

What is the optimal follicular size before triggering ovulation in intrauterine insemination cycles with clomiphene citrate or letrozole? An analysis of 988 cycles

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Objective: To determine the optimal size of the leading follicle before human chorionic gonadotropin (hCG) administration in cycles with clomiphene citrate (CC) and letrozole, and to examine any differences in the optimal leading follicle size between cycles with CC and letrozole.

Design: A retrospective study.

Setting: University hospital-based reproductive center.

Patient(s): 1,075 women undergoing intrauterine insemination cycles with CC or letrozole.

Intervention(s): Leading follicle diameters and endometrial thickness were recorded 24 hours before hCG administration, together with other cycle parameters, and were compared between pregnant and nonpregnant patients.

Main Outcome Measure(s): Leading follicle diameter and intrauterine insemination outcome.

Result(s): Eight percent of patients ($n = 87$) were excluded because their leading follicle was less than 18 mm by days 11 to 13. Pregnancy was recorded as clinical pregnancy with fetal heart activity seen at 6- to 7-week transvaginal ultrasound. For both CC and letrozole, higher pregnancy rates were achieved when the leading follicles were in the 23 to 28 mm range. The optimal size of the leading follicle was not statistically significantly different between cycles using CC or letrozole. However, for each endometrial thickness, the optimal follicular size of the leading follicle was different. Each additional millimeter of endometrial thickness increased the optimal follicular size by 0.5 mm. Thicker endometrial lining led to a higher probability of pregnancy.

Conclusion(s): The optimal size of the leading follicle in ovulation induction with CC and letrozole is similar for both drugs and is closely related to the endometrial thickness. (Fertil Steril® 2012;97:1089–94. ©2012 by American Society for Reproductive Medicine.)

Key Words: Clomiphene citrate, endometrial thickness, intrauterine insemination, leading follicle diameter, letrozole, pregnancy rates

When performing ovulation induction (OI) cycles combined with intrauterine insemination (IUI), the use of exogenous human chorionic gonadotropin (hCG) to trigger ovulation remains a popular practice. This treatment is especially valuable for women who cannot reliably detect the spontaneous luteinizing hormone (LH) surge. The timing of hCG administration is not well standardized but usually relies on there being at least

one follicle greater than 18 mm in mean diameter at ultrasound imaging (1). This timing is important because premature administration of hCG acts like a premature LH surge and may result in follicular atresia (1, 2). Delayed hCG administration can happen after ovulation has already occurred, thus negating any potential benefit.

The first studies to examine follicular sizes to trigger ovulation were in the 1980s and 1990s, and follicular diame-

ters ≥ 16 –18 mm were used as the criteria for hCG administration (1–7). Studies comparing the leading follicle diameter in natural cycles with CC cycles found that CC cycles have significantly larger leading follicles, measuring between 18 and 30 mm (2–5, 8). Because of this wide range, many investigators did not consider this parameter to be a prognostic indicator for IUI success (9–11). More recent studies examining the leading follicle have included cycles stimulated either with CC or with gonadotropins (7, 12–15). They reported different, and at times contrasting, optimal follicular diameters to time the triggering of ovulation; however, in general, cycles using gonadotropin stimulation used a smaller follicular diameter to judge

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hCG administration as compared with CC. In 2003, the American Society for Reproductive Medicine (ASRM) published a practice committee report on the use of CC which said that the average peak diameter in CC cycles ranges between 19 and 30 mm (with median diameter of 25 mm) (16). That statement was based on one prospective study from 1996 (3).

During the last decade, the use of aromatase inhibitors for ovulation induction has rapidly expanded (17). Studies have shown the efficacy of aromatase inhibitors in ovulation induction in patients who have a poor response to CC (18), in patients with polycystic ovary syndrome who are resistant to CC (19), and in patients with unexplained infertility (20). Regarding the size of the leading follicle, we have found two studies demonstrating larger leading follicles with letrozole compared with CC (21, 22), and one study showing no difference between the two (23).

We investigated the optimal size of the leading follicle before hCG administration in cycles with CC and letrozole. Secondly, we examined whether there is a difference in the optimal leading follicle size between cycles with CC and letrozole.

