Published in final edited form as:

Obstet Gynecol. 2008 July ; 112(1): 101–108. doi:10.1097/AOG.0b013e31817d452b.

The Relationship of Bleeding Patterns to Daily Reproductive Hormones in Women Approaching Menopause

Bradley J. Van Voorhis, M.D.¹, Nanette Santoro, M.D.², Sioban Harlow, Ph.D.³, Sybil L. Crawford, Ph.D.⁴, and John Randolph, M.D.³

¹Department of Ob-Gyn, University of Iowa College of Medicine, Iowa City, Iowa, United States, 52242

²Department of Ob-Gyn, Albert Einstein College of Medicine, Bronx, NY, United States, 10461

³Department of Ob-Gyn, University of Michigan College of Medicine, Ann Arbor, Michigan, United States, 58104

⁴University of Massachusetts Medical School, Worcester, Massachusetts, United States 01655

Abstract

Objective—To discover early hormonal predictors of menopause and the stages of the menopausal transition, and to understand the hormonal basis behind the bleeding abnormalities common in the menopausal transition.

Methods—A cohort of 804 women aged 42–52 collected daily first void urine samples for one complete menstrual cycle or 50 days (whichever came first) once a year for 3 years. Urine was assayed for excreted levels of follicle-stimulating hormone, luteinizing hormone, estrogen metabolites, and progesterone metabolites which were normalized for creatinine concentration. Anovulation was defined by an algorithm based on progesterone secretion. Menstrual bleeding parameters were derived from daily calendars. Correlations between bleeding characteristics, hormone concentrations, and other potential clinical predictors were analyzed using multivariable logistic regression models.

Results—An ethnically diverse population of women (mean age of 47) with a majority in the early perimenopause was studied. Approximately 20% of all cycles were anovulatory. Short cycle intervals (fewer than 21 days) were common early in the menopause transition and were associated with anovulation (44%). Long cycle intervals (more than 36 days) also were associated with anovulatory cycles (65%). Both short (1–3 days) and long (more than 8 days) duration of menstrual bleeding were associated with anovulation, 18% and 23%, respectively. Women with anovulatory cycles were less likely to report heavy menstrual bleeding as compared to those with ovulatory cycles. Heavy bleeding was not associated with steroid hormone concentrations but was associated with obesity and with the self-reported presence of leiomyomata.

Conclusion—Among women in the early menopause transition, abnormalities in timing of menstrual bleeding (cycle intervals or bleeding duration) have a hormonal basis and are frequently associated with anovulation. In contrast, abnormally heavy periods do not appear to have a steroid hormonal basis and are less likely after anovulatory cycles. Heavy periods are associated with obesity and leiomyomata.

Corresponding author: Bradley J. Van Voorhis, M.D., Department of Obstetrics and Gynecology, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242, Telephone: 319-356-4536 Fax: 319-353-6659 Email: brad-van-voorhis@uiowa.edu.

For other participants in this study, see the Appendix online at www.greenjournal.org/cgi/content/full/112/7/xxx/DC1.

Financial Disclosure: The authors have no potential conflicts of interest to disclose.

Introduction

Changes in both timing and amount of menstrual bleeding are common in the menopausal transition, but the underlying mechanisms are incompletely understood. In a population-based survey of Australian women between the ages of 45 and 55, women were asked to compare their menstrual periods in the preceding 3 months with periods occurring 12 months prior to the survey. 30 % reported no change, 10 % reported a change in bleeding frequency but not in amount, 22% reported a change in amount but not in frequency, 26% reported a change in both frequency and amount, and 12% reported 3 months of amenorrhea (1). Several longitudinal studies have demonstrated that menstrual cycles become more irregular in the years prior to the final menstrual period (2,3,4). In contrast to the typically regular cycles experienced by younger women, older premenopausal women often have shorter cycle intervals early in the transition and then longer menstrual cycle intervals later in the transition and this cycle irregularity defines the onset of the menopause transition (5).

Changes in the timing of menstrual bleeding, especially longer cycle intervals, are commonly thought to be secondary to anovulation which becomes more frequent as women age. We hypothesized that changes in amount of bleeding and, particularly, heavy bleeding in the menopausal transition might also have a hormonal basis. A study of daily hormone dynamics found that, compared to younger cycling women, 11 perimenopausal women (age 43–52) had increased urinary excretion of follicle stimulating hormone and estrone conjugates with decreased excretion of progesterone (6). Relative hyperestrogenism, if commonly present in the menopause transition, might contribute to gynecologic morbidity, including heavy bleeding.

