JOURNAL OF WOMEN'S HEALTH
Volume 13, Number 8, 2004

Determination of Menopausal Status in Women: The NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study

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ABSTRACT

Purpose: **Accurate classification of menopausal status is important to epidemiological research evaluating the role of reproductive hormones in disease processes. Algorithms relying on repeat hormone assays are unfeasible in large epidemiological studies. This paper summarizes the development of the Women's Ischemia Syndrome Evaluation (WISE) Hormonal menopausal status algorithm for determining premenopausal, perimenopausal, and postmenopausal status using menstrual and reproductive history and reproductive hormone levels obtained at a single clinic visit.**

Methods: **The authors compared the accuracy of this algorithm with two currently used self-report algorithms: Menstrual, based only on months since last menstrual period, and Historical, which adds age and surgical history.**

Results: **The study population consisted of 515 women (329 clearly postmenopausal) enrolled in the WISE study who were undergoing coronary angiography for suspected ischemia. A subgroup of 186, not clearly postmenopausal, was classified by these three algorithms. Results were evaluated against individualized expert consensus classification. The Menstrual and Historical classifications differed significantly ($p < 0.0001$) from expert consensus, with**

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This work was supported by contracts from the National Heart, Lung and Blood Institute, N01-HV-68161, N01-HV-68162, N01-HV-68163, and N01-HV-68164, grant MO1-RR00425 from the National Center for Research Resources, and grants from the Gustavus and Louis Pfeiffer Research Foundation, The Women's Guild, Cedars-Sinai Medical Center, the Ladies Hospital Aid Society of Western Pennsylvania, and QMED, Inc.

32%–26% discordant classifications, respectively. For the WISE Hormonal classification, discordance was 4%.

Conclusions: **The authors conclude that inaccurate classifications of menopausal status occur frequently in self-report algorithms. Use of the relatively simple WISE algorithm can improve the accuracy of menopausal status classification for epidemiological research.**

INTRODUCTION

ACCURATE DETERMINATION OF MENOPAUSAL status is important to epidemiological research evaluating the role of reproductive hormones in various disease processes. Declining ovarian estrogen secretion during perimenopause and menopause has been implicated in bone loss and susceptibility to fractures,[1,2] decline in cognitive function,[3,4] reduced physical functioning,[5] changes in body mass and fat distribution,[6,7] glucose intolerance and diabetes,[8,9] the development of cardiovascular risk factors,[10–14] carotid atherosclerosis,[12,15] cardiac syndrome X,[16,17] and coronary disease.[18] The relatively low frequency of ischemic heart disease deaths prior to the menopause has suggested a protective effect from ovarian function in women,[19] a concept indirectly supported by animal research studies,[20–22] observational epidemiological studies of women who undergo premature natural or surgical menopause,[23–25] and recent Women's Ischemia Syndrome Evaluation (WISE) findings linking estrogen deficiency and coronary artery disease (CAD) in premenopausal women.[26] The role of menopausal status *per se*, as opposed to aging, in these disease processes remains a matter of debate, as such relationships are not uniformly found.[27,28]

Menopause is the cessation of ovarian steroid hormone secretion as a result of the depletion of oocytes and surrounding follicular apparatus. This is a gradual process characterized by menstrual cycle and endocrine changes. The beginning of menopause in women without a hysterectomy is defined as the final menstrual period that is confirmed retrospectively after 12 months of amenorrhea,[29,30] although some women report intermittent vaginal bleeding after that interval.[31] Although varying widely, the median age at natural menopause is around 51 years,[32] but it can occur normally as early as age 40. Perimenopause has been variously defined either as beginning with the first break in menstrual cycle regularity[33–35] or as amenorrhea of 3–11 months[36] that occurs at a median of 47.5 years[32] and lasts up to 1 year after the final menstrual period.[36,37]

Prior investigations of a link between menopausal status and health status in large populations have been limited by methodology. Measures relying on timing of the last menstrual period, menstrual regularity, and menopausal symptoms[35,36] necessarily exclude women with premenopausal hysterectomies without bilateral oophorectomies[38] and may be inaccurate for irregularly cycling women. Other studies using such measures have erroneously classified young women with hysterectomies but intact ovaries as having "surgical menopause."[39,40] In order to include women with hysterectomies in their study samples, some investigators have classified women with a hysterectomy but at least one ovary as premenopausal if they were younger than 55 years,[15] an age where 95% of women are postmenopausal.[41] Conversely, classification systems relying exclusively on hormone levels,[41–43] may be subject to poor reliability[44] and large swings in hormone levels during the perimenopause.[33] What is needed is a classification method that is not only accurate but also inclusive and practical for use in large populations.