MATERIALS AND METHODS

Our retrospective analysis included women undergoing ovulation induction followed by IUI at an academic reproductive medicine center from 2004 to 2009. The study protocol was approved by the institutional review board at the Medical College of Wisconsin. The study group included all women undergoing a first cycle of IUI in our center after treatment with either CC or letrozole in which a midcycle ultrasound was performed and ovulation was triggered with hCG. All patients consented to the use of letrozole as an off-label medication for ovulation induction. Patients whose hCG administration was postponed because of small follicular diameter at midcycle ultrasound were excluded from the study as they did not return for a follow-up ultrasound, and patients who were lost to follow-up observation after the cycles were excluded as well. Maternal age and total motile sperm count in the insemination sample were also recorded, and the sperm assessment was performed in accordance with the 1999 World Health Organization criteria (24). Pregnancy was recorded as an intrauterine pregnancy with fetal heart motion detected at the 6- to 7-week transvaginal scan.

As is standard in our clinic, all women in their first ovulation induction/IUI cycle underwent transvaginal ultrasound monitoring between cycle days 11 and 13 after receiving 5 days of treatment with 100 mg of CC daily or 5 mg of letrozole daily starting on days 3 to 5. At the time of the ultrasound, the mean diameter of the follicle was calculated from measurements in two perpendicular planes for any follicles measuring greater than 14 mm. This was recorded along with the endometrial thickness in the midsagittal plane. The transvaginal ultrasounds were performed by one of two of the coauthors (E.S. or P.R.) with the General Electric Voluson 730 Expert. If at least one follicle ≥ 18 mm in mean diameter was detected, hCG was administered the same morning, and IUI was scheduled 24 hours later. Sperm samples were

prepared by density gradient centrifugation. Patients were instructed to obtain a quantitative serum hCG measurement 14 days after the insemination if they did not menstruate. If the result was positive, the patient was scheduled for a transvaginal ultrasound 6 to 7 weeks after the last menstrual period to document the pregnancy location and fetal heart activity.

Statistical Analysis

Power analysis. The sample size of 1,047 cycles was chosen to achieve an 80% power for detecting a statistically significant difference at the 5% level if the pregnancy rate after one cycle of intrauterine insemination increased from 12% to 26% when the diameter of the leading follicle increased from 18 mm to 30 mm, and the follicular diameter was normally distributed with mean 24 mm and standard deviation of 3 mm (chosen because the diameters are expected to be in the 18 to 30 mm range). The power sample was chosen before the study and was our true estimate, included in the institutional review board protocol. More specifically, the power of a logistic regression to detect a log-odds ratio of 0.08 per 1 mm increase in follicular diameter (slope = 0.08) was used.

Statistical tests. Univariate comparisons were performed using Pearson's chi-square test for categorical data and the Wilcoxon-Mann-Whitney test for continuous measures. Multivariate analysis was performed using logistic regression for the probability of pregnancy. The considered predictors were age, cycle type, postprocessing total motile sperm count, leading follicle size, the size of the second leading follicle, thickness of the endometrial lining, and primary diagnosis. Linearity of continuous covariates was evaluated first using fourth-degree orthogonal polynomials, and only leading follicle size was found to have a statistically significant nonlinear effect. All interactions with leading follicle size—the variable of primary interest—were tested, and those that were statistically significant at the 10% level (interaction with cycle type and endometrial lining thickness) were retained for the final model. Backward selection guided by minimizing the Akaike information criterion (AIC) (25) was used to determine the degree of the polynomial describing the effect of leading follicle size; a second-degree relationship was found to be adequate by providing the lowest AIC value. We collected the information only from each woman's first cycle that was conducted in our clinic; to avoid potential selection bias, repeated cycles of the same patient were not recorded. All analyses determining the probability of pregnancy for each cycle type were adjusted for the following covariates: age, total motile sperm count, and difference in primary diagnosis distribution.

RESULTS

During the specified time period 1,075 women were identified to be qualified for the study. After removing 87 women whose hCG was not administered on the same day as the ultrasound, 988 women remained in the study. Of these patients, 777 received CC and 211 received letrozole for ovulation stimulation.

Descriptive summaries of all the CC and letrozole group variables can be seen in Table 1. The group who was treated with letrozole was found to be slightly younger and had a different primary diagnosis distribution, with a higher percentage (53%) having anovulation and lower percentage (31%) with unexplained infertility. In the CC group, 56% of the patients had a primary diagnosis of unexplained infertility, and only 16% were anovulatory. The overall mean diameter of the leading follicle was 23 mm in the group treated with CC and 22 mm in the group treated with letrozole (see Table 1). There was a difference in pregnancy outcomes between the two groups. Higher pregnancy rates were achieved with letrozole in comparison with CC in the univariate analysis ($P=.024$) (see Table 1). Cycles of ovulation induction with letrozole had a 23% pregnancy rate, whereas cycles with CC had a 16% pregnancy rate. These results were before controlling for other covariates in multivariate analysis.