The Study of Women's health Across the Nation (SWAN) is a multisite, multiethnic longitudinal study of midlife women. Among the goals of SWAN is the characterization of the reproductive hormone patterns that occur in women as they approach and traverse the menopausal transition and correlation of these hormonal changes with menstrual bleeding patterns in these women. By associating hormonal changes with menstrual bleeding patterns, two objectives might be met. First, early hormonal predictors of menopause and the stages of the menopausal transition might be discovered. This might, in turn, justify the clinical measurement of hormone levels in women in the menopausal transition for diagnostic or prognostic purposes. Secondly, the hormonal basis behind the bleeding abnormalities that are so common in the menopausal transition will be better understood.

Material and Methods

Study design

SWAN is a cohort study of 3302 middle-aged women enrolled at seven sites throughout the United States. The design of the main cohort study has been reported previously (7). All women participating in SWAN completed interviewer- administered questionnaires detailing their complete medical history including prior diagnoses of uterine fibroids, thyroid disorders, and diabetes. For fibroid determination, women were asked "Has a doctor, nurse practitioner or other health care provider ever told you that you had fibroids, benign growths of the uterus or womb?" The Daily Hormone Study (DHS) is a sub-study of SWAN in which a subset of women (n = 804) collected first morning voided urine samples daily for one complete menstrual cycle or 50 d (whichever comes first) once a year. Details on specimen collection have been published previously (8). In the present communication, we report findings from the urine samples collected in the first 3 years of the study. We measured the excreted levels of FSH, LH, estrone conjugates (E1c), and pregnanediol glucuronide (PdG). We then used these measurements in validated algorithms (9) to evaluate the menstrual cycles for features consistent with ovulation and corpus luteum function.

Participant population

A subset of women from all SWAN clinical sites was enrolled in the DHS and recruitment details have been previously published (6). This study was approved by all of the sites' Institutional Review Boards, and written informed consent was obtained from each participant. The baseline cohort for SWAN included women of Caucasian (n = 1550), African (n = 935), Chinese (n = 250), Japanese (n = 281), and Hispanic (n = 286) ethnic origins who were aged 42–52 years. Inclusion criteria for recruitment into the DHS were: 1) an intact uterus and at least one ovary, 2) at least one menstrual period in the previous three months, 3) no use of sex steroid hormones in the previous three months, and 4) not pregnant. Women eligible for the DHS were categorized in terms of menopausal status at the onset of the study as well as at each yearly visit prior to the onset of daily urine collections. Premenopausal status was defined as menses in the past three months, with no change over the past year in predictability of menstrual periods. Early perimenopausal status was defined as menses in the past 3 months, with less predictable periods (1,10). Late perimenopause was defined as ≥ 2 skipped cycles and an interval of amenorrhea of ≥ 90 days.

Hormone assays

LH, FSH, Elc, and PdG were measured using newly adapted chemiluminescent assays, previously described (8). Data were normalized for creatinine (Cr) concentration (11). Total-cycle integrated hormone concentrations were also analyzed. Technically, hormone excretion in the urine is being measured. However, this has been shown to correlate closely with hormone production (12) so, for the purposes of clarity, these measures will be considered to reflect LH, FSH, estradiol and progesterone production in this paper.

Evaluation of cycles

A significant increase in PdG concentrations was accepted as evidence of luteal activity, which is consistent with presumed ovulation by a validated algorithm (13). The algorithm locates the 5 nadir days of PdG in the follicular phase using moving averages throughout the cycle. A 3-fold increase in PdG concentrations above this nadir for at least 3 consecutive days was considered evidence of ovulation. Cycles with no evidence of ovulation were further subdivided into those in which the collection ended due to the onset of a bleeding episode or those in which the collection was automatically terminated at 50 days without bleeding. For each of the four hormones, mean daily hormone concentration within a collection was computed as the sum over the collection of a woman's observed daily hormone divided by the total number of daily observations in the collection.

