Follicular phase length is not related to live birth outcome in women with unexplained infertility undergoing ovarian stimulation with intrauterine insemination cycles in a multicenter trial

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Objective: To evaluate the effect of follicular phase length (FPL) on pregnancy outcomes and endometrial thickness (ET) among women with unexplained infertility undergoing ovarian stimulation with intrauterine insemination (OS-IUI) with clomiphene citrate, letrozole, or gonadotropins.
Design: Cohort analysis of the Reproductive Medicine Network's Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation randomized controlled trial.
Setting: Multicenter randomized controlled trial.
Patient(s): A total of 869 couples with unexplained infertility who underwent OS-IUI treatment cycles as part of the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation study.
Intervention(s): FPL was evaluated as a categorical variable defined by quintiles (q1: $\leq$11 days, q2: 12 days, q3: 13 days, q4: 14–15 days, and q5: $\geq$16 days).
Main outcome measure(s): Clinical pregnancy, live birth rates, and ET.
Result(s): Decreasing FPL quintiles did not reduce clinical pregnancy or live birth rates in unadjusted or adjusted models with all treatment groups combined or when stratified by the ovarian stimulation medication. All FPL categories had significantly thinner ET compared with the 5th quintile ($\geq$16 days) among women treated with clomiphene citrate or letrozole. Similar but diminished associations were observed among women who underwent ovarian stimulation with gonadotropins, but the observed differences were limited to those with FPL of 12 days or shorter when compared with FPL $\geq$16 days.
Conclusion(s): Although shorter FPL was associated with reduced ET, it was not associated with the outcomes of clinical pregnancy or live birth in women with unexplained infertility undergoing OS-IUI in all treatment groups combined. Similar patterns existed when analyses of clinical pregnancy and live birth rates were stratified by treatment.
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Key Words: Unexplained infertility, clomiphene citrate, letrozole, gonadotropins, endometrial thickness, follicular phase length, ovarian stimulation, live birth

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Variability in duration between menstrual cycles is predominantly because of variation in follicular phase length (FPL) (1). During the follicular phase, the granulosa cells of the developing follicle produce estrogen in response to gonadotropin stimulation (2). Estrogen induces endometrial proliferation and progesterone receptor expression, and thus primes the endometrium for progesterone's effect in the luteal phase (3).

Shortened FPL has been attributed to early follicular recruitment during the luteal-follicular transition (4). Prior studies have suggested that among women with infertility, a shorter follicular phase occurring in association with early ovulation is associated with poor pregnancy outcomes, compared with a longer follicular phase (5, 6). Another study has demonstrated that treatment with gonadotropin-releasing hormone (GnRH) agonists before ovarian stimulation in women with short FPL lengthened the follicular phase by 3 days and partially restored fecundity (7). These investigators postulated that a shorter follicular phase may not allow sufficient time for full oocyte maturation or may lead to inadequate development of the endometrium. Although conceivable that a similar affect would be observed in women undergoing ovarian stimulation, the literature addressing the impact of shortened FPL in these cycles is sparse.

The use of oral ovarian stimulation agents—clomiphene citrate (CC) or letrozole—in conjunction with intrauterine insemination (OS-IUI) is commonly accepted as first-line therapy for unexplained infertility because of lower cost and lower risk of multiple gestations compared with gonadotropins (8). Although extensively used, to our knowledge, no prior studies have addressed the impact of FPL on endometrial development and OS-IUI cycle outcome. Estradiol is the main secretory product of the follicular phase, and oral agents' mechanism of action is either by selective blockage of estrogen receptors (CC), or decreased estrogen production (letrozole). CC's effects on endometrial receptivity have been questioned because of its anti-estrogenic activity (9). In this study, we aim to evaluate the effect of FPL on pregnancy outcomes and endometrial thickness (ET) as a surrogate marker for endometrial receptivity among women with unexplained infertility undergoing OS-IUI with CC, letrozole, and gonadotropins. We hypothesized that there may be a lower threshold for FPL, specifically in CC/letrozole cycles, beyond which cycle outcomes are negatively affected because of a shortened interval of estrogen exposure and resulting inadequate endometrial development.

