

EDITORIAL

Chronicling of female endocrinology -from “waltz” to the “tango” of transition

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The menstrual cycle has long been simplistically viewed from the lens of procreative competence; realization that menses may serve as a surrogate for a woman’s overall reproductive wellness is a recent acquisition. Ample insights have been gleaned into the female hormonal milieu of the pinnacle reproductive years, driven as much by intellectual curiosity of great minds, as by the market potential that attainment of cycle regulation, fertility optimization, and effective contraception foster. Efforts aimed at improving our understanding of endocrinology of the years when the reproductive capacity is waning remain disproportionately sparse. However, limited data have nonetheless chronicled a choppiness in the reproductive hormone milieu before the still waters of menopause are finally entered.

There are some identifiable reasons that may underlie the paucity of information on the endocrinology of the menopause transition. A recent onset of unpredictability of menstrual cycles and an unanticipated onslaught of vasomotor symptoms may be the first signs of entry into the transition for many—the predictable waltz-like steps of premenopause that subsequently get upstaged by a “spirited tango” of the transition, may allow little time for “preparedness” or even “preemptive” evaluation. Given that the timing of sample collection for hormonal assessment in a menstrual cycle impacts data interpretability, when cycles become unpredictable, the process of sample collection gets onerous and even imprecise. Due to the pulsatile release of pituitary and ovarian reproductive hormones, biologic sampling aimed at characterizing profiles requires frequent sample collections daily over an over an entire menstrual cycle to fully capture the

subtle hormonal fluxes that occur from hour to hour and day to day. Daily measurements, while necessary to allow an understanding of the intra and interindividual cycle variability, however, are burdensome for both the participant and the researcher.¹⁻³ The onset of menstrual irregularity of transition only makes the sampling process more arduous.

Although much has been learnt from cross-sectional studies about the endocrinology of the menopause transition, it is the information gleaned from cohort studies, which has allowed an understanding of how the hormone profiles change over time. Validity of data require that a woman must be sampled at steady intervals to establish a within-person hormonal trend over time.⁴ It is only through the study of reproductive hormones in cohorts of women being followed longitudinally, from the premenopausal period, through the transition until well beyond the final menses, that a reliable understanding of the reproductive endocrinology across stages of reproductive aging and the relationship of hormone profiles with clinical events can be achieved.⁴ Lastly, while reproductive hormones have been studied in blood, urine, and saliva, the preponderance of our understanding of the endocrinology of transition is founded on serum-based reproductive hormone assays and profiles. Serum and urinary measurement of gonadotropins and sex hormones shows agreement and can be used interchangeably in young, reproductive-aged females; however, the perpetuation of these agreements has not been validated in women as they approach menopause.^{3,5}

The Daily Hormone Study (DHS) in the Study of Women’s Health Across the Nation (SWAN) is a community-based, multicenter, longitudinal study, that has furthered our understanding of the endocrinology and symptomatology of the menopause transition.⁶ Middle-aged women of multiethnic origins contributed daily urine collections for one complete menstrual cycle or 50 consecutive days (whichever came first) annually until the woman’s final menstrual period or up to 10 years, respectively. In all, 953 SWAN participants were enrolled in the DHS subgroup, of which 511 patients had completed at least one DHS collection and also had observed cessation of menses within 10 years, and therefore, were included in the analysis.⁶ Patient characteristics (body mass index, lifestyle factors, racial/ethnic background), menstrual cycle patterns, and urinary hormone profiles (luteinizing hormone [LH], follicle-stimulating hormone [FSH], estrone conjugates [E1c], and pregnanediol glucuronide [Pdg]) were

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documented. The SWAN DHS showed that the menstrual cycle hormone patterns of women remained consistent with mid-reproductive age women until 5 years preceding menopause. Particularly, almost 88% of cycles maintained evidence of luteal activity until 5 years before menopause, whereas nearly a quarter (23%) showed evidence of luteal activity until 1 year before complete cessation of menses.⁶ Interestingly, urinary gonadotropins remained stable up until 3 years before menopause at which point they began to rise, whereas the luteal PdG excretion showed a slow, steady decline until menopause.⁶

In the current issue of *Menopause*, Santoro et al evaluate the data from the SWAN DHS to report on the urinary and serum hormone profiles as women approach the 6th decade of life; authors are primarily focusing on luteal phase hormone alterations.⁷ A subset of women from the SWAN DHS had an additional single luteal (day 16-24) serum sample for progesterone level drawn during the DHS collection cycle allowing an examination of the concordance between studied serum and urinary hormone. Critical to this study was determining whether serum gonadotropins, estradiol, and progesterone (P) correlated with urinary gonadotropins, Etc, and PdG, and therefore could be used interchangeably in women approaching menopause. The authors have shown that both serum and urinary gonadotropins and sex hormone measurements maintain a close association, and thus, both modalities can be utilized as indicators of reproductive hormone milieu in women into their 6th decade of life.

A single serum luteal P level is commonly obtained to assess luteal function in reproductive age women, with a level >3ng/mL deemed as a threshold to reflect ovulation; while serum P level at or above the threshold offers a high sensitivity and specificity, the test is invasive, requiring a blood draw.^{5,8-10} Assays of urinary metabolites of progesterone such as PdG, after correcting for urinary creatinine, have been validated in young, healthy women and can also be utilized to assess ovulation.^{3,11} In this study, an assay for integrated-luteal uPdG was used to represent multiple measurements over the entire luteal phase, an approach that allows a more comprehensive assessment of the endocrinology of the luteal phase and function of the corpus luteum. The authors observed a weak correlation between a single serum luteal P when compared with integrated-luteal uPdG levels in the studied population. Others have previously shown that uPdG levels decline as women traverse into menopause; in the SWAN DHS cohort, Santoro et al observed a similar trend in serum P with levels demonstrating a marginal decline with approaching menses cessation ($P = 0.04$).

Understanding the undulations of the reproductive hormone profile as women approach and transition into menopause can help earmark physiologic alterations that underlie symptoms and may serve as potential indicators or mediators of disease. The better grasp one has on the hormonal milieu during the endocrinologically dynamic phase of transition, the better one will be equipped to anticipate and address symptoms and harness potential risks. Santoro et al provided us with a first glance at the luteal hormone profile of women as they approach the 6th decade of life, and established that urine and serum reproductive hormones continue to show a close relationship during this transition in a woman's life. The authors' quest to better understand if a single serum P level in women approaching menopause can be a reliable indicator of the integrated-luteal uPdG profile is commendable, albeit limited by the small population sample for the comparison of urinary and serum hormone data. Santoro et al not only have laid the foundations that allow an improved understanding of female reproductive endocrinology of women entering and traversing the transition, but also provide justification for a need for additional studies; authors observations, if substantiated in larger samples, will be of clinical utility in guiding clinicians' understanding of underpinnings to the prevalent symptomatic bother of transitioning women.

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