In our univariate analysis, age, cycle type, leading follicle size, thickness of endometrial lining, and primary diagnosis were statistically significantly associated with achieving pregnancy (Supplemental Table 1, available online). The average thickness of the endometrial lining in our study at the time of hCG administration was 8.5 mm for CC cycles and 8.7 mm for letrozole cycles (Table 1).

A multivariate analysis was then performed using logistic regression for the probability of pregnancy as described in the "Materials and Methods" section. In this analysis, we found that increasing age decreased the probability of pregnancy, and the size of the second leading follicles and postprocessing total motile sperm count were not predictive (Supplemental Table 2, available online). The largest group, unexplained diagnosis, was used as a reference for comparison with primary diagnosis; only the diagnosis of anovulation showed a statistically significant increase in the probability of pregnancy compared with an unexplained cause.

The relationship between the leading follicle size and the probability of pregnancy was found to be closely related to

the endometrial thickness and the drug type, and is best understood from Figure 1 and Table 2 (1, 5). All the following analyses are adjusted for age, total motile sperm count, diagnosis, and cycle type as described in the method section. Figure 1 shows that the size of the optimal leading follicle was not statistically significantly different for cycles with CC and letrozole ($P=.44$).

For both drugs, the leading follicle size exhibited a nonlinear effect: an optimal follicular size maximized the probability of pregnancy, with lower rates for both larger and smaller sizes. We found that there was no one single size of the leading follicle that will go with any cycle; rather, the data we collected showed that the optimal follicular diameter is different for each endometrial thickness (Fig. 1, Table 3). We estimated that each additional millimeter of endometrial thickness is associated with an increase in the optimal follicular size by 0.5 mm (Table 2). For an endometrial lining of 9 mm, which was the mean thickness in our study, the optimal follicular size was 24 mm with CC and 24.7 mm with letrozole. Table 3 shows that at the optimal follicle size a thicker endometrium leads to higher probability of pregnancy for the given drug cycle (odds ratio [OR] 1.14; 95% confidence interval [CI], 1.05–1.25). This effect is depicted in Figure 1.

In addition, at the optimal follicle size the cycles with letrozole had statistically significantly higher pregnancy rates, after adjusting for other covariates (OR 1.8; 95% CI, 1.07–3.0; $P=.03$) (Supplemental Figure 1). However, moving away from the optimum statistically significantly dropped the pregnancy rates more in the letrozole group compared with the CC group.

DISCUSSION

In this study, we examined the optimal follicular size before hCG administration to yield the highest pregnancy rates in IUI cycles stimulated using CC or letrozole. Predictors of IUI cycle success in achieving pregnancy have been examined by several studies (8–11). Factors that were considered to be

TABLE 1

Descriptive statistics of the study population by cycle type.

	N	CC (n = 777)	Letrozole (n = 211)	Combined (N = 988)	P value
Pregnancy	988	16% (125)	23% (48)	18% (173)	.024 ^a
Age	988	31/34/37 ^c	29/32/36 ^c	30/34/37 ^c	<.001 ^b
Postprocessing TMSC (millions)	985	12.0/28.0/59.0 ^c	17.0/38.5/79.8 ^c	13.0/30.0/64.0 ^c	<.001 ^b
Leading follicle (mm)	988	20/23/26 ^c	19/22/24 ^c	20/23/25 ^c	<.001 ^b
Second follicle present	988	87% (675)	64% (135)	82% (810)	<.001 ^b
Endometrial lining (mm)	988	7.4/8.5/10.0 ^c	7.6/8.7/10.1 ^c	7.5/8.6/10.1 ^c	.325 ^b
Primary diagnosis	988				<.001 ^a
Unexplained		56% (432)	31% (65)	50% (497)	
Anovulation		14% (111)	50% (105)	22% (216)	
Male factor		9% (71)	9% (18)	9% (89)	
Endometriosis		6% (47)	5% (10)	6% (57)	
Tubal factor		6% (45)	2% (4)	5% (49)	
Advanced maternal age		5% (40)	1% (3)	4% (43)	
PCOS		2% (16)	3% (6)	2% (22)	
Recurrent miscarriages		2% (15)	0 (0)	2% (15)	

Note: N is the number of non-missing values, and the numbers after percentages are frequencies. CC = clomiphene citrate; PCOS = polycystic ovary syndrome; TMSC = total motile sperm count.