MATERIAL AND METHODS

This study is a secondary analysis of the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) trial by the Reproductive Medicine Network funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (10). The aim of the study was to evaluate the rate of multiple gestations among women with clinical pregnancies among couples with unexplained infertility treated with up to 4 cycles of ovarian stimulation with gonadotropin (301 women), CC (300 women), or letrozole (299 women). Details on the study treatment protocol have been described previously and the primary outcome reported (10). Noteworthy per the study protocol, no cycles were canceled because of a short FPL or based on ET, and all patients underwent HCG administration to induce the final stages of oocyte maturation and ovulation.

FPL was measured from day 1 of the menses to the day of HCG trigger and evaluated as a categorical variable defined by quintiles (q1: $\leq$11 days, q2: 12 days, q3: 13 days, q4: 14–15 days, and q5: $\geq$16 days). Risk ratios (RR) and 95% confidence intervals (CIs) were calculated using cluster-weighted generalized estimating equations method to estimate modified Poisson regression models with robust standard errors for clinical pregnancy and live birth outcomes and generalized linear regression models with an identity link for ET. Adjustment for covariates was examined in multivariable models. Potential confounding by treatment group, age, race/ethnicity, body mass index, parity, duration of infertility, antimüllerian hormone, treatment group, and number of follicles >14 mm was evaluated. Covariates that changed the RR by >10% when entered in the model were retained in adjusted analyses. Associations between FPL and live birth rates (LBRs) were also examined stratified by treatment group.

RESULTS

A total of 2546 cycles from 869 AMIGOS participants were available for analysis after excluding patients with canceled cycles, duplicate entries, and missing values for FPL. Baseline characteristics of the study population by live birth outcome are shown in Table 1. The median age of women who achieved the outcome of live birth (n = 218) was 1 year younger than those who did not (n = 651), but the distributions of race/ethnicity, prior pregnancy loss, and prior live birth were not different between the 2 groups. Live birth outcome was more common in women treated with gonadotropins than those treated with CC or letrozole.

The overall clinical pregnancy and LBR per cycle was 9.9% in the group treated with gonadotropins vs. 8.6% in the CC or letrozole group. The distribution of clinical pregnancy and LBR as well as unadjusted and adjusted RR according to FPL quintiles is displayed in Table 2. FPL ranged from 7 to 24 days. The only covariate that met the 10% change-in-estimate criteria for confounding was the number of follicles >14 mm. When the 5th quintile (FPL $\geq$16 days) was used as referent, decreasing FPL was not associated with reduced clinical pregnancy or LBRs in unadjusted and adjusted models with all treatment groups combined. When stratified by the treatment groups of oral agents vs. gonadotropins, FPL quintiles were similarly not associated with clinical pregnancy and live birth outcomes (Table 3).

The association between FPL and ET is shown in Table 4. ET on the day of the HCG administration ranged from 3 to 22 mm. Overall, ET was positively correlated with FPL in all treatment groups combined (i.e., ET increases with increasing FPL, Pearson's $r = 0.235$, $P<.0001$). Treatment group and number of follicles >14 mm were the only covariates that met the >10% change-in-estimate criterion. However, analyses stratified by treatment group indicate that it may serve

TABLE 1

Baseline characteristics of the study population by live birth outcome.

	Live birth (n = 218)	No live birth (n= 651)	
	Median (IQR)	Median (IQR)	P[a]
Age (y)	31.0 (6.0)	32.0 (7.0)	.006
Duration of infertility (mo)	24.0 (20.0)	24.0 (30.0)	.0003
BMI	25.2 (9.2)	25.0 (8.0)	.92
	n (%)	n (%)	P[b]
Race/ethnicity			.28
Non-Hispanic White	167 (76.6)	461 (70.8)	
Non-Hispanic Black	12 (5.5)	60 (9.2)	
Hispanic	21 (9.6)	70 (10.8)	
Other	18 (8.3)	60 (9.2)	
Income			.06
<$50,000	25 (11.5)	119 (18.3)	
≥$50,000	152 (69.7)	421 (64.7)	
Wish not to answer	41 (18.8)	111 (17.1)	
History of pregnancy loss			.41
Yes	51 (23.4)	135 (20.7)	
No	167 (76.6)	516 (79.3)	
History of live birth			.58
Yes	46 (21.1)	126 (19.4)	
No	172 (78.9)	525 (80.7)	
Treatment			.0007
Clomiphene	68 (31.2)	226 (34.7)	
Letrozole	55 (25.2)	229 (35.2)	
Gonadotropins	95 (43.6)	196 (30.1)	

