Prospective evaluation of luteal phase length and natural fertility

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Objective: To evaluate the impact of a short luteal phase on fecundity.
Design: Prospective time-to-pregnancy cohort study.
Setting: Not applicable.
Patient(s): Women trying to conceive, ages 30–44 years, without known infertility.
Intervention(s): Daily diaries, ovulation prediction testing, standardized pregnancy testing.
Main Outcome Measure(s): Subsequent cycle fecundity.
Result(s): Included in the analysis were 1,635 cycles from 284 women. A short luteal phase ($\leq$11 days including the day of ovulation) occurred in 18% of observed cycles. Mean luteal phase length was 14 days. Significantly more women with a short luteal phase were smokers. After adjustment for age, women with a short luteal phase had 0.82 times the odds of pregnancy in the subsequent cycle immediately following the short luteal phase compared with women without a short luteal phase. Women with a short luteal length in the first observed cycle had significantly lower fertility after the first 6 months of pregnancy attempt, but at 12 months there was no significant difference in cumulative probability of pregnancy.
Conclusion(s): Although an isolated cycle with a short luteal phase may negatively affect short-term fertility, incidence of infertility at 12 months was not significantly higher among these women.
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Key Words: Short luteal phase, luteal phase deficiency, fecundity, natural fertility

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The luteal phase occurs after ovulation and corresponds to the time when a functioning corpus luteum secretes progesterone (1, 2). Menses is a response to the late luteal phase drop in progesterone after failure of the corpus luteum if pregnancy is not achieved (3–5). Luteal phase deficiency (LPD) is a condition secondary to insufficient progesterone exposure and failure to maintain the normal secretory endometrium required for embryo implantation (6). LPD may be due to lack of adequate progesterone secretion from the corpus luteum or an inappropriate endometrial response to a normal progesterone level (7, 8). A shortened luteal phase is often considered to be a clinical manifestation of LPD (1,9–11).

Despite the essential role of progesterone in establishing the appropriate endometrial environment necessary for conception, LPD has not clearly been linked with delayed time to pregnancy or infertility (2, 12, 13). A luteal phase defect results in dysfunctional endometrial development during the narrow interval when an embryo is present in the uterine cavity and capable of implantation (6, 8, 10, 14). Therefore, women with clinical signs of LPD, such as a shortened luteal phase, may have an impairment of implantation or maintenance of pregnancy (10, 12, 14, 15).

Diagnosing LPD in a clinical setting has proven to be difficult. A luteal phase biopsy showing a lag in endometrial development was previously considered to be the criterion standard diagnostic test (16). However, prospective randomized studies have shown that histologic evaluation of the luteal endometrium is poorly correlated with fertility (17, 18). Therefore, luteal phase biopsy is not currently recommended as part of an evaluation of infertility (6). Although there is no standard approach to diagnosing LPD, this does not mean that such a condition does not exist or that proper luteal phase function is not important to conception.

Because the corpus luteum persists in an ongoing pregnancy, the luteal

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phase does not "end" in conception cycles. This makes evaluating the direct impact of a shortened luteal phase difficult. The association between a shortened luteal phase and natural fertility has not been previously evaluated. We hypothesized that a short luteal phase would impair a woman's fertility. We sought to determine the impact of a short luteal phase on fecundity, the probability of conceiving in a given cycle.

MATERIALS AND METHODS

This is a substudy within Time to Conceive (TTC), an ongoing time-to-pregnancy study approved by the Institutional Review Board of the University of North Carolina. English-speaking women from 30 to 44 years of age, who had been attempting to conceive for $\leq$3 months, were eligible for participation in the study. This analysis includes women recruited from April 2008 to December 2015. Women were recruited by direct advertising, online, and on-air marketing strategies. Women with a history of infertility, polycystic ovarian disease, pelvic inflammatory disease, endometriosis, or pelvic radiation or with a partner with a history of infertility were excluded from participation. After informed consent was obtained, each woman completed a baseline questionnaire, which included survey of demographics, height, weight, and medical history for both the participant and her partner and of behaviors such as tobacco, alcohol, and caffeine use. The baseline questionnaire also queried duration of pregnancy attempt by asking specific questions regarding earlier birth control methods: type, duration of use in the past year, and date of cessation; date the participant started having intercourse without preventing pregnancy; and number of menstrual cycles at risk for pregnancy.