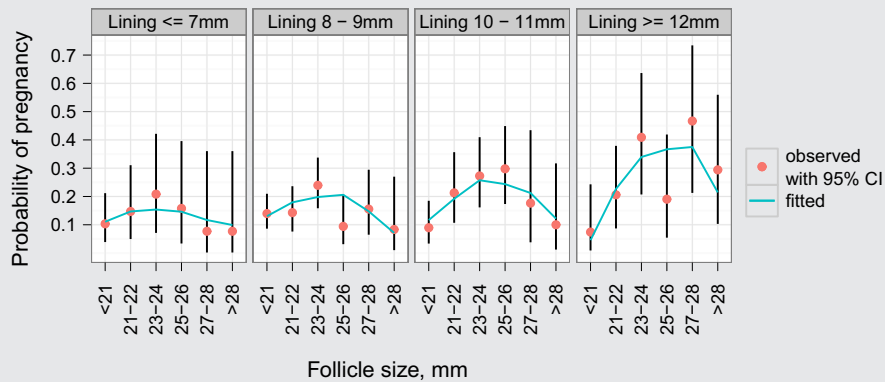
^a Wilcoxon test.

^b Pearson's chi-square test.

^c The lower quartile/median/upper quartile for continuous variables.

Palatnik. Optimal follicular size before hCG. Fertil Steril 2012.

FIGURE 1



The probability of pregnancy by the size of the leading follicle and the endometrial lining thickness. *Points* represent observed proportions with 95% binomial confidence intervals; *lines* connect the average model-based predicted values for each patient in the given follicle size/endometrial thickness group, thus it is adjusted for the observed age, cycle type, and diagnostic group distribution.

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prognostic were the age of the patient, primary infertility diagnosis, duration of the infertility, sperm motility, number of mature follicles, and estrogen level on the day of hCG administration. In our study, the important factors for clinical pregnancy after IUI were found to be maternal age, primary infertility diagnosis, endometrial thickness, the size of the leading follicle, and the drug type. Sperm motility and the presence of other mature follicles were not found to be statistically significantly correlated with pregnancy. One possible explanation for the sperm motility not being a predictive factor of the cycle outcome may be because the majority of men in our couples had total motile sperm count values above the threshold.

Several studies examined the predictive value of the leading follicle size in determining the success of IUI cycles (12–15). Silverberg et al. (12) analyzed IUI cycles after ovulation induction with human menopausal gonadotropins and found that ovulation success was higher in follicles larger than 20 mm on the day of hCG administration, although

there was no relationship between the size of the leading follicle and cycle outcome. There was no difference in that study in the incidence of conception between cycles when the leading follicle was larger or smaller than 16 mm (12). Ghosh et al. (13) examined cycles with CC and gonadotropins and found that cycles in which the leading follicle was ≥ 20 mm were less likely to achieve pregnancy compared with those for which the leading follicles had diameters between 15 and 19.99 mm. The inverse association between follicular diameter and pregnancy was explained by nondifferential misclassification bias (intraobserver, interobserver, machine settings, and measurement of collapsed follicles after they have ovulated). Iberico et al. (14) found higher pregnancy rates when the leading follicle was larger than 20 mm, but this finding was not statistically significant. A recent study by Farhi et al. (15) showed that pregnancy rates are higher when the leading follicle was between 18 and 22 mm, and that they dropped for both smaller and larger diameters.

TABLE 2

Parameters of the parabolic relationship between leading follicle size, endometrial thickness, and probability of pregnancy, adjusted for age and primary diagnosis.

Parameter	Estimate	95% CI	P value
OR for pregnancy rates at optimal follicle size			
Thicker endometrial lining (mm)	1.14	1.05–1.24	.002
Letrozole vs. CC	1.8	1.05–2.9	.03
OR for pregnancy rates 2 mm away from the optimal follicle size			
Increase in 1 mm in endometrial lining	0.99	0.98–0.99	.005
Letrozole vs. CC	0.90	0.83–0.99	.030
Optimal diameter (mm)			
Value when endometrial lining = 9 mm, CC	24 mm	22.4–25.5 mm	
Increase of 1 mm in endometrial lining	+0.5 mm	0.2–0.9 mm	.003
Letrozole vs. CC	+0.8 mm	–1.1–2.7 mm	.44
Value when endometrial lining = 9 mm, letrozole	24.7 mm	23.5–25.9 mm	

Note: CC = clomiphene citrate; CI = confidence interval; OR = odds ratio.