Menstrual period characteristics

Cycle interval and days of bleeding were derived from women's menstrual calendars kept concurrently with urine collection and subsequently. Women were asked to record menstrual bleeding as it occurred, distinguishing spotting, light/moderate bleeding, and very heavy bleeding. Normal menstrual cycle characteristics were defined by values in the literature (14) and consisted of cycle intervals of 21–35 days and duration of bleeding of 4–7 days. Hormone production was correlated with menstrual bleeding characteristics of the period immediately following the daily urine collections. Cycles that did not terminate in bleeding within 7 days of the end of daily urine collections were excluded from analysis due to the belief that associations between daily urinary hormones and subsequent bleeding would be unclear in such cases.

Statistical Analysis

Baseline characteristics of the sample were summarized using frequencies for categorical variables and medians and minimum/maximum for continuous variables. Frequency

distributions of cycle interval and bleeding characteristics were estimated separately for each annual visit. Longitudinal correlates of cycle interval and bleeding characteristics were identified using separate random effects logistic regression models for each outcome (15) to account for within-woman correlation over time. Because proportional odds logistic regression models did not provide an adequate fit to the data- that is, the chi-square test for proportional odds indicated that this assumption was violated, each of the outcomes was modeled using two separate binomial logistic regressions, comparing a reference category to each of the other categories; for example, predictors of short cycles versus normal-length cycles and long cycles versus normal-length cycles were identified in two separate binomial logistic regressions. Predictors included evidence of luteal activity, baseline categorized body mass index (BMI), over- or underactive thyroid at baseline, self-reported fibroids at baseline, diabetes, age, menopause status, mean daily hormone concentrations (adjusted for creatinine), baseline smoking, ethnicity, and region (Eastern, Midwest and West Coast US, included in models using two dummy variables). Backward elimination was used to omit redundant or irrelevant covariates from multivariate models; the resulting statistically significant predictors were similar to those from models including all candidate predictors (results not shown). To handle right-skewness, hormone variables were log-transformed; for ease of interpretation, odds ratios from logistic regressions are presented in terms of comparing the 75th percentile to the 25th percentile, as a 1-unit change in the log-transformed versions would be difficult to interpret. For time-varying predictors (evidence of luteal activity, self-reported fibroids, age, menopause status, and daily hormones), models were adjusted for both baseline values and change in the predictor since baseline (e.g. baseline age and time on study).

Results

Of 848 cycles collected at the baseline visit, eight cycles started with a surge of LH and an increase in PdG, suggesting that periovulatory bleeding occurred and cued women to begin their urine collection at the wrong time, and were not included in subsequent analyses. An additional 36 baseline observations were missing covariate data and also were excluded, yielding an analytic sample of 804 women. We studied an ethnically diverse population of women with a median age of 47 years at the start of the study (range 43.1 to 54.1 years- Table 1). At baseline, a large majority (73%) of these women were in the early perimenopause characterized by experiencing recent variable cycle lengths. Most women were not smokers and 28% of women were obese. 21% reported that they had ever been diagnosed with fibroids. Because there were study drop-outs, characteristics of women participating at visits 2 and 3 are also reported (Table 1).

The most common cycle characteristics included a cycle interval of 21–35 days, a menstrual bleeding duration of 4–7 days, and no days characterized as heavy flow days (Table 2). There was little change in the prevalence of the various cycle characteristics over this 3 year time frame. 20% of all cycles were anovulatory in this population of women. Anovulatory cycles were common in women with short cycle intervals and even more common in women with long cycle intervals (Table 2).

As compared to women with a normal cycle interval, short cycle intervals were more common in older women and as they transitioned into the early perimenopause (Table 3). Anovulation in the concurrent cycle was a risk factor for having a short interval, regardless of ovulatory status at baseline. Women with short cycle intervals had lower daily production of FSH and higher daily production of Elc.

Long cycle intervals were associated with anovulation and transition to the perimenopause (Table 3). Longer cycle intervals were seen more commonly later in the transition and were

associated with greater production of FSH, lower production of progesterone, and the presence of diabetes. (Table 3).

Both short (1–3 days) and long (8+ days) durations of bleeding in the next menstrual period were associated with anovulation as compared to periods with a normal (4–7 days) duration of menstrual bleeding (Table 4). Women with fibroids were also more likely to have a long menstrual period. After correction for anovulation, daily and integrated hormone production had no independent effect on the number of days of bleeding during subsequent menses.