While attempting to conceive, women recorded information in a daily diary and were followed without intervention until pregnancy was detected. The daily diary included information on vaginal bleeding, markers of ovulation (cervical mucus scores, basal body temperature, and ovulation predictor kit [OPK] results), acts of intercourse, and pregnancy test results. Women provided daily data for up to 4 months if no positive pregnancy test occurred. If women were not pregnant after the 4th month, a monthly diary was completed for the remainder of the study, up to 12 months, or until pregnancy was achieved. A subset of women were provided free digital OPK tests and provided standardized testing instructions. However, use of this method of ovulation prediction was not a requirement for study participation and women could use any brand of OPK test they preferred. All women were provided home pregnancy tests (with a sensitivity of 20 mIU/mL hCG) and standardized pregnancy testing instructions. Women were instructed to test for pregnancy on days 28, 31, and 34 of their cycles if they did not have menstrual bleeding. Women who conceived in the first cycle were excluded from this evaluation.

Menses was defined as $\geq$3 days of bleeding or spotting (with $\geq$1 day of bleeding), followed by 2 consecutive days without bleeding or spotting. The 1st day of a cycle was defined as the 1st day of bleeding occurring during menses. Ovulation was estimated to have occurred on the day after a positive OPK test result. Luteal phase length was determined as starting on the day of ovulation (day after a positive OPK test) and ending on the last day before menses. This is the equivalent to subtracting the date of the day after positive OPK test from the date of menses start. A short luteal phase was defined as $\leq$11 days. In sensitivity analysis, fecundity was also evaluated with a luteal phase of $\leq$10 days. Cycles that had a luteal phase length of $<$5 or $>$20 days were excluded from the analysis in an attempt to exclude anovulatory cycles and occult pregnancies. Pregnancy was defined as a positive home pregnancy test.

Covariates were categorized to aid in interpretation. Maternal age was modeled with the use of three categories: $<$35 years, 35–37 years, and $>$37 years. Education level was categorized into four groups: less than a college degree, college graduate, some graduate-level work, and graduate/professional degree. Body mass index (BMI) was categorized into four groups: underweight ($<$18.5 kg/m^2), normal (18.5 to $<$25 kg/m^2), overweight (25 to $<$30 kg/m^2), and obese ($\geq$30 kg/m^2).

Bivariate analyses were conducted to compare women based on their luteal length in their first observed cycle. The Fisher exact test and the Kruskal-Wallis test were used to evaluate relationships between potential covariates and luteal length for categoric and continuous variables, respectively. Subsequently, discrete-time Cox proportional hazards models with time-varying (cycle-specific) exposure variables were created to determine the impact of luteal length on probability of pregnancy in the next cycle (subsequent-cycle fecundity). Because a cycle with an outcome of pregnancy does not have a defined luteal length, only fecundity in a future cycle can be evaluated; therefore the luteal length of the immediately preceding cycle was considered as a predictor for the event of pregnancy in the Cox proportional hazards models. To adjust for potential confounders, covariates were included in models. The full model was reduced to include only covariates strongly predictive of pregnancy in our cohort or in previous studies—our final model included the covariates age and smoking. These models account for both right censoring and left truncation (owing to women enrolling in cycles one, two, three, or four of their pregnancy attempts) which were present in the data; a fecundity ratio (FR) of $<$1.0 suggests reduced fecundity.

As a secondary analysis, adjusted Kaplan-Meier curves were created with the use of the luteal length in the first study cycle as the exposure, assuming the woman did not conceive in the first study cycle, because luteal phase length can not be defined in a conception cycle. The null hypothesis that there was no difference in overall fertility by 6 and 12 months among women in which the first cycle luteal length was $\leq$11 days compared with women in which the first-cycle luteal length was $>$11 days was tested by means of the log-rank test.

Sensitivity analyses were performed to further evaluate the relationship between luteal length and fecundity. First, the luteal length exposure variable was modified to be more stringent, with a short luteal phase being one that was $\leq$10 days in length and FR determined with the use of the model above. Second, the luteal length exposure value was categorized into short (5–11 days), normal (12–15 days), and long

(16–20 days) and FRs determined with the use of the model above, with the normal category as the reference group.

