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A non-hormonal model for emergency contraception: Prostaglandin synthesis inhibitor effects on luteal function and lifespan, a pilot study

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Abstract

Objectives—To determine if the use of a specific prostaglandin endoperoxide-2 (PTGS2) inhibitor will prevent luteal development in women.

Study design—Ovulatory reproductive-age women not using or needing hormonal contraception were prospectively followed for 3 menstrual cycles. Women were randomized into two groups using a cross-over design [Group 1: control cycle, placebo cycle, active drug (Celecoxib 400 mg orally) cycle; Group 2: control cycle, Celecoxib cycle, placebo cycle]. Study drug was dosed daily until the onset of the next menses. Demographics, menstrual cycle length, and twice weekly progesterone (P) levels during the placebo and active drug cycles, were recorded. Endpoints included the change in luteal phase P levels and menstrual cycle length (days) during active drug exposure.

Results—A total of 11 women completed the study (Group 1 n = 7, Group 2 n = 4). No demographic differences were found between groups (age, race, BMI, control cycle length). A comparison of the control and active drug cycles for all participants demonstrated a trend towards a longer menstrual cycle with active drug exposure [control 27.2 days (SD 2.4); study drug 28.5 days (SD 2.5), p = 0.09]. Five women had a delay in the rise of their luteal phase P levels, two women had lower peak P levels, and two women had no elevation of luteal phase P levels during active drug cycle as compared to placebo cycle.

Conclusion—Daily administration of a prostaglandin synthesis inhibitor may delay the timing of luteal events, and therefore fertility, in women. PTSG2 inhibitors may hold potential as an emergency contraceptive.

1. Introduction

Blocking prostaglandin synthesis or action may be an alternative to the currently available hormonal contraceptive methods, including emergency contraception. Hormonal contraception, although highly effective, is not tolerated by some women, and contraindicated in others [1,2]. Hormonal emergency contraception works primarily by inhibition of ovulation, and therefore fails in women who use the method after release of the oocyte [3].

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Prostaglandins have been shown to play a critical role in ovulation as well as the formation and/or maintenance of the corpus luteum [4–11]. Thus, inhibition of their synthesis or action may serve as an effective contraceptive prior to and after fertilization by blocking ovulation and implantation, respectively. Whether one or both of these effects occurs in women is unknown. Obtaining data on the effect of a prostaglandin synthesis inhibitor on cycle length is particularly relevant for their further development as a potential contraceptive. If these agents inhibit luteal development and/or function, then this will lead to premature menstruation rendering them unacceptable as an ongoing daily method of contraception. However, for achieving emergency contraception, preventing luteal development and function would provide superior protection than currently available forms since protection against pregnancy would occur even after ovulation.

As an initial step toward understanding the contraceptive potential of blocking prostaglandin synthesis, we tested the hypothesis that the use of a specific prostaglandin endoperoxide-2 (PTGS2) inhibitor would prevent luteal development and function, thereby leading to a shorter menstrual cycle in women.

2. Materials and methods

A prospective randomized study was conducted at Oregon Health & Science University (OHSU) in Portland, Oregon, from January 2008 to January 2009. The OHSU Institutional Review Board approved the study protocol and all patients underwent informed written consent.

Healthy, reproductive-aged (18–35 years old) women with regular cycles, not currently using or needing hormonal contraception, were recruited. To ensure enrollment of ovulatory women, a screening progesterone (P) level of ≥ 3 ng/mL was confirmed during the luteal phase (Days 18 to 25) of the menstrual cycle prior to study entry. Additional exclusion criteria included allergy to nonsteroidal anti-inflammatories, cardiac risk factors (i.e., hypertension, obesity, cardiac disease, and diabetes) and heart burn or gastroesophageal reflux.

A computer generated randomized scheme was created by OHSU's research pharmacy. A unique consecutive study number was assigned to each participant. Study drug (Celecoxib 400 mg, tradename Celebrex, Pfizer, NY, NY) and an identical placebo were obtained from the research pharmacy. The research team and study participants were blinded to group allocation. Women were randomized into two groups using a cross-over design [Group 1: control cycle, placebo cycle, active drug (Celecoxib 400 mg orally) cycle; Group 2: control cycle, active drug (Celecoxib) cycle, placebo cycle]. Study drug and placebo were dosed daily until the onset of the next menses (defined as 2 consecutive days of spotting or bleeding). The randomization code was revealed to the research investigators only after data analysis.

Demographic information was gathered at study entry. Women filled out menstrual diaries to track menstrual cycle length, pill compliance, and symptoms. During the active study drug and placebo cycles (Cycle 2 and 3), women returned biweekly (no more than 3 days apart) for blood sampling for measurement of serum P levels.

Since menstruation will occur within 48 h of a decline in P, this would lead to onset of bleeding within 2–8 days following ovulation, depending on the extent of prostaglandin blockade. Therefore, we assumed that treatment with Celecoxib would result in a 6 day reduction in menstrual cycle length (from 28 to 22 days, SD 4 days). This calculated to a sample size of 5 subjects in each group to have 80% power to show this difference with an alpha of 0.05. Analysis for the primary outcome (menstrual cycle length in days) was

performed with a paired t-test for between cycle comparisons for all participants and each group. Progesterone levels were graphed based on cycle day and then categorized as a delay in P rise (yes/no) as compared to the subject's placebo cycle. Descriptive statistics were used to compare demographics.

