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A prospective evaluation of luteal phase length and natural fertility

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Abstract

Objective—To evaluate the impact of a short luteal phase on fecundability.

Design—Prospective, time to pregnancy cohort study

Setting—Community-based cohort

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 fecundability

Result(s)—1,635 cycles from 284 women were included in the analysis. A short luteal phase (length of 11 days or less 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 (95% CI: 0.46–1.47) in the subsequent cycle immediately following the short luteal phase when compared to 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 impact short-term fertility, incidence of infertility at 12 months was not significantly higher among these women.

Capsule

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A short luteal phase length may have negative impact on natural fertility.

Keywords

short luteal phase; luteal phase deficiency; fecundability; natural fertility

Introduction

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). Thus, women with clinical signs of a 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 difficult. A luteal phase biopsy showing a lag in endometrial development was previously considered the gold standard diagnostic test (16). However, prospective randomized studies have shown that histologic evaluation of the luteal endometrium is poorly correlated with fertility (17, 18). Thus, luteal phase biopsy is not currently recommended as part of an evaluation of infertility (6). Although there is no standard approach to diagnosing a LPD, this does not mean that such a condition does not exist nor does it mean that proper luteal phase function is not important to conception.

Because the corpus luteum persists in an ongoing pregnancy, the luteal 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 fecundability, the probability of conceiving in a given cycle.

Material and Methods

This is a sub-study 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 between 30 and 44 years of age, who were attempting to conceive for 3 months or less, were eligible for participation in the study. This analysis includes women

recruited between April 2008 and 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, pelvic radiation, or with a partner with a history of infertility were excluded from participation. After informed consent was obtained, women 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 prior birth control methods: type, duration of use in the past year, and date of cessation; date 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 four months if no positive pregnancy test occurred. If women were not pregnant after the fourth 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 human chorionic gonadotropin (hCG) per mL) 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 3 or more days of bleeding or spotting (with at least one day of bleeding), followed by 2 consecutive days without bleeding or spotting. The first day of a cycle was defined as the first 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 prior to menses. This is the equivalent to subtracting the date of the day after positive OPK from the date of menses start. A short luteal phase was defined as 11 or fewer days. In sensitivity analysis, fecundability was also evaluated with a luteal phase of 10 days or less. Cycles which 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 3 categories: <35 years, 35–37 years and >37 years. Education level was categorized into 4 groups: less than a college degree, college graduate, some graduate level work, and graduate/professional degree. Body mass index (BMI) was categorized into 4 groups: underweight (<18.5 kg/m^2), normal (≥18.5 and <25 kg/m^2), overweight (≥25 and <30 kg/m^2), and obese (≥30 kg/m2).

Bivariate analyses were conducted to compare women based on their luteal length in their first observed cycle. Fisher's exact test and the Kruskal-Wallis test were used to evaluate relationships between potential covariates and luteal length for categorical 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 fecundability). As a cycle with an outcome of pregnancy does not have a defined luteal length, only fecundability in a future cycle can be evaluated; thus 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 prior studies - our final model included the covariates age and smoking. These models account for both right censoring and left truncation (due to women enrolling in cycles 1, 2, 3 or 4 of their pregnancy attempt), which were present in the data; a fecundability ratio (FR) of less than 1.0 suggests reduced fecundability.

As a secondary analysis, adjusted Kaplan-Meier curves were also created using the luteal length in the first study cycle as the exposure, assuming the woman did not conceive in the first study cycle, as 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 no more than 11 days compared to women in which the first cycle luteal length was more than 11 days was tested using the log-rank test.