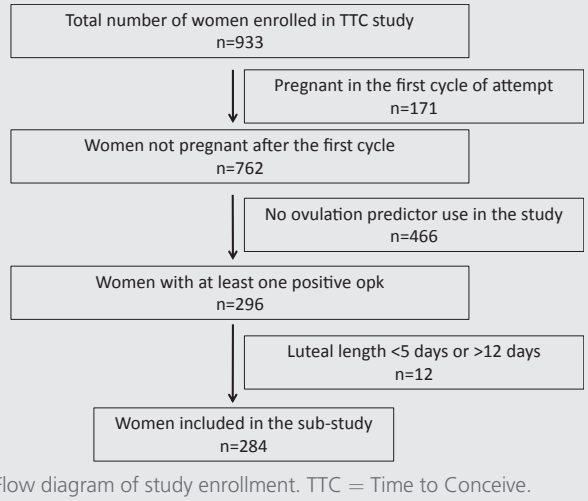
In an attempt to explore the impact of recurrent cycles with a short luteal phase, we evaluated women who provided at least three study cycles. In this investigation, women who failed to conceive in the first two study cycles were evaluated for pregnancy in the subsequent cycle. Women were grouped according to: 1) no cycles with a short luteal length; 2) one cycle with a short luteal length; 3) both observed cycles with a short luteal length. Because of the limited number of women in this evaluation, only descriptive statistics are provided.

RESULTS

The TTC cohort included observations from 933 women. Thirty-two percent of women (n = 296) in the cohort reported at least one cycle with a positive OPK. Out of 3,999 total cycles in the TTC data, 598 had luteal length determined through the use of a positive OPK test (15%). Of those women who had at least one cycle with luteal length determined through the use of a positive OPK test, 149 had at least one case where two consecutive cycles had luteal length determined through the use of a positive OPK test (50%). Figure 1 represents the selection for inclusion in the present substudy. A total of 1,635 cycles from 284 women were included in this analysis, excluding women who conceived in the first cycle of attempt (fecundity in the first study cycle was 18%). Fifty-nine percent of women included in the analysis become pregnant (n = 159). Although the study enrolled women 30–45 years of age, 68% of the participants were <35 years of age, 20% 35–37 years of age, and 12% >37 years of age. The majority of patients were white (77%) and highly educated (65% with a graduate degree). The majority of women (63%) had a normal BMI, 4% were underweight, and 33% were overweight or obese.

In the first observed cycle, 18% of women had a short luteal phase (≤11 days). Most observed cycles did not have a short luteal phase. Mean luteal phase length in our cohort was

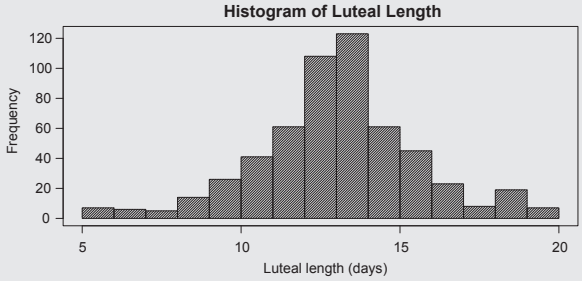
FIGURE 1



Flow diagram of study enrollment. TTC = Time to Conceive.

Crawford. Luteal length and natural fertility. Fertil Steril 2016.

FIGURE 2



Lengths (in days) of the luteal phase.

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14 days (Fig. 2). Women with a short luteal phase were more likely to be smokers than those who did not have a short luteal phase (6% vs. 1%, respectively). No other significant differences in baseline characteristics were observed between women who had a short luteal phase and those who did not (Table 1).