The recently convened Stages of Reproductive Aging Workshop (STRAW) has identified seven stages of normal reproductive aging in women.[29] Placement of a woman in any one of these stages relies primarily on regularity of menstrual cycles and follicle-stimulating hormone (FSH) levels while considering chronological age and concomitant estradiol (E_2) levels. For maximum accuracy, the conference panel recommended that women keep prospective menstrual calendars, to return on certain days of their cycle for repeat serum or urine sampling if hormone levels are questionable, and to undergo ultrasonography or other imaging of the uterus. Clearly, such intensive patient contact is not feasible in most large epidemiological and clinical investigations. Moreover, the STRAW committee stated that this staging system could not be accurately applied under

the following conditions: cigarette smoking, extremes of body weight (body mass index [BMI]<18 or >30 kg/m^2), heavy exercise, chronic menstrual cycle irregularity, prior hysterectomy, abnormal uterine anatomy (e.g., fibroids), or abnormal ovarian anatomy (e.g., endometrioma). This effectively excludes as many as half of all women and, therefore, is of limited usefulness in populations undergoing various disease processes.

The WISE is National Heart, Lung and Blood Institute (NHLBI)-sponsored, four-center study designed to improve the diagnostic reliability of cardiovascular testing in the evaluation of ischemic heart disease in women.[45] One of the major objectives of the WISE is to evaluate the influence of cyclical hormones, menopausal status, and blood reproductive hormone levels on cardiovascular physiology, symptoms, and diagnostic testing results. The WISE investigators have developed an algorithm for classifying menopausal status that combines menstrual and reproductive history with serum hormone assays. This algorithm is best suited for larger investigative studies that afford only one patient contact and permits reasonably accurate determination of premenopausal, perimenopausal, and postmenopausal status, including women with hysterectomies.

MATERIALS AND METHODS

Study population

We examined 515 women, aged 21–86 years, undergoing a clinically ordered angiogram for suspected myocardial ischemia. Because of the FSH-suppressive action of oral contraceptive (OC) use, women currently on OC were not included in these determinations. Similarly, because blood hormonal effects vary by hormone therapy (HT) preparation[46,47] we excluded women currently on HT. Baseline evaluation for all women included clinical measures; demographic, medical, and reproductive histories; psychological and anginal symptom evaluations; blood drawn for WISE core laboratory hormone and lipid assays; and core laboratory quantitative assessment of coronary angiograms.[45]

Reproductive status questionnaire

The WISE reproductive status questionnaire includes a history of menarche, date of last menstrual period, current and prior menstrual cycling patterns, reproductive events (pregnancy, hysterectomy, oophorectomy), menopausal symptoms (e.g., hot flashes, night sweats), and history of OC and HT use. As the questionnaires were personally administered by trained study coordinators, the subjects were able to ask questions while responding to specific items, and coordinators were able to clarify responses. This information was collected at baseline, prior to the work of the WISE hormone committee. Neither the patients nor the study coordinators were aware how this information would be used in classifying menopausal status.