Women with heavy menstrual flow in the current cycle were less likely to have had an anovulatory cycle regardless of whether they had an ovulatory or anovulatory cycle at the baseline study cycle (Table 5). Other factors associated with heavy periods were the reported presence of uterine fibroids and a BMI of 30 and above. The only hormonal association with heavy menses was elevated production of FSH at the baseline cycle. Conversely, in the concurrent cycle, reduced production of FSH was associated with 1–2 days of heavy bleeding. No other hormonal measures, either daily or integrated, predicted heavy bleeding.

Factors that had no independent effect on menstrual cycle characteristics included ethnicity, smoking history and medical conditions including thyroid disorders and diabetes.

Discussion

Menstrual bleeding irregularities are a hallmark of the menopausal transition but frequently result in women seeking gynecologic consultation (16). Although an overwhelmingly probable marker of the normal transition, bleeding irregularity raises concerns about possible pregnancy, endometrial hyperplasia or gynecologic malignancy and leads to diagnostic and therapeutic interventions including hysterectomy. Hysterectomies are more common as women approach the menopause transition with a median age of hysterectomy being 45 in the United States (17). The major indication for hysterectomy is uterine fibroids although at least 10% of hysterectomies are done for menstrual bleeding disorders as the primary diagnosis.

We have confirmed that anovulation is highly associated with variability in the *timing* of menstrual bleeding. Fully 20% of cycles were found to be anovulatory in this group of women predominantly in the early perimenopause. Anovulation was associated with both short and long cycle intervals as well as both short and long duration of the ensuing menstrual period. Short cycle intervals are seen more often early in the menopausal transition. Thus, short intervals may be the first sign of women entering the transition, while longer cycle intervals are seen later and are associated with higher FSH production indicating even fewer functioning ovarian follicles. The presence of fibroids also is associated with a greater chance of having a longer duration of bleeding.

In contrast to timing issues, an increased *amount* of bleeding is not positively associated with anovulation. In fact, anovulatory cycles were more often associated with lighter bleeding in the following menstrual period. Heavy bleeding was associated with obesity and with the self-reported presence of uterine fibroids. In contrast to our initial hypothesis, we could find no association between heavy bleeding and either estrogen (E1c) or progesterone (PdG) production when evaluated as mean daily production, cycle integrated production, or when expressed as ratios of E1c to PdG production.

Given the higher prevalence and symptomatology of fibroids among African-Americans, we expected to see ethnic differences in reports of heavy bleeding. In fact, there were statistically significant *unadjusted* ethnic differences of 3+ heavy bleeding days versus no heavy bleeding with African Americans and Hispanics more likely and Chinese and Japanese women less likely to have this complaint compared to Caucasians (data not shown). Adjustment for

prevalent fibroids reduced the ethnic differences slightly but they remained statistically significant. Upon further adjustment for BMI, ethnic differences were no longer statistically significant, suggesting that any perceived ethnic differences in reported heavy bleeding are accounted for primarily by BMI differences.

Our findings would suggest that, if a clinician encounters a woman in the early menopausal transition with abnormal timing of menstrual bleeding (short or long cycle intervals, short or long duration of menstrual bleeding), the first thought should be anovulation as the cause. In contrast, if the complaint is only heavy bleeding, then anovulation is less likely and careful evaluation for structural lesions including polyps and fibroids is warranted. The association of heavy bleeding with obesity is interesting and also concerning given the epidemic of obesity in the United States.

Strengths of this study include the large and ethnically diverse population being studied. In addition, this is a large prospective study evaluating daily hormone production over an entire menstrual cycle. Hence, we can accurately correlate hormone production with menstrual bleeding patterns.

Weaknesses of the study lie primarily in the determination of heavy bleeding, which was by self-report. Several studies have shown a lack of correlation between the subjective complaint of heavy bleeding and objectively measured blood loss. However, more recent reports have found that, depending on the types of questions asked, there is a better correlation between a woman's report of heavy bleeding and measured blood loss (18,19). We simply asked women to record days when they experienced "very heavy bleeding". From a practical standpoint, objective measures of actual blood loss during menses are not performed clinically, so our reliance on a woman's self-report may mimic clinical practice. Another weakness was the reliance on self-report for uterine fibroids. Since fibroids are known to be somewhat more common than the 21% rate reported in our study, it is likely that some were missed and only the larger and more clinically significant fibroids were discovered and reported by the women. In addition, it is known that polyps can lead to abnormal bleeding and no systematic means of detecting these lesions was performed.

