and patents for Methods of embryo screening – PAPP-A and Methods of embryo screening – AFP, outside the submitted work. S.-H.C. has nothing to disclose. N.F. has nothing to disclose. A.F. reports funding from The National Science Foundation under Cooperative Agreement AST-2421782 and The Good Systems at the University of Texas at Austin; honoraria from The University of North Texas Health Science Center Myself, to serve as an expert in AIM-AHEAD PAIR program <a href="https://www.aim-ahead.net/experts-grant-writing-coaches/">https://www.aim-ahead.net/experts-grant-writing-coaches/</a>) outside the submitted work. R.M.-F. has nothing to disclose. K.I.A. has nothing to disclose. J.C. has nothing to disclose. P.K.K. is a consultant for PS Fertility and reports honoraria from Halozyme therapeutics and PS Fertility outside the submitted work.

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