Sensitivity analyses were performed in order to further evaluate the relationship between luteal length and fecundability. First, the luteal length exposure variable was modified to be more stringent, with a short luteal phase being one that was 10 days or less in length and FR determined using 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 were determined using the model as 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 3 study cycles. In this investigation, women who failed to conceive in the first 2 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. Due to 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 (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 this sub-study. A total of 1,635 cycles from 284 women were

included in this analysis, excluding women who conceived in the first cycle of attempt (fecundability in the first study cycle was 18%). Fifty-nine percent of women included in the analysis become pregnant (159 women). Although the study enrolled women between 30 and 45 years of age, 68% of the participants were less than 35 years of age, 20% between 35 and 37 years of age, and 12% 38 years or older. The majority of patients were Caucasian (77%) and highly educated (65% with a graduate degree). The majority of women had a normal BMI (63%), while 4% were underweight and 33% were overweight or obese.

In the first observed cycle, 18% of women had a short luteal phase (11 or fewer days). Most observed cycles did not have a short luteal phase, as a short luteal phase was present in 18% of all observed cycles. Mean luteal phase length in our cohort was 14 days (Figure 2). Women with a short luteal phase were more likely to be smokers than those who did not have a short luteal phase (6% versus 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 these 284 women were used to evaluate fecundability. Both unadjusted and adjusted cycle-specific fecundability ratios suggested lower subsequent cycle fecundability in cycles in women with a short luteal phase, although this finding was not statistically significant. Compared to women with a normal luteal phase, those with a short luteal phase had 0.82 times the probability of pregnancy in the subseqeuent cycle (95% 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 or less 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) as compared to women with a luteal length of >10 days. Further, in a sensitivity analysis using luteal length as a categorical 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 a short or long luteal phase (as compared to normal), respectively.

Adjusted Kaplan-Meier curves with 95% CI demonstrated that the overall probability of pregnancy over 12 cycles of attempt was not different for women who had a short luteal length as compared to those with a normal luteal length in the first observed cycle (Figure 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=0.02). By 12 months, there was no significant difference in cumulative probability of pregnancy nor were the curves statistically significantly different (p=0.08).

In an evaluation of recurrent short luteal phase, 126 women provided at least 3 cycles for analysis. Of these, 18 women had 1 short luteal length cycle (and 1 normal cycle) and 4 women had 2 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, while 2/18 and 0/4 women with 1 or 2 short luteal cycles conceived, respectively.

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 those women without short luteal phase. Our findings suggest that women who had an isolated episode of short luteal phase may have reduced immediate fecundability. 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. Prior cohorts evaluating menstrual cycle characteristics have not included populations trying to conceive. Schliep et al. reported in a prospective evaluation of cycle characteristics in healthy eumenorrheic women (the 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% (11). In a further analysis looking at a definition of <11 days (the same criteria we have used), the prevalence of an isolated episode of short luteal phase was 14.9% (11). Older evaluations in young, ovulatory, reproductive aged women have estimated the prevalence of a short luteal phase to be around 5% (19, 20).

The prevalence of short luteal phase in our cohort is higher than previously reported in older 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 with regard to test results; this may have resulted in a higher response rate when compared to other methods of ascertainment. In addition, our cohort is comprised of women 30–44 years of age. Prior studies included younger women. There are data that suggest that luteal phase length may decrease with age (21, 22).

In our 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, as compared to the BioCycle study which evaluated current smoking versus prior smoking) (11). It is important to note that our cohort is distinctly different, as 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) attempting conception (24). Although this study did not distinguish between the menstrual cycle phases, women with shorter overall cycle lengths were more likely to be smokers (24). Presuming some of these women with shorter cycle lengths may also have a shorter luteal phase, this finding is consistent with our results.

Smoking has been associated with anti-estrogenic 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 aged women (n=403) who were smokers and found lower luteal phase progesterone levels and higher FSH levels at baseline (31). In addition, in vitro studies support lower progesterone release from luteal cells exposed to nicotine (32). Thus, it is possible that smoking interferes with endocrine function and sex steroids at the level of the ovary, predisposing women who smoke to have a luteal phase defect.

