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Impact of the prostaglandin synthase-2 inhibitor celecoxib on ovulation and luteal events in women☆,☆☆

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Abstract

Background: Ovarian prostaglandins are critical in normal ovulation processes; thus, their inhibition may provide contraceptive benefits. This study was performed to determine the effect of the cyclooxygenase-2 (COX2) inhibitor celecoxib on ovulation and luteal events in women.

Study Design: The study had a randomized, double-blind, crossover design. Ovulatory, reproductive-aged women underwent ovarian ultrasound and serum hormone monitoring during four menstrual cycles (control cycle, treatment cycle 1, washout cycle, treatment cycle 2). Subjects received study drug (oral celecoxib 400 mg or placebo) either (a) once daily starting on cycle day 8 and continuing until follicle rupture or the onset of next menses if follicle rupture did not occur [pre-luteinizing hormone (LH) surge dosing] or (b) once daily beginning with the LH surge and continuing for 6 days (post-LH surge dosing). Subjects were randomly assigned to one of the above treatment schemes and received the other in the subsequent treatment cycle. The main outcomes were evidence of ovulatory and luteal dysfunction as determined by inhibited/delayed follicle rupture and reduced luteal progesterone synthesis or lifespan, respectively.

Results: A total of 20 women enrolled and completed the study (Group 1=10, Group 2=10), with similar demographics between groups. Nineteen subjects exhibited normal ovulation in the control cycle (one had a blunted LH peak). In comparison to control cycles, treatment cycles resulted in a significant increase in ovulatory dysfunction [pre-LH treatment: 30% (6/20), p=.04; post-LH treatment: 25% (5/20), p=.04]. Mean peak progesterone, estradiol, and LH levels and luteal phase length did not differ significantly between control and either treatment cycle.

Conclusions: Although treatment with celecoxib before or after the LH surge increases the rate of ovulatory dysfunction, most women ovulate normally. Thus, this selective COX2 inhibitor appears to be of limited usefulness as a potential emergency contraceptive.

Keywords: COX 2 inhibitor; Prostaglandin; Emergency contraception; Celecoxib; Dysfunctional ovulation

1. Introduction

Currently available hormonal emergency contraception (EC), such as levonorgestrel or ulipristal acetate, work by inhibiting ovulation [1,2]. Although levonorgestrel inhibits ovulation in 83% of menstrual cycles at a follicular measurement of 12–14 mm, it blocks ovulation in only about 12% of cycles when the follicle is larger (18–20 mm) [1]. By contrast, ulipristal acetate prevents ovulation in 60% of cycles up to a follicular measurement of 18–20 mm. Thus, ulipristal can block follicle rupture when given at the time of the luteinizing hormone (LH) surge, which explains its greater efficacy than a levonorgestrel-based EC and longer treatment window of up to 120 h after unprotected intercourse [3]. Failures occur principally in women having unprotected sexual intercourse after the peak of the LH surge, as they receive no benefits from either of these emergency therapies.

Ovarian prostaglandins (PGs) synthesized through the rate-limiting enzyme cyclooxygenase-2 [COX2; also known as prostaglandin-endoperoxide synthase (PTGS)2] play a critical role in ovulation and luteal development [4–14]. The

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inability to synthesize ovarian PGs in COX2 null mutant mice causes infertility by preventing ovulation or cumulus–oocyte expansion (C-OE) [13,14]. The role of PGs in fertility appears to be dependent on PGE2 synthesis as the deletion of the PGE2 subtype 2 receptor results in female sterility due to a failure of cumulus–oocyte complexes to undergo C-OE [13]. Moreover, the expression of genes encoding proteins involved in PGE2 synthesis and signaling is highly expressed after follicle rupture in primate and domesticated animal species [15,16], suggesting a role for PGs in the development of the corpus luteum. Thus, a COX2-selective inhibitor may offer a much broader window of treatment as an EC through interfering with both ovulatory and luteal activities. Nonhuman primate and human studies using the COX2 inhibitor meloxicam (Glenmark Generics Inc., Mahwah, NJ, USA) have demonstrated that the drug creates ovulatory dysfunction when dosed before the LH surge (late follicular phase) and may enhance the inhibitory effects of the levonorgestrel-based EC [17–20]. Another COX2 inhibitor, rofecoxib, also demonstrated delayed follicle rupture when dosed before the LH surge, but this formulation was voluntarily withdrawn from the market in 2004 [21].