A total of 598 cycles from 284 women were used to evaluate fecundity. Both unadjusted and adjusted cycle-specific FRs suggested lower subsequent cycle fecundity in cycles in women with a short luteal phase, although this finding was not statistically significant. Compared with women with a normal luteal phase, those with a short luteal phase had 0.82 times the probability of pregnancy in the subsequent cycle (95% confidence interval [CI] 0.67–1.47) in unadjusted analysis. After adjusting for age and smoking, the estimate did not change significantly (FR 0.89, 95% CI 0.50–1.6). In a sensitivity analysis, a luteal length of ≤10 days yielded similar results, with an unadjusted FR of 0.71 (95% CI 0.34–1.47) and an adjusted FR of 0.71 (95% CI 0.34–1.48) compared with women with a luteal length of >10 days. Furthermore, in a sensitivity analysis using luteal length as a categoric variable (short: 5–11 days; normal: 12–15 days; and long: 16–20 days), the odds of pregnancy were 0.83 (95% CI 0.46–1.51) and 1.02 (95% CI 0.55–1.89) for women with short and long luteal phases (compared with normal), respectively.

Adjusted Kaplan-Meier curves with 95% CIs demonstrated that the overall probability of pregnancy over 12 cycles of attempt was not different for women who had a short luteal length compared with those with a normal luteal length in the first observed cycle (Fig. 3). However, women with a short luteal length in the first observed cycle did have significantly lower fertility for the first 6 months of attempt (P=.02). By 12 months, there was no significant difference in cumulative probability of pregnancy, nor were the curves statistically significantly different (P=.08).

In an evaluation of recurrent short luteal phase, 126 women provided at least three cycles for analysis. Of these, 18 women had one short luteal length cycle (and one normal cycle) and four women had two cycles with short luteal length. The prevalence of recurrent short luteal phase was 3%. Nineteen of 104 women without a short luteal length conceived over the course of the study, whereas two of the 18 women with one short luteal cycle and none of the four women with two short luteal cycles conceived.

TABLE 1

Patient characteristics for the overall sample and stratified by luteal phase length.

Characteristic[a]	Overall (n = 284)	Normal luteal length (n = 230)	Short luteal length (n = 54)	*P* value
Age (y)				.61
<35	68	69	63	
35–37	20	19	24	
>37	12	12	13	
Race				.86
Non-Hispanic white	77	77	63	
Other	23	23	24	
Education level				.32
Less than college degree	7	7	9	
College degree	20	19	28	
Some graduate work	7	7	7	
Completed postgraduate	65	68	56	
Gravid				.76
No	58	58	55	
Yes	42	42	45	
BMI (kg/m^2)				.33
<18.5	4	3	4	
18.5–<25	63	65	55	
25–<30	19	20	18	
≥30	14	12	22	
Current smoking				.04
No	98	99	94	
Yes	2	1	6	
Current alcohol use				.88
No	30	30	31	
Yes	70	70	69	
Recent hormone contraception[b]				.54
No	54	55	50	
Yes	46	45	50	
Mean cycle length (d)	28.7 (3.7)	29.1 (3.5)	27.1 (4.3)	–

Note: Data presented as percent, unless stated otherwise.
[a] Patient characteristics in the first observed study cycle.
[b] Oral contraceptive pills, contraceptive patch, or contraceptive vaginal ring use in the preceding year.

Crawford. Luteal length and natural fertility. Fertil Steril 2016.

DISCUSSION

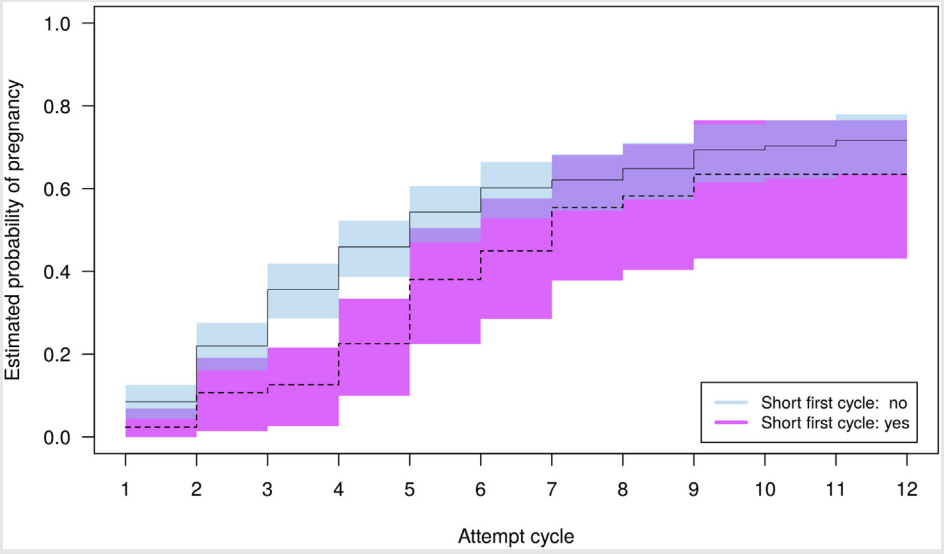
An isolated cycle with a short luteal phase was relatively common in our cohort. Women with a short luteal phase were more likely to be smokers than women without a short luteal phase. Our findings suggest that women who had an isolated episode of short luteal phase may have reduced immediate fecundity. By 6 months of attempt, they were less likely to have conceived; however, probability of infertility, lack of conception by 12 cycles of attempt, was not significantly higher in women with one short luteal phase. Recurrent cycles with a short luteal phase are uncommon in women trying to conceive.