Reproductive hormone analysis

Blood for reproductive hormone determinations was drawn following an overnight fast within 1 week of WISE baseline evaluation. All blood draws were performed when the patient was available, without consideration of her menstrual cycle. Validated steroid and protein assay methods were used by the WISE hormone core laboratory to determine levels of total E_2, bioavailable estradiol (bioE_2), estrone (E_1), pro-gesterone (PO), FSH, and luteinizing hormone (LH).[48] For FSH, the Diagnostics Products Corporation (Los Angeles, CA) coat-a-count kits were used. The assay was calibrated against the WHO Second International Reference Preparation of Pituitary FSH (ICSH) human for bioassay (coded 78/549). Specimens were assayed in batches of 150–350, and each determination was measured in duplicate. The core laboratory is experienced in performing reproductive hormone level determinations for NIH-sponsored studies, such as the Postmenopausal Estrogen and Progesterone Intervention (PEPI) study.[49] Previous work from this laboratory has demonstrated the sensitivity and the between-assay coefficients of variation (CV), respectively, to be 15% and 16% for E_2, 8% and 12% for E_1, and 3.7% and 4.2% for bioE_2.[28]

Expert consensus individualized menopausal determination

The WISE menopausal status algorithm was developed by the WISE hormone committee, which included two reproductive endocrinologists (G.D.B., S.L.B.), two clinical cardiologists (C.N.B.M., V.B.), a statistician (B.D.J.), and a nurse (T.K.H.). Each member of the hormone committee examined the complete data available for each

patient, including the patient's age, BMI, smoking, whether she had a hysterectomy with or without bilateral or unilateral oophorectomy, whether the cycles (if present) were regular or irregular, months or days since last menstrual period, and levels of serum FSH, LH, E_2, E_1, and PO. Each member then classified the patient into premenopausal (follicular, luteal, or midcycle, if possible), postmenopausal, perimenopausal, or unclear, including a group of women we eventually classified as having hypothalamic hypoestrogenemia or hypothalamic amenorrhea or both. Following these preliminary classifications, the committee as a group reviewed and adjudicated menopausal status for each of 186 individual women who could not definitely be classified as postmenopausal.

For example, woman 1 is a 52-year-old African American woman without a hysterectomy, with three pregnancies, BMI 30.2, who reports a history of menopausal symptoms but no HT. Her last menstrual period occurred 8 months ago. She has smoked for over 20 years. Her medical history includes diabetes, congestive heart failure, and balloon angioplasty. Hormone levels are $E_2 = 33$, $E_1 = 67$, FSH = 31.7, LH = 29.4, PO = 0.26. The Menstrual algorithm classified her as perimenopausal, the Historical algorithm as premenopausal, and the Hormonal algorithm as postmenopausal. The hormone committee decided that her final menstrual period had occurred and adjudicated her to be postmenopausal.

Woman 2 is a 48-year-old white woman who had a hysterectomy at age 28, with both ovaries left intact. She has been pregnant four times. Her BMI is 29.8, and she reports current menopausal symptoms and a brief use of HT at age 44. She has been a smoker since age 15. Her medical history includes balloon angioplasty, cancer, and depression. Her hormone levels are $E_2 = 30$, $E_1 = 82$, FSH = 28, LH = 4.1, PO = 0.39. The Menstrual algorithm classified her as postmenopausal, the Historical algorithm as premenopausal, and the Hormonal algorithm as perimenopausal. The hormone committee adjudicated her to be (late) perimenopausal.

In a few cases, historical and hormone variables could not be reconciled, and the study coordinators were requested to clarify HT use ($n = 4$) or verify the self-reported surgical information ($n = 8$). After the hormone committee reached consensus, the algorithm was established by looking at the most important variables that would allow one to arrive at the same conclusion as the experts. Results from the expert consensus classifications represent the reference standard against which the three following algorithms were evaluated. Each algorithm represents incremental information used for classifying women.

Algorithms

Menstrual menopausal status algorithm. For comparison, we classified all women according to the frequently used Menstrual algorithm of menopausal status determination, a classification system used, with several variations, in many large-scale epidemiological investigations of women.[12,14,50,51,52] All women were asked to provide the date of their last menstrual period. Women who were amenorrheic in the preceding 12 months were classified as postmenopausal, those amenorrheic in the preceding 3–12 months were classified as perimenopausal, and all other women were classified as premenopausal (Fig. 1).