This large study of hormonal production in the early menopause transition confirms a hormonal basis for changes in menstrual cyclicity and timing. Shortened menstrual cycle intervals are the earliest change in the transition and these cycles are often anovulatory. Longer menstrual cycle intervals are more common later in the menopause transition and are also associated with anovulation. Both longer and shorter duration of bleeding in a menstrual period are also associated with anovulation. Contrary to our original hypothesis, we found no evidence for a hormonal basis for heavy bleeding in the early menopause transition. Therefore, evaluation of estrogen, progesterone, LH or FSH levels in women with this complaint is not warranted. Instead, attention should be directed towards obesity or lesions including polyps or fibroids as possible causes.

Acknowledgements

The authors thank the study staff at each site and all the women who participated in SWAN.

The Study of Women's Health Across the Nation (SWAN) received grant support from the National Institutes of Health, DHHS, through the National Institute on Aging, the National Institute of Nursing Research and the NIH Office of Research on Women's Health (Grants NR004061; AG012505, AG012535, AG012531, AG012539, AG012546, AG012553, AG012554, AG012495).

References

1. Dudley EC, Hopper JL, Taffe J, Guthrie JR, Burger HG, Dennerstein L. Using longitudinal data to define the perimenopause by menstrual cycle characteristics. *Climacteric* 1998;1:18–25. [PubMed: 11907922]
2. Treloar AE, Boynton RE, Behn BG, Brown BW. Variation of the Human Menstrual Cycle through Reproductive Life. *Int J Fertil* 1967;12:77–126. [PubMed: 5419031]
3. Treloar A. Menstrual Cyclicity and the Pre-Menopause. *Maturitas* 1981;3:249–264. [PubMed: 7334935]
4. Taffe JR, Dennerstein L. Menstrual patterns leading to the final menstrual period. *Menopause* 2002;9:32–40. [PubMed: 11791084]
5. Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). *Fertil Steril* 2001;76:874–878. [PubMed: 11704104]
6. Santoro N, Rosenberg Brown J, Adel T, Skurnick JH. Characterization of Reproductive Hormonal Dynamics in the Perimenopause. *J Clin Endocrinol Metab* 1996;81:1495–1501. [PubMed: 8636357]
7. Sowers MF.; Crawford SL.; Sternfeld B. SWAN: a multicenter, multiethnic community-based cohort study of women and the menopausal transition. In: Lobo, RA.; Kelsey, J.; Marcus, R., editors. *Menopause: biology and pathobiology*. Vol. eds. New York: Academic Press; p. 175-188.
8. Santoro N, Crawford SL, Allsworth JE, Gold EB, Greendale GA, Korenman S, et al. Assessing menstrual cycles using urinary hormone assays. *Am J Physiol Endocrinol Metab* 2003;284:E521–E530. [PubMed: 12441312]
9. Prior JC. Perimenopause: the complex endocrinology of the menopausal transition. *Endocr Rev* 1998;19:397–428. [PubMed: 9715373]
10. Brambilla DJ, McKinlay SM, Johannes CB. Defining the perimenopause for application in epidemiologic investigations. *Am J Epidemiol* 1994;140:1091–1095. [PubMed: 7998591]
11. Taussky HH. A microcolorimetric determination of creatinine in urine by the Jaffe reaction. *J Biol Chem* 1954;208:835–861.
12. Waller K, Swan SH, Windham GC, Fenster L, Elkin EP, Lasley BL. Use of urine biomarkers to evaluate menstrual function in healthy premenopausal women. *Am J Epidemiol* 1998;147:1071–1080. [PubMed: 9620051]
13. Kassam A, Overstreet JW, Snow-Harter C, De Souza MJ, Gold EB, Lasley BL. Identification of anovulation and transient luteal function using a urinary pregnanediol-3-glucuronide ratio algorithm. *Environ Health Perspect* 1996;104:408–413. [PubMed: 8732951]
14. Wood C, Larsen L, Williams R. Menstrual Characteristics of 2,343 Women Attending the Shepard Foundation. *Aust NZ J Obstet Gynaec* 1979;19:107–110.
15. Molenberghs, G.; Verbeke, G. *Models for discrete longitudinal data*. New York: Springer; 2005.
16. Santoro N. The menopause transition: an update. *Hum Reprod* 2002;8:155–160.
17. Farquhar C, Steiner C. Hysterectomy Rates in the United States 1990–1997. *Obstet Gynecol* 2002;99:229–234. [PubMed: 11814502]
18. Warner PE, Critchley HO, Lumsden MA, Campbell-Brown M, Douglas A, Murray G. Menorrhagia I: Measured blood loss, clinical features, and outcome in women with heavy periods: A survey with follow-up data. *Am J Obstet Gynecol* 2004;190(5):1216–1223. [PubMed: 15167821]
19. Warner PE, Critchley HO, Lumsden MA, Campbell-Brown M, Douglas A, Murray G. Menorrhagia II: Is the 80-mL blood loss criterion useful in management of complaint of menorrhagia? *Am J Obstet Gynecol* 2004;190(5):1224–1229. [PubMed: 15167822]