Point estimates suggest that an isolated cycle with a short luteal phase is associated with reduced short-term fertility. No prior studies have directly evaluated the association between luteal phase length and natural fertility. In the previously described prospective study of women trying to conceive by Wise et al., shorter cycle lengths (< 25 days) were associated with less than half the odds of pregnancy as compared to women with “normal” cycles of 27–29 days in length (24). However, this study did not directly look at the length of the cycle phases, so an association between luteal phase length and fecundability cannot be concluded from this data. Baird et al. evaluated 32 women comparing menstrual cycle characteristics and hormonal profiles for paired conception and non-conception cycles (33). Although conception cycles tended to have higher luteal progesterone levels and more rapid luteinization, there was no difference in luteal phase length between conception and non-conception cycles (34). Evaluating the relationship between luteal phase length and fecundability is admittedly difficult due 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 theoretical sample size calculation for a log-rank test (method of Freedman), 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). Thus, our results of no difference in pregnancy rates at 12 months may be a Type 2 error, other factors contributing to fecundability, or lack of an association. This was a secondary analysis, so findings should be viewed as exploratory.

Recurrent short luteal phase cycles occurred in only 3% of women. This is consistent with findings in prior studies evaluating menstrual characteristics in healthy women not trying to conceive. Schliep et al reported that 3.4% of women had 2 cycles with a short luteal phase (11). No prior studies have evaluated the impact of a recurrent short luteal phase on fecundability. Although this may be an uncommon finding in women trying to conceive and our evaluation is limited by sample size, this preliminary data suggests that recurrent short luteal cycles are associated with reduced fertility. Thus, luteal phase defect, 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, ours is the first study to examine the impact of short luteal phase length on fecundability in a population of women with unproven reproductive potential. Our study

does have limitations. The cohort was composed of mostly Caucasian, 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. Thus, these results are likely generalizable to women using any OPK. However, these 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 only including 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 fecundability between groups. In addition, the definition of a short luteal phase varies widely in the literature. Because we defined a short luteal phase using a cutoff of 11 or fewer days (including the day of ovulation), our definition is similar to prior cohorts that define a short luteal phase as 10 days or less starting the day after ovulation. We also performed a sensitivity analysis with the exposure defined as 10 days or less (including the day of ovulation), without any significant change in our fecundability ratios. An additional sensitivity analysis evaluating luteal length as a categorical 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 non-infertile population trying to conceive. Furthermore, recall bias was reduced by use of the daily diary to 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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References

1. Mesen TB, Young SL. Progesterone and the luteal phase: a requisite to reproduction. Obstet Gynecol Clin North Am. 2015; 42:135–151. [PubMed: 25681845]
2. Young SL, Lessey BA. Progesterone function in human endometrium: clinical perspectives. Semin Reprod Endocrinol. 2010; 28:5–16.
3. Harlow SD, Ephross SA. Epidemiology of menstruation and its relevance to women's health. Epidemiol Rev. 1995; 17:265–286. [PubMed: 8654511]
4. Direito A, Bailly S, Mariani A, Ecochard R. Relationships between the luteinizing hormone surge and other characteristics of the menstrual cycle in normally ovulating women. Fertil Steril. 2013; 99:279–285. [PubMed: 22999798]
5. Chiazze L Jr, Brayer FT, Macisco JJ Jr, Parker MP, Duffy BJ. The length and variability of the human menstrual cycle. JAMA. 1968; 203:377–380. [PubMed: 5694118]