Palatnik. *Optimal follicular size before hCG. Fertil Steril* 2012.

TABLE 3

Observed pregnancy rates by endometrial lining thickness and size of leading follicle.

Lining	Leading follicle size													
	≤20 mm		21–22 mm		23–24 mm		25–26 mm		27–28 mm		≥ 29 mm		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
≤7 mm	58	10	34	15	24	21	19	16	13	8	13	8	161	13
8–9 mm	136	14	84	14	96	24	53	9	45	16	24	8	438	16
10–11 mm	67	9	47	21	55	27	47	30	17	18	20	10	253	20
≥ 12 mm	27	7	34	21	22	41	21	19	15	47	17	29	136	25
Total	288	11	199	17	197	26	140	19	90	20	74	14	988	18

Palatnik. Optimal follicular size before hCG. *Fertil Steril* 2012.

In our study, we found that there is an optimal size for the leading follicle that maximizes the probability of pregnancy, with lower rates for both smaller and larger leading follicles. This optimal size is influenced by the endometrial thickness. For both drugs, higher pregnancy rates were achieved with the leading follicle being in the range of 23 to 28 mm (Table 3). Within that range, pregnancy rates were higher when the larger follicles were accompanied by a thicker endometrium and vice versa (see Table 3). These findings can be seen as a similar response of the endometrium and the follicles to the ovulation-induction agent, letrozole or CC: an appropriate response affected both the follicles and the endometrium in the same way. Possibly, this reflects coordination between follicular growth and the endometrial lining. Larger follicles would be expected to produce higher levels of estradiol that would then stimulate the endometrial lining more, and smaller follicles would produce lower levels of estradiol and thus produce a thinner lining. When this coordination is disrupted, lower pregnancy levels are the result.

The size of the leading follicle that resulted in a pregnancy was not statistically significantly different in cycles with CC and letrozole. However, it appears that cycles stimulated with CC had a wider range of follicle sizes, which resulted in similar rates of pregnancy as compared with letrozole (Fig. 1).

The role of endometrial thickness in the success of IUI cycles is a matter of debate, with some studies supporting the benefit of thicker endometrium and others dismissing its importance (26–29). In our study, endometrial thickness was not found to be statistically significantly different among the cycles with CC and letrozole. In addition, endometrial lining was found to be a predictive factor of achieving pregnancy, and thicker endometrial lining resulted in higher pregnancy rates when the leading follicle size was close to the optimum ($P=.002$).

We did find that higher pregnancy rates were achieved with letrozole (23%) in comparison with CC (16%) ($P=.024$). However, in a univariate analysis, these groups were not directly comparable, so these findings might be biased. The letrozole group was slightly younger (averaging 32 years old vs. 34 years old for CC) and included more women with anovulation as their primary infertility diagnosis, whereas more than half the women in the CC group had a diagnosis of unexplained infertility. In addition, as was shown in Figure 1, moving away from the optimum size dropped

pregnancy rates more in the letrozole than the CC cycles. Therefore, although letrozole had higher pregnancy rates at the optimal follicle size because the deviation from the optimal size had a higher effect for letrozole cycles, this effect disappeared and even potentially reversed for leading follicle sizes that were 3 mm or more away from the optimum.

Among the weaknesses of our study was our short-term follow-up observation. We evaluated the patients only until their clinical pregnancy was documented via a 6- to 7-week ultrasound and did not document delivery rates. In addition, we did not perform serial ultrasounds during the cycles, and we based the definition of the dominant follicle on one midcycle scan. On the other hand, these procedures are similar to the IUI surveillance protocol in our hospital as well as in many other reproductive clinics. We had 87 patients who, on the day of the midcycle ultrasound, had a leading follicle size smaller than 18 mm; their hCG administration was postponed. These patients were excluded from our analysis because they did not return for a follow-up ultrasound, so we cannot make any conclusions regarding pregnancy rates among the patients with a smaller size follicle on cycle days 11 to 13 who were not ready to be triggered on those days.

