Low-dose progestin-releasing contraceptives are associated with a higher pain threshold in healthy women

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Objective: To determine the pain thresholds of women taking different formulations of hormonal contraceptives.
Design: Cross-sectional study.
Setting: Basic health care unit.
Patient(s): Eighty-nine healthy nonusers and 188 users of hormonal contraceptives.
Intervention(s): Subject interviews were followed by the application of a semistructured questionnaire, including a psychometric assessment with the Beck Depression Inventory and the State-Trait Anxiety Inventory. After the interview, a 10-mL peripheral blood sample was collected. Pain thresholds were obtained by performing pressure algometry.
Main Outcome Measure(s): Serum concentrations of E_2, P, and T (free fraction) were determined via chemoluminescence. The menstrual cycle phase was determined according to hormonal level and identification of an LH surge in urine. Pain threshold was evaluated with a dynamometer applied to the forearm skin of the nondominant limb and abdominal wall.
Result(s): Progestin-only contraceptive users showed a higher pain pressure threshold in the forearm (2.94 ± 0.96 vs. 2.74 ± 0.89 vs. 2.62 ± 0.92) and right (2.11 ± 0.87 vs. 1.83 ± 0.81 vs. 1.78 ± 0.77) and left abdomen (2.12 ± 0.88 vs. 1.79 ± 0.76 vs. 1.73 ± 0.70) than did combined hormonal contraceptive users and nonusers of hormonal contraceptives, respectively. Users of contraceptives that continuously release etonogestrel (subcutaneous implant, vaginal ring) or levonorgestrel (intrauterine devices) had higher pain thresholds.
Conclusion(s): Women who used hormonal contraceptives enabling continuous release of etonogestrel or levonorgestrel tended to have higher pain thresholds than did nonusers of hormonal contraceptives. (Fertil Steril® 2015;104:1182–9. ©2015 by American Society for Reproductive Medicine.)
Key Words: Hormonal contraceptives, pain threshold, etonogestrel, levonorgestrel

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Chronic pain is a highly prevalent medical problem worldwide. One in 5 individuals is affected by persistent painful conditions, with not only negative repercussions on health but also significant social and economic consequences (1). Women are known to be more affected than men by diseases involving persistent pain (2, 3). From a laboratory viewpoint (sensitivity to experimentally induced pain), evidence shows that the pain threshold of women is lower than that of men, when determined via pressure or with an electrical stimulus (4). The quantitative assessment of experimental pain perception under controlled conditions is relevant to various clinical situations, such as detection of individual differences in the pain processing mechanisms in the central nervous system (5), prediction of postoperative pain (6), and prediction of clinical response to

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analgesics (7), in addition to being potentially useful for coping strategy training (8).

Many factors are known to interfere with the perception of pain stimuli (9–11), all of them possibly interacting to explain the difference in pain sensitivity observed between sexes (12). Indeed, as expected, hormonal factors are some of the most extensively studied (13). Some evidence shows that gonadal steroid hormones may interfere with various pain mechanism pathways (14, 15). The role of these hormones has been more extensively documented in animal models (14,16–19), whereas no consensus has been reached on the influences of these hormones in humans (20, 21). Previous literature reviews have indicated that greater pain sensitivity occurs during ovulation or in the luteal phase of the menstrual cycle (14, 22, 23). This effect is believed to be attributable to the role of gonadal steroid hormones in the process of neuromodulation, in which predominance of excitatory over inhibitory control occurs during the premenstrual period (24, 25). However, a recent review has shown that these findings are inconsistent (20). Other studies have stated that the menstrual cycle does not influence the magnitude of the sex effect on differences in pain perception (26). Studies of the use of hormonal contraceptives are scarce, and in most cases do not show significant effects of these agents on pain sensitivity (27–31), although no consensus has been reached about this topic (32, 33). Usually, these studies do not specify drug class, dose, or route of administration of specific hormonal formulations, a fact that, of itself, compromises the elaboration of a hypothesis about the possible influence of this drug class on pain sensitivity. In contrast, recent studies have reported that combined oral contraceptives may be associated, at minimum, with a less effective endogenous modulation of pain, particularly regarding diffuse noxious inhibitory control (34).