6. Practice Committee of the American Society for Reproductive Medicine. The clinical relevance of luteal phase deficiency: a committee opinion. Fertil Steril. 2012; 98:1112–1117. [PubMed: 22819186]
7. Boutzios G, Karalaki M, Zapanti E. Common pathophysiological mechanisms involved in luteal phase deficiency and polycystic ovary syndrome. Impact on fertility. Endocrine. 2013; 43:314–317. [PubMed: 22930247]
8. Usadi RS, Groll JM, Lessey BA, Lininger RA, Zaino RJ, Fritz MA, et al. Endometrial development and function in experimentally induced luteal phase deficiency. J Clin Endocrinol Metab. 2008; 93:4058–4064. [PubMed: 18647810]
9. Jones GS. Luteal phase defect: a review of pathophysiology. Curr Opin Obstet Gynecol. 1991; 3:641–648. [PubMed: 1958796]
10. Sonntag B, Ludwig M. An integrated view on the luteal phase: diagnosis and treatment in subfertility. Clin Endocrinol. 2012; 77:500–507.
11. Schliep KC, Mumford SL, Hammoud AO, Stanford JB, Kissell KA, Sjaarda LA, et al. Luteal phase deficiency in regularly menstruating women: prevalence and overlap in identification based on clinical and biochemical diagnostic criteria. J Clin Endocrinol Metab. 2014; 99:E1007–E1014. [PubMed: 24606080]
12. Jones GE. Some newer aspects of the management of infertility. JAMA. 1949; 141:1123–1129. illust.
13. Moszkowski E, Woodruff JD, Jones GE. The inadequate luteal phase. Am J Obstet Gynecol. 1962; 83:363–372. [PubMed: 14476579]
14. Muechler EK, Huang KE, Zongrone J. Superovulation of habitual aborters with subtle luteal phase deficiency. Int J Fertil. 1987; 32:359–365. [PubMed: 2889681]
15. Jones GS. The luteal phase defect. Fertility and sterility. 1976; 27:351–356. [PubMed: 1269800]
16. Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. Am J Obstet Gynecol. 1975; 122:262–263. [PubMed: 1155504]
17. Coutifaris C, Myers ER, Guzick DS, Diamond MP, Carson SA, Legro RS, et al. Histological dating of timed endometrial biopsy tissue is not related to fertility status. Fertil Steril. 2004; 82:1264–1272. [PubMed: 15533340]
18. Murray MJ, Meyer WR, Zaino RJ, Lessey BA, Novotny DB, Ireland K, et al. A critical analysis of the accuracy, reproducibility, and clinical utility of histologic endometrial dating in fertile women. Fertil Steril. 2004; 81:1333–1343. [PubMed: 15136099]
19. Strott CA, Cargille CM, Ross GT, Lipsett MB. The short luteal phase. J Clin Endocrinol Metab. 1970; 30:246–251. [PubMed: 5413650]
20. Lenton EA, Landgren BM, Sexton L. Normal variation in the length of the luteal phase of the menstrual cycle: identification of the short luteal phase. Br J Obstet Gynaecol. 1984; 91:685–689. [PubMed: 6743610]
21. Vanden Brink H, Robertson DM, Lim H, Lee C, Chizen D, Harris G, et al. Associations Between Antral Ovarian Follicle Dynamics and Hormone Production Throughout the Menstrual Cycle as Women Age. J Clin Endocrinol Metab. 2015; 100:4553–4562. [PubMed: 26465392]
22. Hale GE, Zhao X, Hughes CL, Burger HG, Robertson DM, Fraser IS. Endocrine features of menstrual cycles in middle and late reproductive age and the menopausal transition classified according to the Staging of Reproductive Aging Workshop (STRAW) staging system. J Clin Endocrinol Metab. 2007; 92:3060–3067. [PubMed: 17550960]
23. Andrews MA, Schliep KC, Wactawski-Wende J, Stanford JB, Zarek SM, Radin RG, et al. Dietary factors and luteal phase deficiency in healthy eumenorrheic women. Hum Reprod. 2015; 30:1942–1951. [PubMed: 26082480]
24. Wise LA, Mikkelsen EM, Rothman KJ, Riis AH, Sorensen HT, Huybrechts KF, et al. A prospective cohort study of menstrual characteristics and time to pregnancy. Am J Epidemiol. 2011; 174:701–709. [PubMed: 21719742]
25. Gu F, Caporaso NE, Schairer C, Fortner RT, Xu X, Hankinson SE, et al. Urinary concentrations of estrogens and estrogen metabolites and smoking in caucasian women. Cancer Epidemiol Biomarkers Prev. 2013; 22:58–68. [PubMed: 23104668]

