ORIGINAL ARTICLE: ENVIRONMENT AND EPIDEMIOLOGY

Differences in ovarian hormones in relation to parity and time since last birth

Emily S. Barrett, Ph.D.,[a] Lauren E. Parlett, Ph.D.,[b] Gayle C. Windham, Ph.D.,[c] and Shanna H. Swan, Ph.D.[d]

[a] Department of Obstetrics and Gynecology, School of Medicine and Dentistry, University of Rochester, Rochester, New York; [b] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland; [c] Division of Environmental and Occupational Disease Control, California Department of Public Health, Richmond, California; and [d] Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai, New York, New York

Objective: To examine ovarian function in relation to parity and time since last birth.
Design: Cross-sectional study.
Setting: Health-care program in California.
Patient(s): 346 naturally cycling women, aged 18 to 39 years.
Intervention(s): None.
Main Outcome Measure(s): Mean follicular urinary estradiol metabolite concentration (E1C) (cycle days −8 to −1), mean luteal progesterone metabolite concentration (PdG) (days 0 to +10), and cycle phase lengths in ovulatory cycles.
Result(s): After the women had collected daily urine samples for up to eight menstrual cycles, we measured the E1C and PdG using enzyme-linked immunoassay. The cycle phase lengths were calculated from the hormone profiles and daily diaries. Women who had given birth within the previous 3 years had lower E1C than the nulliparous women and women who last given birth >3 years earlier. Among the parous women, E1C was positively associated with the time since last birth. Women who last gave birth >3 years earlier had longer follicular phases than the nulliparous women. There were no associations between parity and PdG or luteal phase length.
Conclusion(s): Our cross-sectional data suggest that ovarian function differs in nulliparous and parous women and is positively associated with the time since last birth. Longitudinal research is needed to explore within-woman changes in ovarian function prepartum and postpartum. (Fertil Steril® 2014;■: ■–■. ©2014 by American Society for Reproductive Medicine.)
Key Words: Estradiol, fecundity, motherhood, menstrual cycle, ovarian function

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Concentrations of the ovarian steroid hormones estradiol and progesterone can vary considerably from cycle to cycle and woman to woman, which is not surprising given that the ovary is highly responsive to ecological cues (1). This is most clearly illustrated by extreme examples, such as the prevalence of amenorrhea and oligomenorrhea among highly trained athletes including dancers, gymnasts, and distance runners (2–6). Within ovulatory cycles, ovarian hormone production varies in relation to more subtle cues, including minor weight gain (7, 8) and loss (9, 10), recreational physical activity (11, 12), dietary intake (13–17), sleep variation (18), and possibly even psychosocial stress (19–21). Ovarian function also varies in relation to demographic factors such as age and race (22–29).

Somewhat surprisingly, there has been relatively little research on whether reproductive history, particularly parity, predicts ovarian steroid hormone levels in reproductive-aged women. Recently, in a Norwegian cohort, we found that testosterone, a hormone partly ovarian in origin, is lower in parous women as compared with nulliparous women (30), results

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Reprint requests: Emily S. Barrett, Ph.D., Department of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue, Box 668, Rochester, New York 14642 (E-mail: emily_barrett@urmc.rochester.edu).

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that echoed earlier findings in women in the Philippines (31). In both cases, the investigators proposed that there might be down-regulation of testosterone production in relation to a transition from mating to parenting (30, 31). However, it is also possible that lower testosterone levels among parous women are indicative of a more general suppression of ovarian function, which could include modulation of estradiol and progesterone as well. Only a handful of studies have examined these hormones in relation to parity, and most, but not all, reported that estrogen is lower in parous than nulliparous women, adjusting for age and other covariates (26, 28, 32–34).

Understanding predictors of variation in these hormones is important because of their relevance to fecundity as well as other health outcomes. Within and across women, naturally occurring conception cycles are characterized by higher average follicular estradiol levels and luteal progesterone levels than nonconception cycles (35–37) and assisted reproductive technologies are more successful in cycles with higher follicular estradiol before ovarian stimulation (38, 39). Beyond fertility, ovarian hormones may play an important role in osteoporosis (40, 41), reproductive cancers (42–44), and cardiovascular disease (45, 46).