3. Results

Fifteen subjects were screened for enrollment into the study with 13 subjects meeting eligibility criteria and 11 subjects who completed the entire study protocol (Group 1 n = 7, Group 2 n = 4) (Fig. 1). There were no significant demographic differences between groups (Table 1).

For all participants, no differences in cycle length were found between control and placebo cycles [placebo 27.8 days (SD 3); control 27.2 days (SD 2.4)]. A comparison of control and active drug cycles for all participants demonstrated a trend towards a longer menstrual cycle with active drug exposure [active drug 28.5 days (SD 2.5), $p = 0.09$]. This trend was not found between placebo and active drug cycles ($p = 0.5$). Within group comparisons revealed no statistical menstrual cycle length differences between the control and placebo cycles, control and active drug cycles, and placebo and active drug cycles for either group.

All subjects had P levels above 3 ng/mL in their placebo cycles. Nine out of 11 subjects (Group 1 = 5, Group 2 = 4) had P levels above 3 ng/mL in their active drug cycle. Comparing luteal phase P level patterns between placebo and active drug cycles for these 9 women, 2 women had no change between cycles, 2 had a late rise and a lower peak P level in active drug cycles, 3 had a late rise but a similar peak P level in active drug cycles as compared to placebo cycles, and 2 had a similar rise but a lower peak P in active drug cycles as compared to placebo cycles (Fig. 2). Two women, both in Group 1 (control, placebo, active drug cycle), demonstrated no rise in luteal phase P levels during their active drug cycle (peak P levels 3 and 2.6 ng/mL). Both of these women had luteal phase P values > 3 ng/mL in their placebo cycles.

4. Discussion

We hypothesized that PTGS2 inhibitors would limit luteal development resulting in premature onset of menstruation or shorter menstrual cycles. However, we did not find a shorter menstrual cycle with daily administration of a PTGS2 but a trend towards a longer menstrual cycle with either a delay in the rise or no rise in luteal phase P levels. Collectively, these findings support the hypothesis that prostaglandin synthesis is critical for luteal development [4–11]. Unfortunately, our study design did not allow us to discriminate if its action was pre-ovulatory, post-ovulatory, or both.

There are several additional limitations including our small sample size. However, a randomized cross-over study design increased our ability to find differences even within a small study population. Due to dropout in Group 2, we did not achieve our desired sample size of 5 subjects in each group. One additional subject may have helped to strengthen the trends found. Additionally, our findings were contrary to what we predicted. We originally assumed that the menstrual cycle would be shorter due to inadequate luteal development but our results found a slightly longer menstrual cycle. A longer menstrual cycle correlates with our P level findings, whereby in several instances, celecoxib resulted in a delayed rise or no rise of luteal phase P. It also appears that we had two non-responders with no changes in luteal phase P with active drug treatment. Individual phenotypic differences in response to PTGS2 inhibitors have been found which may explain this lack of response [12].

Interestingly, removing these ‘non-responders’ from analysis causes the findings of a longer menstrual cycle length with celecoxib use to be statistically significant ($p = 0.01$).

Studies in non-human primates have shown that mid-cycle administration of the non-selective PTGS inhibitor (sodium meclofenamate) causes premature menses [11]. Perhaps the daily administration of treatment drug in our study influenced ovulation differently than intermittent treatment. Other animal and human studies have demonstrated that PTGS2 inhibitors can prevent or delay follicle rupture which would lead to a longer menstrual cycle and a hormone profile similar to what we found [13–19]. Additionally, as recent studies utilizing non-human primates found that the levels of PTGS2 and microsomal prostaglandin E2 (PGE2) synthase (necessary for PGE2 synthesis) as well as the PGE2 receptor subtype 3 (PTGER3) increase during luteal development [20], one can hypothesize that blocking PTGS2 activity should delay or reduce luteal development.

Taken together, these observations suggest two potential mechanisms through which PTGS2 inhibitors might function as contraceptives: 1) delay or inhibit ovulation, and 2) delay luteal development. However, as mentioned earlier, if daily use of a PTGS2 inhibitor results in premature luteolysis, this would result in shortened menstrual cycles and would be unacceptable as an ongoing method of contraception. But, this dual activity might offer advantages as a post-coital contraceptive pill as it would work prior to and at or immediately after ovulation. These findings serve as the basis for additional studies to determine the effectiveness of a selective PTGS2 inhibitor as a pre- and post-ovulatory emergency contraceptive.

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Fig 1.
CONSORT flowchart

Fig 2.

Examples of responses to treatment for individual subjects (placebo cycle = dark grey, drug cycle = light grey). Panel 1: No change; Panel 2: delay in rise and blunted peak of luteal phase progesterone levels during drug cycle; Panel 3: delay in rise but normal peak luteal phase progesterone levels during drug cycle.

Table 1

Demographics

	Group 1^a	Group 2^b
Age, years	27.3 (SD 5.2)	28.8 (SD 6.1)
Race		
Non-Hispanic, Caucasian	7	4
Other	0	0
BMI	24.1 kg/m ² (SD 2.5)	22.6 kg/m ² (SD 2.5)
Average cycle length in days prior to study entry (self-reported)	28.0 (SD 1.3)	28.5 (SD 0.58)
Control cycle length in days	27.3 (SD 2.9)	27.0 (SD 1.4)

^aGroup 1 = Cycle 2 placebo, Cycle 3 active study drug;

^bGroup 2 = Cycle 2 active study drug, Cycle 3 placebo.