A short luteal phase (≤11 days from day of ovulation until day before menses) occurred in 18% of all evaluable cycles. Earlier studies evaluating menstrual cycle characteristics have not included populations trying to conceive. Schliep et al. (11) reported in a prospective evaluation of cycle characteristics in healthy eumenorrheic women (Biocycle study; n = 259) that the prevalence of a cycle with a short luteal phase (defined as ≤10 days from the day after ovulation until the day before next menses) was 8.9%. In a further analysis looking at a definition of ≤11 days (the same criteria we used), the prevalence of an isolated episode of short luteal phase was 14.9% (11). Older evaluations in young ovulatory reproductive-age women have estimated the prevalence of a short luteal phase to be ~5% (19, 20).

The prevalence of short luteal phase in our cohort is higher than reported in earlier studies. Our study may differ from those because of our definition of a short luteal phase. In our study, we defined the luteal phase as starting on the day of ovulation. In addition, ovulation was defined as positive only in women who obtained a positive OPK test result. Women were queried daily about test results; this may have resulted in a higher response rate than with other methods of ascertainment. In addition, our cohort is composed of women 30–44 years of age. Earlier studies included younger women. There are data that suggest that luteal phase length may decrease with age (21, 22).

In the present cohort, the only patient characteristic associated with a short luteal phase was smoking. In the Biocycle study, evaluating women not attempting conception, a short luteal phase was seen more commonly in younger, nulliparous, not sexually active patients and in those undertaking vigorous activity (11, 23). Smoking was not associated with luteal length; however, the definition of smoking was obtained differently (our study evaluated current smoking versus no smoking, whereas the Biocycle study evaluated current smoking versus earlier smoking) (11). It is important to note that our cohort is distinctly different because women in our study were all over the age of 30 years and actively trying to conceive. Wise et al. evaluated menstrual cycle characteristics in Danish women (n = 2,653)

FIGURE 3



Adjusted Kaplan-Meier curves according to short luteal phase in the first observed cycle.

Crawford. Luteal length and natural fertility. Fertil Steril 2016.

attempting conception (24). Although that study did not distinguish between the menstrual cycle phases, women with shorter overall cycle lengths were more likely to be smokers (24). Presuming that some of these women with shorter cycle lengths may also have a shorter luteal phase, that finding is consistent with our results.

Smoking has been associated with antiestrogenic effects such as a decrease in endometrial cancer, earlier age of natural menopause, and increased risk for osteoporosis (25, 26). Smoking may be associated with abnormal sex steroid synthesis or metabolism, although studies have not been consistent in establishing the exact relationship between smoking and sex steroid hormones (25–30). Windham et al. prospectively evaluated reproductive-age women (n = 403) who were smokers and found lower luteal phase P levels and higher FSH levels at baseline (31). In addition, in vitro studies support lower P release from luteal cells exposed to nicotine (32). Therefore, it is possible that smoking interferes with endocrine function and sex steroids at the level of the ovary, predisposing women who smoke to have LPD.

