Hypoestrogenic “inactive phases” at the start of the menstrual cycle: changes with age and reproductive stage, and relationship to follicular depletion

Rebecca J. Ferrell, Ph.D.,[a] Germán Rodríguez, Ph.D.,[b] Darryl Holman, Ph.D.,[c] Kathleen O'Connor, Ph.D.,[c] James W. Wood, Ph.D.,[d] and Maxine Weinstein, Ph.D.[e]

[a] National Institute on Aging, National Institutes of Health, Bethesda, Maryland; [b] Office of Population Research, Princeton University, Princeton, New Jersey; [c] Department of Anthropology and Center for Studies in Demography and Ecology, University of Washington, Seattle, Washington; [d] Department of Anthropology and Population Research Institute, Pennsylvania State University, University Park, Pennsylvania; and [e] Center for Population and Health, Georgetown University, Washington, D.C.

Objective: To investigate hypoestrogenic “inactive phases” (IP) in the follicular phase of the menstrual cycle, with respect to age, reproductive stage, and follicular depletion.
Design: Analysis of prospectively collected menstrual bleed and estrone-3-glucuronide data.
Setting: Center for Population and Health, Georgetown University.
Patient(s): White women (n = 88, aged 25–59 years, mean = 44.7 years) from the population-based Biodemographic Models of Reproductive Aging (BIMORA) project.
Intervention(s): None.
Main Outcome Measure(s): The IP durations by age and reproductive stage. Estimated follicular depletion rate based on IP durations.
Result(s): Mean IP duration and variability decreased and then increased with age/reproductive stage. The proportion of very short (≤ 1 day) IP durations increased and then decreased with age/stage. Long IPs occurred most, but not exclusively, in the oldest age/latest stage. Follicular depletion rate estimates were a plausible 2%–4% per year of age, but these models were a poor fit because IP durations did not consistently increase across ages/stages.
Conclusion(s): Follicular depletion models alone do not explain the observed pattern of IPs. Our data suggest that IPs reflect both follicular depletion and hyperstimulation in premenopausal and perimenopausal women. Knowledge of underlying IP patterns in the menstrual cycle could inform decisions about hormone sampling and contraception during the perimenopause. (Fertil Steril® 2012;98:1246–53. ©2012 by American Society for Reproductive Medicine.)
Key Words: Follicular depletion, hypoestrogenic, inactive phase, female reproductive aging, perimenopause

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/ferrellrj-hypoestrogenic-age-reproductive-stage-follicular-depletion/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for “QR scanner” in your smartphone’s app store or app marketplace.

Received January 13, 2012; revised June 1, 2012; accepted July 10, 2012; published online August 14, 2012.
R.J.F. has nothing to disclose. G.R. has nothing to disclose. D.H. has nothing to disclose. K.O. has nothing to disclose. J.W.W. has nothing to disclose. M.W. has nothing to disclose.
Dr. Ferrell contributed to this article in her personal capacity. The views expressed are her own and do not necessarily represent the views of the National Institutes of Health or the United States Government.
Supported by grants NIH R01AG015141, NIH R01HD034159, NIH F32HD007994, and NIH R24HD042828.
Reprint requests: Rebecca J. Ferrell, Ph.D., National Institute on Aging, National Institutes of Health, 7201 Wisconsin Avenue, Room 2C212, Bethesda, MD 20892 (E-mail: rebecca.ferrell@nih.gov).

Fertility and Sterility® Vol. 98, No. 5, November 2012 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2012.07.1101

Population-level, longitudinal studies show characteristic changes in menstrual cycle length as women age (1, 2). Mean cycle length and variability reach a minimum during late premenopause, and shorter cycles are interspersed with longer cycles during perimenopause, even after mean cycle length begins to increase (1–5). Increased mean cycle length and substantially elongated menstrual cycles (>60 days) are hallmarks of late perimenopause (6).

