The Biodemographic Models of Reproductive Aging (BIMORA) Project: Methods and Steroid Hormone and Menstrual Cycle Findings in a Five Year Prospective of the Transition to Menopause

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The endocrinological and menstrual cycle changes that occur during the menopausal transition (perimenopause) are of interest to women, clinicians, and researchers. Women are interested in understanding the symptoms they experience during perimenopause, their risk of pregnancy after their menstrual cycles have become irregular, and health risks that they may face in relation to declining estrogen levels and hormone replacement therapy (HRT). Clinicians need data that will help them predict the onset of menopause and related health risks for individual women. Researchers strive to provide such data and seek to understand the etiology of menopause and its relationship to other physical and behavioral characteristics of women.

In order to understand perimenopause, a more detailed understanding of the hormonal and menstrual cycle changes occurring during perimenopause, and how those changes relate to demographic, environmental, and health characteristics, is needed. These changes have been investigated previously in both cross-sectional and longitudinal studies. However, limitations of research design (e.g. study length, sample size, and selectivity of sample) combined with the high level of variation in hormone and menstrual cycle patterns within and across perimenopausal women, complicate the interpretation, comparability, and applicability of the data.

Here, we report on the Biodemographic Models of Reproductive Aging (BIMORA) project – a five-year, prospective, population-based study of a well-defined cohort of women that examines the endocrinological and menstrual cycle characteristics of the transition to menopause and the links between these characteristics and previously collected menstrual, reproductive and health data. This study was designed to maximize both number of subjects and number of hormone samples in order to capture details about the variation and changes in hormone levels and menstrual cycles during perimenopause.

Here, we describe the recruitment, sampling and collection methods, and present results from analyses of the menstrual cycle and steroid hormone data.

We recruited a cohort of women enrolled in the TREMIN Research Program on Women's Health, an existing longitudinal study of menstrual cycles and health, which began in the 1930s. These women have been providing detailed prospective reports of menstrual and reproductive histories, and information on life-cycle events and health status for up to 30 years. One hundred fifty six of these women provided daily urine specimens and menstrual cycle information for sixth month intervals in each year from 1998 through 2002. Data collection occurred during the same time frame each year, from January 14 to July 15, to avoid possible confounding by seasonal variation in menstrual cycle characteristics or hormone concentrations. Eligible participants included women between the ages of 25 and 60 who were not using any exogenous prescription reproductive hormones (e.g., birth control, hormone replacement therapy) and who had at least one intact ovary. Women without a uterus were included for the hormonal part of the study but are not included in analyses of menstrual bleed patterns. Pregnant and breastfeeding women and women receiving cancer treatment were not eligible. Enrollment was on a continual basis with some women enrolled or re-enrolled following cessation of pregnancy, breastfeeding, or exogenous hormone use. Monetary compensation was provided for participation. All participants provided written informed consent, and the institutional review boards of Georgetown University, the University of Utah, the Pennsylvania State University and the University of Washington approved all procedures.

Specimens were self-collected daily (usually first morning specimens) by subjects in their homes on small pure cellulose sponges, which were placed inside a plastic vial, sealed, labeled, and then placed into a home freezer until time for monthly delivery to the laboratory at the University of Washington. For each day, subjects also listed all medication or supplement use, any vaginal bleeding, and any unusual specimen treatment. At the laboratory, specimens were stored at -20°C for up to 3 months prior to assay. The specimens were then thawed and extracted from the sponges using a centrifuge. Specific gravity of the specimens was measured, 17 mg/mL of boric acid was added as a preservative, and an aliquot was taken for assay. The remainder of each specimen was re-frozen at -20C and archived for future use.

All urine specimens were assayed in duplicate for estrone-3-glucuronide (E1G, a urinary metabolite of estradiol) and pregnanediol-3-glucuronide (PDG, a urinary metabolite of progesterone). These metabolites closely parallel the serum levels of estradiol and progesterone. Enzyme-immunoassays (EIAs) using monoclonal capture antibodies were employed to quantify the urinary levels of E1G and PDG. Inter- and intra-assay CV's were 9.2% and 10.3% for the PDG EIA, and 4% and 3.6% for the E1G EIA. The PDG EIA cross reacts 100% with pregnanediol-3-glucuronide, 187% with 20α hydroxy-4-pregnen-3-one, 13.4% with pregnanediol, and 4.3% with 20β hydroxy-4-pregnen-3-one and less than 1% with other progestins. The E1G EIA cross-reacts 100% with estrone-3-glucuronide, 83% with estradiol-3-glucuronide, and less than 5% with other estrogens.

Menstrual cycle lengths were defined from the first day of one menstrual period to the day before the first day of the next menstrual period. A menstrual period was defined as at least two days of bleeding out of three consecutive days, bounded on either side by at least two non-bleed days. In a given study year, if a woman had no bleeds in the six-month collection interval, she was recorded as having zero menstrual cycles for that year.

The average year-to-year subject retention rate was approximately 90 percent; the most common reason for dropout was HRT. There was an average of 21 months of collection per woman, and a total of 3,289 woman-months of data. Of the uncensored cases, there were 25 women who definitively made the transition to non-menstruating status.

We conducted an initial cross-sectional analysis of the first-year bleed data for women who had provided at least 150 of 182 possible daily samples (n=105 out of 141). Cycle length is highly variable at all ages, with women experiencing between zero and eleven menstrual cycles in the six-month study period. The variation is greatest between 40 and 55 years of age; there is much lower variation at later ages, when many women are menopausal. The first-year progesterone and estradiol data for the same sample of women show that, like the bleed data, there is a large amount of within- and across-woman variation in the steroid levels. The variation is greatest between ages 45 and 50, and the highest absolute values for the steroids occur in this age range.

We report the changes in cycle lengths and in steroid means and variances with age, and measure the proportion of variation in cycle length and in steroid levels that are attributable to within- and across-woman differences, using MLwiN, a multilevel modeling package.