ORIGINAL ARTICLE: INFERTILITY

A 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.
Clinical Trial Registration Number: NCT01028365. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
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