BMI = body mass index; IQR = interquartile range.
[a] Wilcoxon rank-sum test.
[b] Chi-square test for independence.

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as an effect modifier of the association between FPL and ET. Within the groups treated with CC/letrozole, all categories with FPL <16 days had thinner endometrium compared with the referent (5th quintile ≥16 days). In women who underwent ovarian stimulation with gonadotropins, more modest associations of the same direction were observed for FPL categories of 12 days or shorter (adjusted coefficients [95% CI] for FPL ≤11 days: −1.00 [−1.77, −0.24) and for FPL of 12 days: −1.45 [−2.25, −0.64]), but slighter decreases in ET observed for FPL categories of 13 and 14–15 days, where an FPL of 13 days did not differ meaningfully from the reference group of ≥16 days group.

DISCUSSION

Ovarian stimulation agents paired with IUI are considered first-line treatment for unexplained infertility. In this study, we explored the effect of FPL on pregnancy outcomes and ET among women with unexplained infertility undergoing OS-IUI cycles with CC, letrozole, and gonadotropins. We also evaluated whether the outcomes listed above differed by FPL quintile when stratified by treatment groups of oral agents vs. gonadotropins. Our study found that although shorter FPL was associated with reduced ET, it was not associated with clinical pregnancy or LBRs after OS-IUI in couples with unexplained infertility. When stratified by the treatment groups of oral agents vs. gonadotropins, the lack of evidence of association between FPL quintiles and live birth or clinical pregnancy outcomes remained unchanged, but the magnitude of associations with ET were attenuated among women receiving gonadotropins. Differences attributed to decreased precision in the smaller subgroup strata; however, cannot be ruled out.

There is no consensus in the current literature as to a specific cut-off to define short FPL. Consistent with prior studies of natural and stimulated cycles (11–15), this study revealed variation in length of the follicular phase ranging from 7 to 24 days. Recently published studies examined cycle phase lengths in women using mobile phone applications that track the menstrual cycle (12, 14–17). The day of ovulation in the apps is determined by urinary LH and/or basal body temperature. Among 98,903 users of Ovia Fertility, the median cycle length was 28 days and FPL of 17 days (12). Among 27,378 users of Kindara, median cycle length was 28 with median FPL of 15 days (15). Among 28,483 users of Sympto, median cycle length was 28 with median follicular phase of 16 days (15). Finally, among 124,648 women using Natural Cycles, the mean cycle length was 29.3 (SD: 5.2), with FPL of 16.9 (SD: 5.3) (14). In each of these studies, <50% of the cycles had complete data, data on parity were not available, and only ovulatory cycles were analyzed. Given the limitations of the literature, any decision

TABLE 2

Associations between follicular phase length and pregnancy outcomes among 2546 cycles in 869 patients.

		Clinical pregnancy			Live birth		
Follicular phase length	Cycles	Pregnancy n (%)	Unadjusted RR (95% CI)	Adjusted RR[a] (95% CI)	Live births n (%)	Unadjusted RR (95% CI)	Adjusted RR[a] (95% CI)
Quintile 1 (≤11 d)	603	52 (8.6)	0.75 (0.50–1.12)	0.71 (0.48–1.05)	51 (8.5)	0.87 (0.56–1.34)	0.81 (0.53–1.25)
Quintile 2 (12 d)	539	52 (9.7)	0.77 (0.52–1.15)	0.71 (0.48–1.06)	44 (8.2)	0.76 (0.48–1.20)	0.69 (0.44–1.09)
Quintile 3 (13 d)	521	48 (9.2)	0.77 (0.51–1.16)	0.71 (0.47–1.06)	40 (7.7)	0.78 (0.49–1.23)	0.71 (0.45–1.11)
Quintile 4 (14–15 d)	588	66 (11.2)	0.94 (0.65–1.36)	0.90 (0.62–1.30)	55 (9.4)	0.96 (0.63–1.47)	0.91 (0.60–1.39)
Quintile 5 (≥16 d)	295	35 (11.9)	Ref	Ref	28 (9.5)	Ref	Ref

[a] Model adjusted for number of follicles >14 mm.