On this basis, the objective of the present study was to evaluate pain thresholds in women taking different formulations of hormonal contraceptives.

MATERIALS AND METHODS

Study Design

Setting. This was a cross-sectional study conducted from January 2012 to October 2013 at the Teaching Health Center of the Ribeirão Preto Medical School, University of São Paulo (CSE-FMRP-USP per the Portuguese acronym), a primary care unit. The study was approved by the Research Ethics Committee of CSE-FMRP-USP (protocol no. CAAE-0012.0.175.000-11), and all women provided written, informed consent to participate.

Participants (eligibility criteria, sources, and methods of selection). Eligibility criteria were as follows: healthy women aged 18–40 years with a body mass index <30 kg/m^2 and no clinical history or record of comorbidities who were registered in the health system of the municipality; taking no pain killers, antidepressants, or anti-inflammatory agents; wishing to start a hormonal contraceptive regimen; and having a regular menstrual cycle during the previous 3 months (control group) or using hormonal contraception for at least 6 months (study group). Women were excluded from the study if they had a condition in which the theoretical or proven risks of hormonal contraception usually outweigh the advantages of using the method (category 3) or a condition that carried an unacceptable health risk if the contraceptive method were used (category 4) according to the eligibility criteria of the World Health Organization (2010), and women with clinical significant dysmenorrhea (35). Women were invited to participate in the study by telephone or in person after an appointment at the health unit.

Variables and data measurement. An initial interview was held with all the women, during which all procedures were first explained, followed by the administration of a semistructured questionnaire, including a psychometric assessment with the Brazilian version of the Beck Depression Inventory and the State-Trait Anxiety Inventory, State Scale (36, 37).

After the interview, a 10-mL peripheral blood sample was collected for the determination of E_2, P, and T (free fraction). The samples were collected at approximately 10:00 AM and centrifuged at 3,540 $\times$ *g* for 10 minutes. After separation, serum was stored frozen at -80°C until the time for analysis.

Quantitative Variables

Determination of the phase of the menstrual cycle. The beginning of the menstrual cycle was determined by self-report, and the first day of the cycle was considered to be day 1. To assign women to the control group (nonusers of hormonal contraceptives), we considered the self-reported beginning of the menstrual cycle (with the beginning of the last menstruation considered to be day 1) and the characteristics of the woman's cervical mucus, as assessed by the consultant gynecologists. Recruitment during the follicular phase occurred between the 3rd and 7th day of the menstrual cycle, and recruitment during the luteal phase occurred between the 22nd and 25th day of the menstrual cycle. The periovulatory period was confirmed by using the commercial kit Confirme Fertilidade (Alamar Tecno Científica Ltda), which identifies the LH surge in urine, and the luteal phase was confirmed when serum P concentration was >3 ng/mL (38).

Hormonal measurements. Serum concentrations of E_2, P, and T (free fraction) were determined by performing chemoluminescence using the commercial Immulite system and the Immulite 2000 analyzer (Siemens Medical Solutions Diagnostics). The detection limits and analytical sensitivity for E_2, P, and T were 20.0–2000.0 pg/mL (15 pg/mL), 0.20–40.0 ng/mL (0.1 ng/mL), and 20.0–1600.0 ng/dL (10 ng/dL), respectively.

Pain thresholds. Initially, all volunteers received training to familiarize themselves with the procedure and were instructed regarding the ideal threshold rating (39). The measurements obtained during training were not used for data analysis.

We used a model DD-500 portable digital dynamometer (Instrutherm Instrumentos de Medição Ltda) with 20 kgf $\times$ 5 gf capacity that consists of a pressure-sensitive rod fitted with a 1-cm^2 rubber base on the distal extremity. Two points were tested on the abdominal wall (right and left in an area corresponding to the uterine viscerotome) (40), and one point