Since meloxicam is only moderately selective for COX2, we hypothesized that treatment with the more highly selective COX2 inhibitor celecoxib (Pfizer Inc., New York, NY, USA) [22] would be a more effective agent in terms of causing ovulatory dysfunction [22]. Furthermore, since PG synthesis and action have been implicated in luteal development in animal models [15,16], we hypothesized that treatment with celecoxib would adversely affect luteal function. Our prior pilot study [23] demonstrated that daily administration of celecoxib caused a delay in luteal phase events in some women, but the study was not designed to monitor ovulation or to allow us to determine the timing of this effect. Therefore, in the current study, we sought to further isolate celecoxib's mechanism of action and its window of effectiveness by evaluating its effects specifically prior to and after the LH surge.

2. Materials and methods

A prospective randomized, double-blind, crossover study was conducted at Oregon Health & Science University (OHSU) in Portland, OR, from January 2010 to February 2011. The OHSU Institutional Review Board approved the study protocol, and subjects volunteered to participate after reviewing and signing a written informed consent.

Healthy reproductive-aged (18–35 years old) women with regular cycles (every 26–34 days), not currently using or needing hormonal contraception, were recruited. To ensure enrollment of ovulatory women, we required that subjects demonstrate a single progesterone (P) level of at least 3 ng/mL during the luteal phase (days 18–25) of the menstrual cycle prior to study entry. Additional exclusion criteria included allergy to or routine use of nonsteroidal anti-inflammatory drugs (e.g., aspirin, ibuprofen), known cardiac risk factors (i.e., personal history of hypertension, obesity, cardiac disease and/or diabetes) and pyrosis or gastroesophageal reflux.

A computer-generated randomized scheme was created by the OHSU research pharmacy. A unique consecutive study number was assigned to each participant. Study drug (celecoxib 400 mg po daily) and an identical placebo were obtained from the research pharmacy. Women were randomized into one of two dosing schedules using a crossover design for four menstrual cycles (control cycle, treatment 1, washout cycle, treatment 2). In each treatment cycle, subjects received study medication for both "pre-LH" surge (initiated on cycle day 8 and continued until follicle rupture or until the onset of next menses if follicle rupture did not occur) and "post-LH" surge (initiated at the time of LH surge as determined by home urine LH testing and continued for a total of 6 days). If an LH surge was not detected, the "post-LH" surge treatment was not taken. An LH surge identified by home urine testing was verified with a serum LH assay at the end of the study.

In order to maintain allocation concealment, all study subjects received two bottles for each treatment cycle — one with the study drug and the other with an identical placebo. They were instructed when to initiate drug 1 and when to switch to drug 2 based on the dosing schedule above. The onset of next menses was defined at least as 2 consecutive days of spotting or bleeding. Group 1 received pre-LH surge dosing of celecoxib and post-LH dosing of placebo during treatment cycle 1 and pre-LH dosing of placebo with post-LH dosing of celecoxib during treatment cycle 2. Group 2 received the opposite order of active and placebo treatments during the two cycles. Women were seen for twice-weekly visits (no more than 4 days apart) during the control and treatment cycles to obtain blood samples for pituitary (LH) and ovarian hormone levels [P4 and estradiol (E2)] and to perform transvaginal ultrasound (TVUS) to monitor ovarian activity. Starting on cycle day 8, subjects performed daily home urine LH testing (Clearview, Shared Services Center, Orlando, FL, USA) and reported for daily clinic visits and TVUS starting within 24 h of an LH surge. These daily visits were continued until follicle rupture was observed by ultrasound or for up to 4 days. Visits then resumed twice weekly until menses.

LH, E2 and P4 assays were performed at the Endocrine Technology Services Laboratory at the Oregon National Primate Research Center (Beaverton, OR, USA) using an automated Immulite 2000 chemiluminescent assay system (Siemens, Deerfield, IL 60015, USA). All assays were analyzed altogether at the completion of the study. Assay sensitivity of LH, E2 and P4 assays is 0.1 ng/mL, 20 pg/mL and 0.2 ng/mL, respectively. Three quality controls with low, median and high values for LH, E2 or P4 were routinely analyzed before each sample run, and the quality control (QC) values were confirmed within 10% of the mean values detected over the last 12 months (n=9). For LH, the intraassay coefficient of variation (CV) was 6.3% at 10.8