To that end, in this analysis, our primary objective was to examine ovarian function in relation to parity in a large population-based sample of cycling, reproductive-aged women in the state of California. We first asked whether levels of urinary ovarian hormone metabolites differ in relation to parity, comparing nulliparous women to women who gave birth within the last 3 years, and women who last gave birth more than 3 years ago, a time cutoff selected based on our previous work (30). To examine the possibility that parity-related differences in the rate of follicular development might contribute to any relationships found, we looked at whether cycle phase lengths (most notably follicular, but also total and luteal phase lengths) differed in these 3 groups. Finally, we examined whether, within parous women, estradiol and progesterone metabolite levels were related to time since last birth.

MATERIALS AND METHODS

Study Population

Women were recruited into the Women's Reproductive Health Study (WRHS) from 1990 to 1991. To be eligible, women had to be currently enrolled in the Kaiser Permanente Medical Care Program in Northern California, be aged 18 to 39 years, be married, be at risk of becoming pregnant (e.g., not using hormonal contraception, no history of hysterectomy, neither woman nor partner sterilized), have had a menstrual period within the past 6 weeks, and be willing to collect and freeze morning urine samples for up to 6 months (or their second missed menstrual period). Nearly 6,500 women were screened by phone interview, of which 1,092 were eligible. Of those, 561 agreed to participate; 150 dropped out or became ineligible, which left 411 women who completed the urine collection and all study activities. Women who either collected 60 or more days of daily urine samples through two or more menstrual cycles or became clinically pregnant during their participation were considered to have successfully completed the study. More detailed summaries of study recruitment and methods have been previously published (26, 47). The human subjects review boards at all participating institutions approved the study before implementation (including the University of Rochester, RSRB 00039941), and all subjects signed informed consent before participation.

Questionnaire Data

At intake, all women were interviewed over the phone by trained examiners on topics including demographics, reproductive history, and lifestyle. Subjects reported on age, race, weight, height, alcohol use, smoking, and employment. Height and weight were used to calculate body mass index (BMI: weight in kg/(height in m)^2). The participants reported how much time they spent doing various sports and physical activities, and from that a metabolic units (met)/week composite was created using the 2011 Compendium of Physical Activities (48). In a series of questions about reproductive characteristics, the women reported their age at menarche and history of oral contraceptive use. They also reported the month and year of all previous pregnancies and their outcomes. This information was used to calculate the time since last birth at baseline.

Urine Sample Collection and Laboratory Methods

Participants collected and froze first morning urine samples daily. These samples were regularly collected by study staff and sent to the University of California at Davis, where enzyme-linked immunoassay (ELISA) was used to assay the samples for creatinine, a progesterone metabolite (pregnanediol-3-glucuronide [PdG]), and estradiol metabolites (estrone sulfate and estrone glucuronide, collectively referred to as E1C). Hormone concentrations under the limit of detection were assigned the minimum value of detection for analysis (PdG <0.15 μg/mL; E1C $<$ 7.8 ng/mL). To adjust for differences in urine concentration, the PdG and E1C levels were divided by the creatinine levels; only the creatinine-adjusted values are used in the current analyses. Samples within a single menstrual cycle were assayed on the same microtiter plate (along with internal controls and standards). The intraplate coefficient of variation (CV) for E1C was 1.6% and the interplate CV for the high, medium, and low pools were 4.9%, 6.6%, and 11.2%, respectively. The intraplate CV for PdG was 1.8%, and the interplate CV for the high, medium, and low pools was 5.2%, 6.9%, and 11.0%, respectively.

Ovarian Hormone Concentrations and Cycle Phase Determination

Urine samples were split into cycles based on prospectively recorded menstrual diary data combined with urinary ovarian steroid concentrations, using methods published elsewhere (47). The participants contributed data and urine samples from one to eight cycles, depending on their cycle length and the duration of their participation. Ovulatory status and day of ovulation were assigned using a validated algorithm (47, 49), and the quality control procedures have been

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