26. Key TJ, Pike MC, Baron JA, Moore JW, Wang DY, Thomas BS, et al. Cigarette smoking and steroid hormones in women. J Steroid Biochem Mol Bio. 1991; 39:529–534. [PubMed: 1832941]
27. Thomas EJ, Edridge W, Weddell A, McGill A, McGarrigle HH. The impact of cigarette smoking on the plasma concentrations of gonadotrophins, ovarian steroids and androgens and upon the metabolism of oestrogens in the human female. Hum Reprod. 1993; 8:1187–1193. [PubMed: 8408515]
28. Key TJ, Pike MC, Brown JB, Hermon C, Allen DS, Wang DY. Cigarette smoking and urinary oestrogen excretion in premenopausal and post-menopausal women. B J Cancer. 1996; 74:1313–1316.
29. Duskova M, Simunkova K, Hill M, Velikova M, Kubatova J, Kancheva L, et al. Chronic cigarette smoking alters circulating sex hormones and neuroactive steroids in premenopausal women. Physiol Res. 2012; 61:97–111. [PubMed: 22188108]
30. Saladin ME, McClure EA, Baker NL, Carpenter MJ, Ramakrishnan V, Hartwell KJ, et al. Increasing progesterone levels are associated with smoking abstinence among free-cycling women smokers who receive brief pharmacotherapy. Nicotine Tob Res. 2015; 17:398–406. [PubMed: 25762749]
31. Windham GC, Mitchell P, Anderson M, Lasley BL. Cigarette smoking and effects on hormone function in premenopausal women. Environ Health Perspect. 2005; 113:1285–1290. [PubMed: 16203235]
32. Miceli F, Minici F, Tropea A, Catino S, Orlando M, Lamanna G, et al. Effects of nicotine on human luteal cells in vitro: a possible role on reproductive outcome for smoking women. Biol Reprod. 2005; 72:628–632. [PubMed: 15548733]
33. Baird DD, Weinberg CR, Wilcox AJ, McConnaughey DR, Musey PI, Collins DC. Hormonal profiles of natural conception cycles ending in early, unrecognized pregnancy loss. J Clin Endocrinol Metab. 1991; 72:793–800. [PubMed: 2005203]
34. Baird DD, Wilcox AJ, Weinberg CR, Kamel F, McConnaughey DR, Musey PI, et al. Preimplantation hormonal differences between the conception and non-conception menstrual cycles of 32 normal women. Hum Reprod. 1997; 12:2607–2613. [PubMed: 9455822]
35. Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. Stat Med. 1982; 1:121–129. [PubMed: 7187087]
36. DiZerega GS, Hodgen GD. Luteal phase dysfunction infertility: a sequel to aberrant folliculogenesis. Fertil Steril. 1981; 35:489–499. [PubMed: 6785111]