Point estimates suggest that an isolated cycle with a short luteal phase is associated with reduced short-term fertility. No previous studies directly evaluated the association between luteal phase length and natural fertility. In the previously described prospective study by Wise et al. of women trying to conceive, shorter cycle lengths (<25 days) were associated with less than one-half the odds of pregnancy compared with women with "normal" cycles of 27–29 days in length (24). However, that study did not directly look at the length of the cycle phases, so an association between luteal phase length and fecundity can not be concluded from their data. Baird et al. evaluated 32 women comparing menstrual cycle characteristics and hormonal profiles for paired conception and nonconception cycles (33). Although conception cycles tended to have higher luteal P levels and more rapid luteinization, there was no difference in luteal phase length between conception and nonconception cycles (34). Evaluating the relationship between luteal phase length and fecundity is admittedly difficult owing to the inability to accurately define luteal length in a conception cycle. In an attempt to overcome this difficulty, we evaluated conception in the cycle immediately following one with a shortened luteal phase. Although not statistically significant, our point estimates are suggestive that a short luteal phase does impair short-term fertility. Supporting this further, pregnancy rates for the first 6 months after an isolated cycle with a short luteal phase were decreased. However, we were unable to observe significant differences by 12 months. When using a theoretic sample size calculation for a log-rank test (Freedman method), 962 subjects are needed to achieve 80% power with a type I error rate of 5%, assuming a relative risk of 0.70 for subjects with short luteal length in the previous cycle, and 23% of subjects being in the short luteal length class (35). Therefore, our results of no difference in pregnancy rates at 12 months may represent type 2 error, other factors contributing to fecundity, or lack of an association. This was a secondary analysis, so the findings should be viewed as exploratory.

Recurrent short luteal phase cycles occurred in only 3% of women. This is consistent with findings in earlier studies evaluating menstrual characteristics in healthy women not trying to conceive. Schliep et al. reported that 3.4% of women had two cycles with a short luteal phase (11). No previous studies have evaluated the impact of a recurrent short luteal phase on fecundity. Although this may be an uncommon finding in women trying to conceive, and although our evaluation is limited by sample size, these preliminary data suggest that

recurrent short luteal cycles are associated with reduced fertility. Thus, LPD, as represented by recurrent cycles with a short luteal phase, may represent the first stage of a spectrum in ovulatory dysfunction potentially impairing fertility or delaying time to pregnancy (36).

To our knowledge, This is the first study to examine the impact of short luteal phase length on fecundity in a population of women with unproven reproductive potential. Our study does have limitations. The cohort was composed of mostly white, well educated, and older women. These findings may not be generalizable to other groups. Women choosing to use OPKs may be a select group. Some women were provided Clearblue Easy OPK tests. However, many used other brands. Therefore, these results are likely generalizable to women using any OPK. However, the results are not generalizable to women using other methods to detect ovulation, such as basal body temperatures or cervical mucus monitoring. Also, sampling bias may have been introduced by including only women who had ovulation determined by use of an OPK test. Although the overall size of our cohort is large (933 women), the number of women providing adequate information to determine luteal length available for analysis was lower (284). This sample size may limit our power to detect a change in fecundity between groups. In addition, the definition of a short luteal phase varies widely in the literature. Because we defined a short luteal phase as $\leq$11 days (including the day of ovulation), our definition is similar to earlier cohorts that defined a short luteal phase as $\leq$10 days starting the day after ovulation. We also performed a sensitivity analysis with the exposure defined as $\leq$10 days (including the day of ovulation), without any significant change in our fecundity ratios. An additional sensitivity analysis evaluating luteal length as a categoric variable (in case longer cycles represented occult pregnancies or anovulation), yielded similar results. Further strengths of this study include the size of the cohort, modeling with adjustment for potential confounders, and the prospective nature of this study in a noninfertile population trying to conceive. Furthermore, recall bias was reduced by use of the daily diary for cycle characteristics and at-home test results.

In summary, an isolated cycle with a short luteal phase is relatively common in a population trying to conceive; however, recurrent cycles with a short luteal phase are uncommon. Point estimates suggest that an isolated cycle with a short luteal length may be associated with reduced short-term fertility. However, future larger studies are needed to determine the long-term impact of a short luteal phase and to evaluate the reproductive implications of recurrent cycles with a short luteal phase.

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