Table 1

Characteristics of participants at each visit

	N (%) or median (range)		
	Baseline	1 st followup	2 nd followup
Ovulatory status:			
Ovulatory	652 (81.1)	470 (79.0)	373 (78.5)
Anovulatory	152 (18.9)	125 (21.0)	102 (21.5)
Concurrent age in years – median (minimum – maximum)	47.1 (43.1 – 54.1)	47.8 (44.1 – 54.8)	48.5 (45.0 – 56.0)
Menopausal Status			
Premenopausal	219 (27.2)	177 (29.8)	159 (33.5)
Early perimenopausal	585 (72.8)	418 (70.3)	316 (66.5)
Ethnicity			
Caucasian	247 (30.7)	186 (31.3)	146 (30.7)
African American	168 (20.9)	117 (19.7)	87 (18.3)
Chinese	149 (18.5)	116 (19.5)	96 (20.2)
Hispanic	74 (9.2)	47 (7.9)	33 (7.0)
Japanese	166 (20.7)	129 (21.7)	113 (23.8)
Baseline Smoking			
Never	519 (64.6)	386 (64.9)	322 (67.8)
Past	201 (25.0)	143 (24.0)	110 (23.2)
Current	84 (10.5)	66 (11.1)	43 (9.1)
Baseline body mass index (kg/m ²)			
Underweight/normal (<25)	364 (45.3)	276 (46.4)	233 (49.1)
Overweight (25–29.9)	211 (26.2)	149 (25.0)	121 (25.5)
Obese (30 +)	229 (28.5)	170 (28.6)	121 (25.5)
Baseline Thyroid Condition	45 (5.6)	37 (6.2)	28 (5.9)
Baseline Fibroids	169 (21.0)	123 (20.7)	101 (21.3)
Baseline Diabetes	45 (5.6)	30 (5.0)	20 (4.2)
N	804	595	475

Table 2

Cycle interval and bleeding characteristics by yearly visit.

	Visit 1: N (%)	Visit 2: N (%)	Visit 3: N (%)	% anovulatory ^(a)
Cycle interval (days):				
< 21	40 (5.0)	31 (5.2)	29 (6.1)	44.1
21–35	630 (78.4)	445 (74.8)	354 (74.5)	8.1
36+	134 (16.7)	119 (20.0)	92 (19.4)	64.7
Total N for observed cycle interval	804	595	475	
Flow days:				
1–3	71 (10.9)	45 (9.7)	29 (7.7)	17.6
4–7	493 (75.7)	335 (72.0)	279 (74.4)	9.8
8+	87 (13.4)	85 (18.3)	67 (17.9)	23.2
Heavy-flow days:				
0	343 (52.7)	240 (51.6)	202 (53.9)	18.3
1–2	251 (38.6)	189 (40.7)	144 (38.4)	5.9
3+	57 (8.8)	36 (7.7)	29 (7.7)	11.1
Total N for observed flow outcomes	651	465	375	

^(a) Estimated from repeated measures logistic regression models including data from all three visits

Table 3

Independent factors associated with a short cycle interval (<21 days) or a long cycle (36+ days) compared to a normal cycle interval (21–35 days), from logistic regression with backward elimination