Historical menopausal status algorithm. This algorithm considered additional questionnaire information to the Menstrual algorithm, such as age and surgical history. Thus, if a woman had a hysterectomy, at least one intact ovary, and was <55 years of age, she was classified as premenopausal (Fig. 2). Because of the inclusion of women with hysterectomies, with no confirmatory menstrual cycling information, no attempt was made to use this algorithm to classify perimenopausal status.[53]

WISE Hormonal menopausal status algorithm. The WISE Hormonal algorithm was developed ancillary to the ongoing individualized hormone committee classifications. This was an iterative process that involved simplifying the classification process into a decision tree, testing the re-

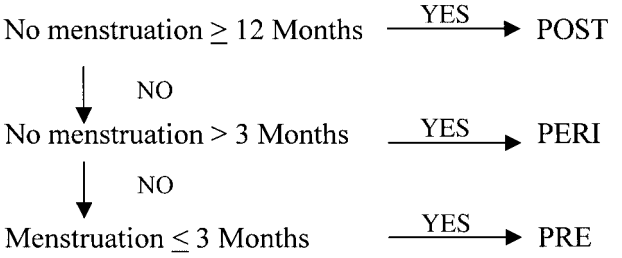

FIG. 1. Single time self-report Menstrual algorithm. PRE, premenopausal; PERI, perimenopausal; POST, postmenopausal.

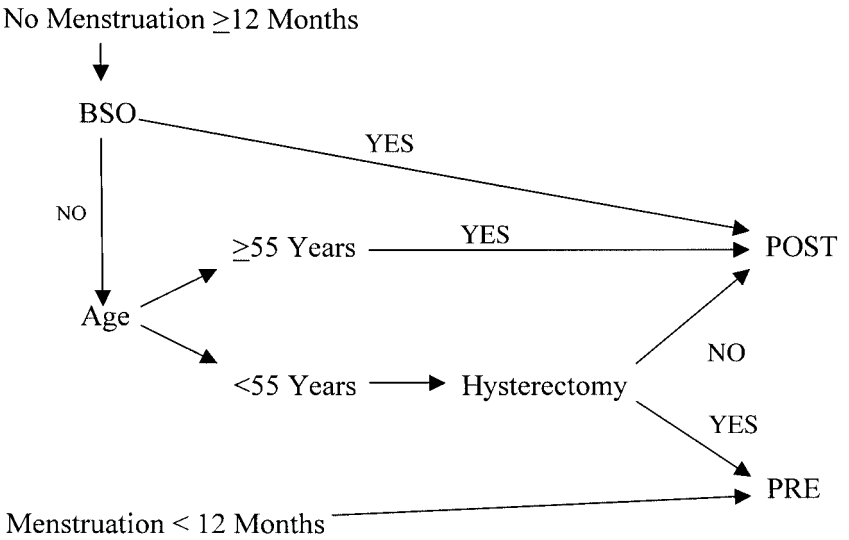

FIG. 2. WISE Historical algorithm. PRE, premenopausal; PERI, perimenopausal; POST, postmenopausal; BSO, bilateral salpingo-oophorectomy.

sulting algorithm against the committee's classifications, rediscussing women with divergent committee and algorithm classifications, and reformulating the algorithm. Through this iteration procedure, we developed consistent classifications and rules. The flow diagram depicted in Figure 3 summarizes the rules and decisions generated through this process.

The first step of the algorithm divides women into five categories according to their current menstrual status: (1) definitely postmenopausal, (2) regular cycling, (3) irregular cycling, (4) no menstrual period in the past 12 months without hysterectomy, and (5) no menstrual period in the past 12 months with hysterectomy. Definitely postmenopausal women were those who either had had a bilateral salpingo-oophorectomy (BSO) or were aged >55 years and amenorrheic. Women reporting regular menstrual periods during the preceding 12 months (Fig. 3A) were assumed to be premenopausal, and reproductive hormone levels were used to corroborate this assumption. Women reporting irregular menstrual periods during the preceding 12 months were equally likely to be premenopausal or perimenopausal and required additional reproductive information, such as hormone levels, age, and last menstrual period, in order to be classified. Among women without a menstrual period during the preceding 12 months (Fig. 3B), those without a hysterectomy had a high probability of being postmenopausal. If they did not fit the postmenopausal hormone profile (E_2<50, FSH≥20), their cases were more closely examined for other possible reasons for their amenorrhea (e.g., hypothalamic amenorrhea[26]). Women with a hysterectomy lacked the menstrual confirmation of their menopausal status. For these women, the combination of age and reproductive hormone levels was used for classification.