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TABLE 3

Associations between follicular phase length and pregnancy outcomes stratified by ovarian stimulation treatment.

	Clinical pregnancy						Live birth					
	Clomiphene/letrozole			Gonadotropins			Clomiphene/letrozole			Gonadotropins		
Follicular phase length	Cycles	Clinical pregnancy (%)	Adjusted RR[a] (95% CI) n = 1767	Cycles	Clinical pregnancy (%)	Adjusted RR[a] (95% CI) n = 760	Cycles	Live births (%)	Adjusted RR[a] (95% CI) n = 1767	Cycles	Live births (%)	Adjusted RR[a] (95% CI) n = 760
Quintile 1 (≤11 d)	409	35 (8.6)	0.75 (0.44–1.27)	194	17 (8.8)	0.67 (0.37–1.21)	409	34 (8.3)	0.89 (0.49–1.61)	194	17 (8.8)	0.75 (0.40–1.40)
Quintile 2 (12 d)	402	25 (6.2)	0.55 (0.30–1.00)	137	27 (19.7)	1.07 (0.63–1.80)	402	20 (5.0)	0.52 (0.26–1.04)	137	24 (17.5)	1.05 (0.59–1.89)
Quintile 3 (13 d)	383	26 (6.8)	0.65 (0.37–1.14)	138	22 (15.9)	0.90 (0.51–1.58)	383	20 (5.2)	0.66 (0.34–1.26)	138	20 (14.5)	0.90 (0.48–1.66)
Quintile 4 (14–15 d)	393	43 (10.9)	1.07 (0.65–1.76)	195	23 (11.8)	0.71 (0.40–1.27)	393	34 (8.7)	1.13 (0.63–2.01)	195	21 (10.8)	0.71 (0.38–1.33)
Quintile 5 (≥ 16 d)	191	19 (10.0)	Ref	104	16 (15.4)	Ref	191	15 (7.9)	Ref	104	13 (12.5)	Ref

[a] Model adjusted for number of follicles >14 mm.

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regarding a "normal" or "short" FPL could be considered arbitrary. Thus, we defined FPL according to observed quintiles to allow for comparisons of the lowest with the highest percentiles of the data distribution. Accordingly, a short FPL in our study was defined as values at or below the 20th percentile of the FPL distribution (≤11 days) and values above the 80th percentile served as the reference group (≥16 days).

Our results are consistent with recent studies that evaluated the association of FPL and pregnancy outcome in the context of treatment with assisted reproductive technology (18, 19) and natural cycle frozen-thawed embryo transfer (11, 20). All of these studies report no association between FPL and pregnancy outcomes. The findings are, however, in contrast to prior studies that evaluated the effect of FPL on pregnancy outcome among infertile women (5, 21). These 2 studies by Check et al. (5, 21) used ovulation before day 11 as the definition for short FPL, and showed lower pregnancy rates in women with short FPL when compared with infertile women who ovulated on day 11 or beyond. In addition, pregnancy rates increased in the subset of women with short FPL whose FPL was lengthened by administration of ethynyl estradiol (21). A more recent study by Bakkensen et al. (22) also reported a positive relationship between FPL and clinical pregnancy for IUI in women undergoing ovarian stimulation with gonadotropins. In this study, the odds of clinical pregnancy increased by 6% with each additional day of follicular phase beyond 8 days after adjusting for potential confounding factors, including age and ovarian reserve (adjusted odds ratio: 1.06, 95% CI: 1.03–1.09, $P<.01$). Although informative, this study was limited to gonadotropins as the sole ovarian stimulation agent used. Moreover, the study population differed from this of the current study because it included women of all infertility diagnoses, potentially confounding cycle outcomes.