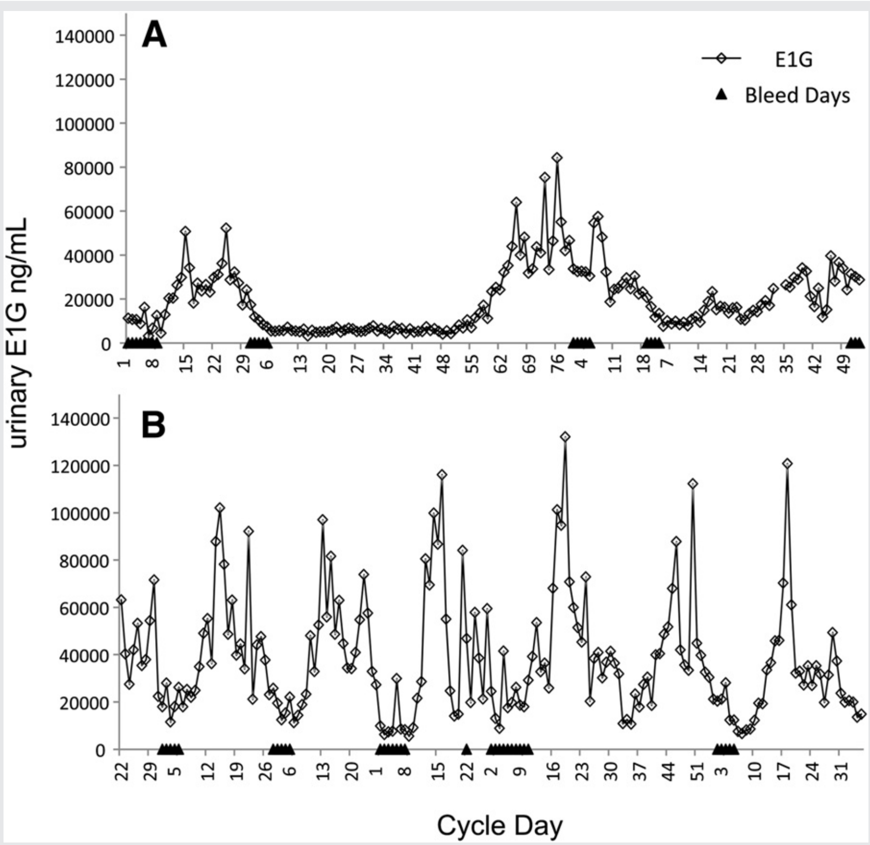
A primary determinant of cycle length variability is follicular phase length, which varies in both premenopausal and perimenopausal women (7–9). Miro et al. (9) have shown that it is the early portion of the follicular phase, before an increase in E_2 level, that varies most as women age. The proximate causes of shorter and longer follicular phases are not fully established; however, growing evidence implicates advanced, out-of-phase, and delayed initiation of follicular development with reproductive aging (7, 10–12).

Short follicular phases appear to be related to follicular development that begins earlier in the menstrual cycle in older compared with younger reproductive-aged women (12). Hale et al. (10) identified out-of-phase onset of follicular growth from daily E_2 in both long and short cycles in perimenopause, where follicular growth of a new cohort begins during the luteal phase of an already ovulatory cycle (3, 13, 14). Long follicular phases, in contrast, are thought to be related to delayed follicular development. Hypoestrogenic "inactive phases" (IP) (Fig. 1) have been observed at the start of menstrual cycles, most often in perimenopausal women (3, 7, 10, 15–20), and have been identified as a primary cause of elongated menstrual cycles associated with reproductive aging (7). During an IP, a woman's hormone profile appears postmenopausal, with low steroid hormone levels and fluctuating gonadotropin levels resulting from release of steroid negative feedback (16, 18, 19, 21–23).

Here we define an IP as the interval (long or short) starting just after the decline of E_2 level associated with the previous cycle's luteal phase to the substantial increase in E_2 level during the follicular phase. We use IP data from the Biodemographic Models of Reproductive Aging (BIMORA) project (24) to explore age-related changes in IP duration (length) using a flexible piecewise exponential hazards model. The outcomes of interest are the durations of IPs for four age categories (<40, 40–44, 45–49, 50+ years) and three reproductive stages (premenopausal, early perimenopausal, and late perimenopausal).

In addition, we test an existing model that explicitly connects IPs with the follicular depletion process, where age and IP duration are linked to depletion rate and follicle pool size (18, 19). This model is consistent with data from postmortem and ultrasound follicle counts (25–29) indicating constant or accelerating rates of depletion, with the accelerating rate (29) supported by recent analyses (30–32). The rationale for the model is that IPs are a stochastic consequence of a dwindling follicle pool, and there will be

FIGURE 1



Six-month profiles of estrone-3-glucuronide (E1G) and menstrual bleeds for two women. (A) age 47 years, perimenopausal. The long menstrual cycle in the center of the profile begins with an inactive phase of approximately 50 days in length. (B) age 41 years, late premenopausal, with several short inactive phases.

Ferrell. Inactive phases and follicular depletion. Fertil Steril 2012.