Factor	Short cycle vs. normal cycle: 1529 observations – 100 short and 1429 long – from 712 women Odds ratio (95% CI) ^(a)	Long cycle vs. normal cycle: 1774 observations – 345 long and 1429 normal – from 792 women Odds ratio (95% CI)
Baseline ovulatory status/concurrent ovulatory status:		
Ovulatory – Ovulatory	Reference	Reference
Ovulatory – Anovulatory	11.98 (5.44, 26.37)	1.39 (0.68, 2.82)
Anovulatory – Ovulatory	0.31 (0.03, 3.15)	3.53 (1.28, 9.80)
Anovulatory – Anovulatory	10.61 (5.12, 21.96)	2.86 (1.56, 5.23)
Baseline age (1-year difference)	1.18 (1.05, 1.31)	__ ^(c)
Time since baseline (1-year increase)	0.97 (0.69, 1.36)	__ ^(c)
Baseline menopause status / concurrent menopause status:		
Pre – pre	Reference	Reference
Pre – early peri	5.02 (1.89, 13.34)	2.51 (1.16, 5.47)
Early peri – early peri	1.12 (0.57, 2.17)	1.81 (1.07, 3.06)
Baseline fibroids	1.83 (1.04, 3.20)	__ ^(c)
Baseline diabetes	__ ^(c)	2.06 (1.00, 4.22)
Baseline mean daily FSH ^(b)	0.76 (0.54, 1.07)	2.03 (1.67, 2.48)
Change since baseline in mean daily FSH ^(b)	0.72 (0.64, 0.81)	1.21 (1.14, 1.30)
Baseline mean daily PdG ^(b)	__ ^(c)	0.31 (0.23, 0.41)
Change since baseline in mean daily PdG ^(b)	__ ^(c)	0.65 (0.57, 0.73)
Baseline mean daily E1c ^(b)	1.51 (1.10, 2.07)	__ ^(c)
Change since baseline in mean daily E1c ^(b)	1.14 (1.04, 1.25)	__ ^(c)

^(a) Also adjusting for region of country

^(b) Odds ratio computed comparing 75th percentile to 25th percentile of log-transformed hormone variable

^(c) Excluded from model using backward elimination

Table 4

Independent factors associated with either a short (1–3 days) or long (8+ days) duration of menstrual bleeding compared to an average duration (4–7 days), from logistic regression using backward elimination

Factor	Short period vs. average duration: 1252 observations – 145 short and 1107 normal – from 649 women Odds ratio (95% CI)	Long period vs. average duration: 1346 observations – 239 long and 1107 normal – from 669 women Odds ratio (95% CI)
Baseline ovulatory status/concurrent ovulatory status:		
Ovulatory – Ovulatory	Reference	Reference
Ovulatory – Anovulatory	1.78 (0.79, 4.02)	3.92 (2.25, 6.81)
Anovulatory – Ovulatory	0.72 (0.15, 3.48)	2.26 (0.90, 5.68)
Anovulatory – Anovulatory	2.36 (1.22, 4.59)	2.46 (1.41, 4.27)
Baseline fibroids	— ^(a)	1.46 (1.01, 2.13)

^(a) Excluded from model using backward elimination

Table 5

Independent factors associated with days of heavy bleeding during a menses, from logistic regression using backward elimination

Factor	1–2 heavy days vs. 0 heavy days: 1369 observations – 584 1–2 heavy days and 785 0 heavy days – from 665 women Odds ratio (95% CI)	3+ heavy days vs 0 heavy days: 907 observations – 122 3+ days and 785 0 heavy days – from 509 women Odds ratio (95% CI) ^(a)
Baseline ovulatory status/concurrent ovulatory status:		-- ^(b)
Ovulatory – Ovulatory	Reference	
Ovulatory – Anovulatory	0.32 (0.16, 0.63)	
Anovulatory – Ovulatory	1.21 (0.42, 3.46)	
Anovulatory – Anovulatory	0.15 (0.07, 0.33)	
Baseline BMI:	-- ^(b)	
Underweight / normal	Reference	Reference
Overweight		1.55 (0.80, 2.99)
Obese		2.59 (1.36, 4.94)
Baseline fibroids	2.24 (1.48, 3.40)	1.90 (1.07, 3.39)
Baseline mean daily FSH ^(c)	1.28 (1.02, 1.61)	-- ^(b)
Change since baseline in mean daily FSH ^(c)	0.92 (0.86, 0.98)	-- ^(b)

^(a) Adjusting for region of country

^(b) Predictor omitted in backward elimination

^(c) Odds ratio computed comparing 75th percentile to 25th percentile after adjustment for ovulatory status