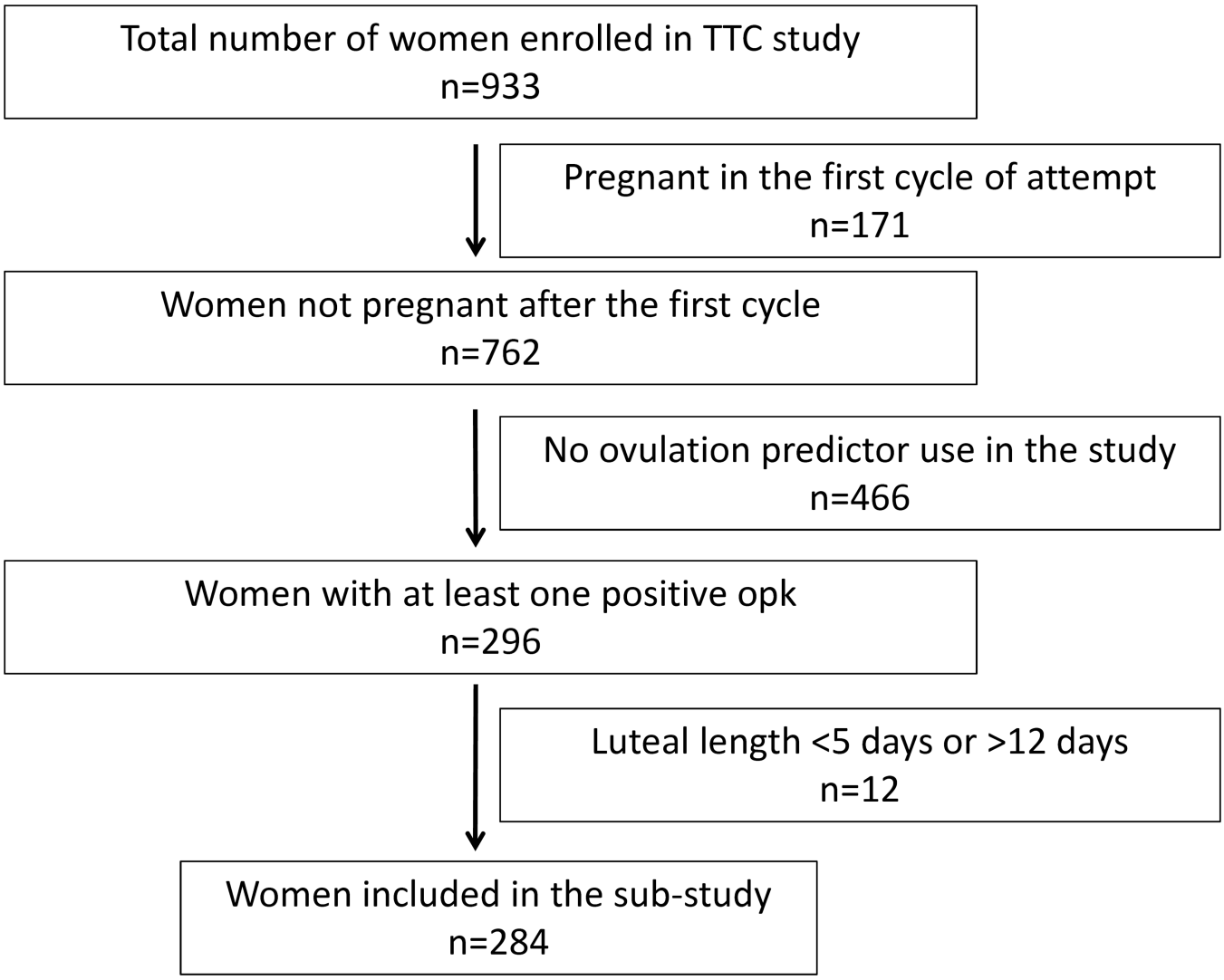

Figure 1.
Flow diagram of study enrollment

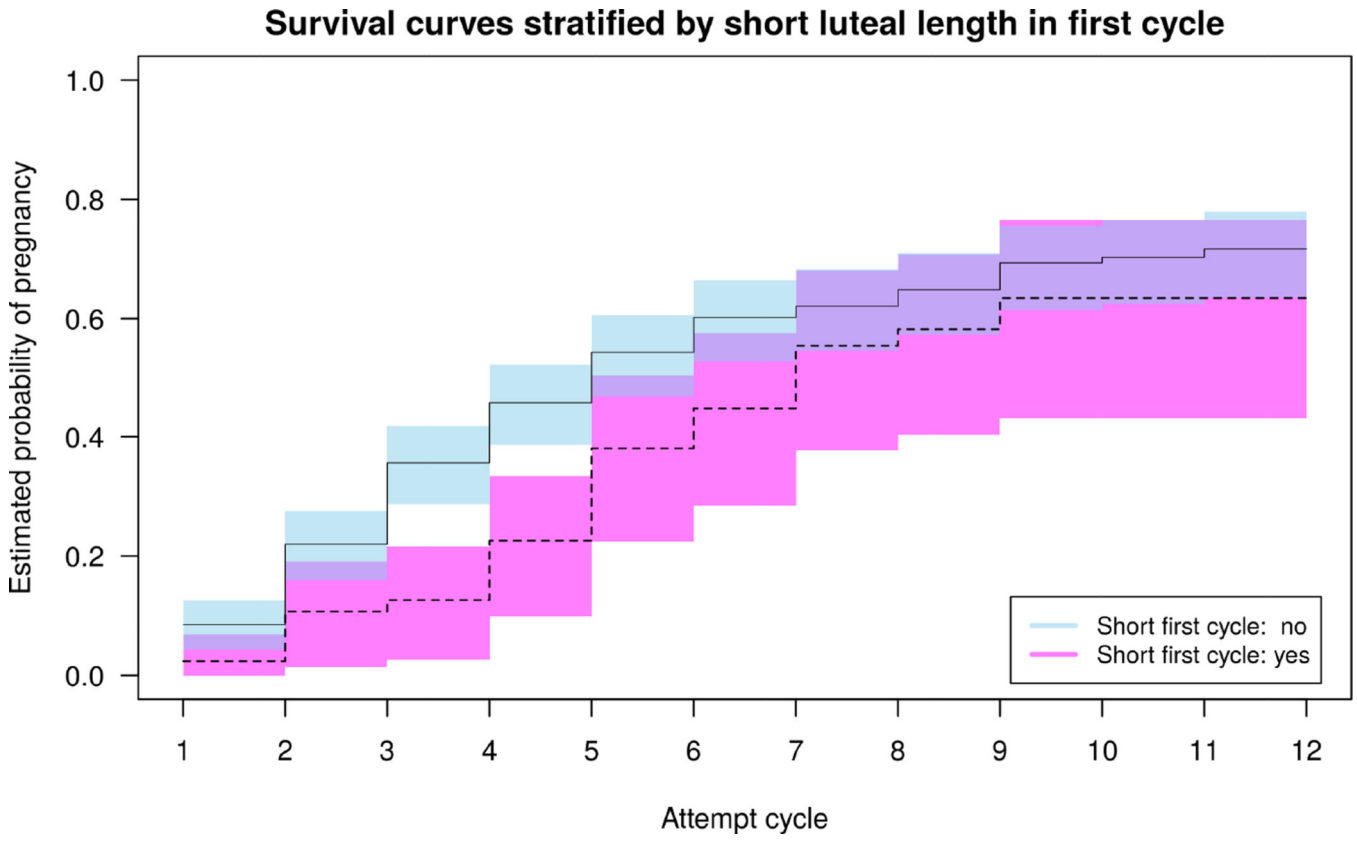

Figure 2.
Mean length (in days) of the luteal phase

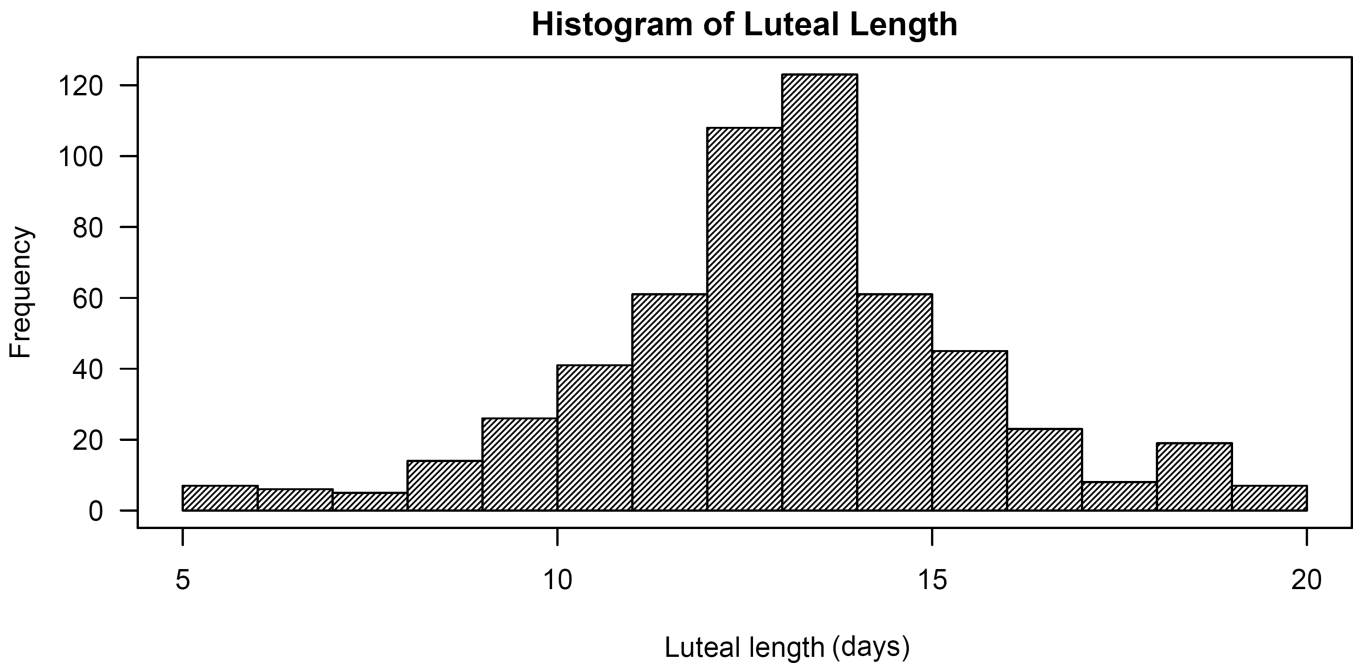

Figure 3.
Adjusted Kaplan Meier curve by short luteal phase in the first observed cycle

Table 1

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

Characteristic	Overall mean (sd) or % (n=284)	Normal luteal length mean (SD) or % (n=230)	Short luteal length Mean (SD) or % (n=54	P value
Age (years)				0.61