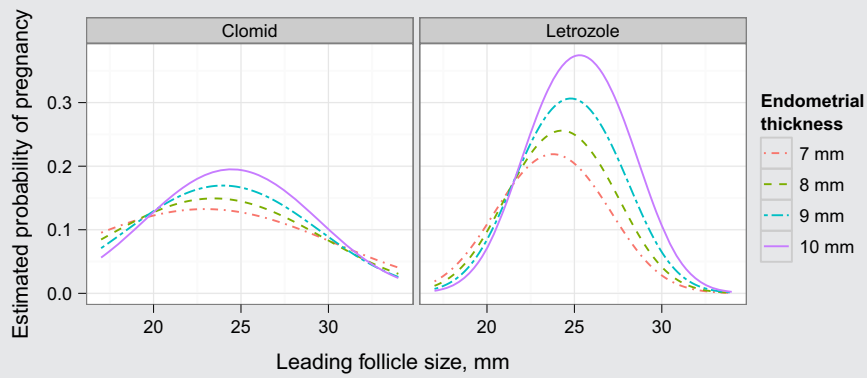
Our study has shown that the optimal size of the leading follicle in ovulation induction with CC and letrozole is similar for both drugs and is closely related to the endometrial thickness of the cycle. Keeping that relationship in mind can help in planning the IUI cycle and in timing the hCG administration.

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SUPPLEMENTAL FIGURE 1



The estimated effect of the leading follicle size on the probability of pregnancy depending on endometrial thickness and cycle type. The figure is adjusted for other covariates via logistic regression. Reference levels (mean for continuous and mode for discrete variables): age = 34 years; primary diagnosis = unexplained.

Palatnik. Optimal follicular size before hCG. Fertil Steril 2012.

SUPPLEMENTAL TABLE 1

Summary of predictors by pregnancy status: all patients.

	N	Pregnant (n = 173)	Not pregnant (n = 815)	P value
Age	988	30.0/32/36.0 ^a	30.5/34/37 ^a	.005 ^b
Cycle type: letrozole	221	28% (48)	20% (163)	.024 ^c
Postprocessing TMSC	988	16/35/62 ^a	13/29/64.2 ^a	.197 ^b
Leading follicle (mm)	988	21/23/25 ^a	20/22/25 ^a	.015 ^b
Second follicle present	988	81% (140)	82% (670)	.69 ^c
Endometrial lining (mm)	988	7.9/9/10.7 ^a	7.4/8.5/10.0 ^a	.001
Primary diagnosis				.013 ^c
Unexplained		45% (77)	52% (420)	
Anovulation		29% (50)	20% (166)	
Male factor		9% (15)	9% (74)	
Endometriosis		3% (6)	6% (51)	
Tubal factor		6% (10)	5% (39)	
Advanced maternal age		2% (4)	5% (39)	
PCOS		3% (5)	2% (17)	
Recurrent miscarriages		3% (6)	1% (9)	

Note: N is the number of non-missing values, and the numbers after percentages are frequencies. CC = clomiphene citrate; PCOS = polycystic ovary syndrome; TMSC = total motile sperm count.

^a The lower quartile/median/upper quartile for continuous variables.

^b Wilcoxon test.

^c Pearson's chi-square test.

Palatnik. Optimal follicular size before hCG. *Fertil Steril* 2012.

SUPPLEMENTAL TABLE 2

Effect of predictors on the probability of pregnancy in a multivariate logistic analysis adjusted for the effects of endometrial thickness and leading follicle size via a quadratic polynomial.

Predictor	OR	95% CI	P value
Age	0.94	0.90–0.99	.012
Second leading follicle (mm)	1.01	0.98–1.04	.32
Postprocessing TMSC (log10-transformed)	1.23	0.83–1.83	.22
Primary diagnosis			
Anovulation vs. unexplained	1.63	1.04–2.55	.035
Male factor vs. unexplained	1.26	0.69–2.31	.45
Endometriosis vs. unexplained	0.48	0.18–1.27	.14
Tubal factor vs. unexplained	1.89	0.91–3.93	.086
Advanced maternal age vs. unexplained	0.77	0.25–2.43	.66
PCOS vs. unexplained	1.43	0.48–4.28	.52
Recurrent miscarriages vs. unexplained	3.10	1.00–9.57	.049

Note: CI = confidence interval; OR = odds ratio; PCOS = polycystic ovary syndrome; TMSC = total motile sperm count.

Palatnik. Optimal follicular size before hCG. *Fertil Steril* 2012.