Regarding the effect of FPL on the endometrium, our data revealed that shorter FPL was associated with decreased ET. A recent study by Quaas et al. (23) evaluated the effect of ET on pregnancy outcomes in women with unexplained infertility undergoing OS-IUI, reporting higher LBR with increasing ET. However, ET was not significantly associated with LBR after adjustment for OS treatment group. Appreciable LBRs were seen at all ET, even those of ≤5 mm. Several other studies reported a positive correlation between ET and chance of implantation and pregnancy during IUI cycles (24, 25). Our findings indicate that although FPL is positively correlated with ET, especially in the CC/Letrozole groups, the pregnancy outcomes were not affected.

The most notable strength of our study consists of the fact that the AMIGOS trial was a multicenter randomized controlled trial with a large number of well-characterized participants. Extensive data on baseline and in-cycle characteristics were collected; treatments were administered under standardized protocols; and LBR outcomes were available for all participants. Our statistical methods were robust, accounting for multiple treatment cycles in the same patient and adjusting for confounding covariates. However, the AMIGOS trial was not designed or powered to address the association between FPL and pregnancy outcomes in OS-IUI

TABLE 4

Associations between follicular phase length and endometrial thickness stratified by treatment.

	Total			Clomiphene/letrozole		Gonadotropins	
Follicular phase length	Cycles	Unadjusted Coefficient (95% CI)[a] n = 2445	Adjusted Coefficient[a,b] (95% CI) n = 2435	Cycles	Adjusted Coefficient (95% CI)[c] n = 1698	Cycles	Adjusted Coefficient (95% CI)[c] n = 737
Quintile 1 (≤11 d)	576	−1.99 (−2.52, −1.46)	−2.06 (−2.55, −1.58)	389	−2.59 (−3.21, −1.98)	186	−1.00 (−1.77, −0.24)
Quintile 2 (12 d)	516	−1.55 (−2.06, −1.04)	−1.54 (−2.04, −1.05)	381	−1.53 (−2.14, −0.91)	133	−1.45 (−2.25, −0.64)
Quintile 3 (13 d)	508	−1.60 (−2.12, −1.09)	−1.48 (−1.96, −1.01)	369	−1.84 (−2.44, −1.24)	134	−0.74 (−1.52, 0.05)
Quintile 4 (14–15 d)	563	−0.93 (−1.42, −0.44)	−0.95 (−1.42, −0.45)	377	−1.02 (−1.61, −0.43)	184	−0.80 (−1.54, −0.06)
Quintile 5 (≥16 d)	282	Ref	Ref	182	Ref	100	Ref

[a] Generalized estimating equations method used to estimate cluster-weighted generalized linear regression models with an identity link.
[b] Model adjusted for treatment group and number of follicles >14 mm.
[c] Model adjusted for number of follicles >14 mm.

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cycles. Therefore, we cannot exclude the possibility that this study lacked power to detect small differences, or that other variables correlating with exposure and outcome may have introduced unmeasured confounding. FPL did not vary significantly among the FPL quintiles of our population, and importantly, the lowest quintile included FPL length of 11 days or shorter that may not be clinically considered short. Another limitation of our study is that we were not able to analyze the potential effect of the endometrial echo pattern, because this parameter was not recorded for AMIGOS participants. Finally, because the AMIGOS trial included only patients with unexplained infertility, we cannot extrapolate our findings to those with other diagnoses.

In summary, although FPL was positively associated with ET, it was not associated with live birth or clinical pregnancy outcomes in women with unexplained infertility undergoing OS-IUI in all treatment groups combined. Similar patterns existed when analyses of clinical pregnancy and live birth were stratified by the treatment group, despite the stronger positive relationship between the FPL and ET in the oral agents group. Our data suggest that there may be no FPL cut-off that meaningfully impacts OS-IUI outcome, and thus modifying stimulation protocols or adding GnRH antagonist may be unnecessary. Further studies are needed to determine whether the duration of follicular phase impacts outcome in patients with other diagnoses such as diminished ovarian reserve and/or advanced reproductive age.

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