<35	68%	69%	63%	
35–37	20%	19%	24%	
>37	12%	12%	13%	
Race				0.86
Non-Hispanic Caucasian	77%	77%	63%	
Other	23%	23%	24%	
Education level				0.32
Less than college degree	7%	7%	9%	
College degree	20%	19%	28%	
Some graduate work	7%	7%	7%	
Completed postgraduate	65%	68%	56%	
Gravid				0.76
No	58%	58%	55%	
Yes	42%	42%	45%	
BMI (kg/m^2)				0.33
<18.5	4%	3%	4%	
18.5–24.9	63%	65%	55%	
25–29.9	19%	20%	18%	
≥30	14%	12%	22%	
Current smoking				0.04
No	98%	99%	94%	
Yes	2%	1%	6%	
Current alcohol use				0.88
No	30%	30%	31%	
Yes	70%	70%	69%	
Recent hormone contraception[2]				0.54
No	54%	55%	50%	
Yes	46%	45%	50%	
Mean cycle length (days)	28.7 (3.7)	29.1 (3.5)	27.1 (4.3)	
Recent hormone contraception[2]				0.54

Characteristic	Overall mean (sd) or % (n=284)	Normal luteal length mean (SD) or % (n=230)	Short luteal length Mean (SD) or % (n=54	P value
No	54%	55%	50%	
Yes	46%	45%	50%	

[1]Patient characteristics in the first observed study cycle

[2]Oral contraceptive pills, contraceptive patch, or contraceptive vaginal ring use in the past year