Verification

Although true verification requires testing the algorithm in other populations, we used two methods to verify or further describe our classifications. One was to compare basic classification variables among the following subgroups of women aged <55 years: those with self-reported (1) regular cycles, (2) irregular cycles, (3) no menstrual periods and no hysterectomy, (4) BSO, and (5) amenorrheic women without hysterectomy or BSO. The second method relied on follow-up information to determine menstrual status and regularity for women classified as premenopausal, perimenopausal, and postmenopausal by the WISE Hormone algorithm at 6 weeks and 1 year of follow-up. The 6-week follow-up, limited to a maximum interval of 3 months, provided an indication of test-retest reproducibility of self-reported menstrual history. The 1-year follow-up (range 10–25 months) determined whether women without hysterectomies who were classified as premenopausal or perimenopausal continued

to have menstrual periods and whether those classified as postmenopausal did not resume menstruating.

Statistical analysis

Classifications via the three algorithms were compared with the individualized expert consensus menopausal determination. For each algorithm, the number correct for each status is the number of women correctly identified by the algorithm to have that status. Sensitivity, specificity, predictive value, and overall predictive accuracy were derived for each classification within each algorithm. These proportions were then compared across the three algorithms using chi-square analysis. The classifications were compared with the expert consensus adjudications by the kappa measure of agreement. Kappas were computed by comparing classification into a specified menopausal status group vs. all others. For example, classification as premenopausal was compared against classification as perimenopausal or postmenopausal. According to standard convention, a kappa>0.75 was considered very good agreement.[54]

RESULTS

The demographic and menopausal characterization of the overall study participants is shown in Table 1. The WISE population age ranged from 21 to 86 years, and 41% had CAD, defined as ≥50% stenosis in ≥1 coronary artery. Overall, 19% of the women had BSO, and 43% were ≥55 years of age and amenorrheic for a year or more without BSO. These women (n = 321) were automatically classified as postmenopausal. This status was verified by their hormone profiles in virtually every case. In the few (n = 7) discrepant cases, we requested their medical and surgical charts and found in all cases that the woman had not correctly reported her surgical history (e.g., hysterectomy with at least one ovary left intact). Of the remaining 194 women, 4% had information missing on at least one relevant reproductive variable (current HT use, BSO, hysterectomy, menstrual history). No woman aged ≥55 years reported a menstrual period within the prior 12 months.

Among the 186 women who were not automatically classified as postmenopausal, were not on HT or OC, and had complete data required for the WISE Hormonal algorithm (Table 1), ages ranged from 21 to <55 years, and 28% were nonwhite minorities (primarily African American). Most (69%) of the women had at least two cardiac risk factors, half (50%) were obese, a third (30%) were current smokers, and 27% had CAD; 24% of these women had had a hysterectomy without BSO. Notably, 88% of these women had underlying conditions that would render the STRAW staging system inapplicable. By WISE expert consensus hormone committee determinations, 66% were premenopausal, 17% were perimenopausal, and 17% were postmenopausal.

Comparison of menopausal status determination by three algorithms

Comparative frequencies of menopausal status classifications by the three algorithms are shown in Table 2. Because of the inherently low agreement for women with hysterectomy (kappa< 0.10), Table 2 is presented only for those women (n = 141) without hysterectomy. One major difference among these three tools was the ability to classify women as perimenopausal. The criterion of "months since last period = 3–12," used in the menstrual algorithm, identified only 3 women (2%) as perimenopausal, compared with the WISE Hormonal algorithm, which classified 23 women (16%) as perimenopausal. For reasons cited previously, perimenopausal status was not determined by the Historical algorithm. For women without hysterectomy, both the Menstrual and Historical algorithms overclassified women as premenopausal (kappa = 0.50–0.60), whereas the agreement for postmenopausal status was very good (kappa = 0.86).

The major benefit of the WISE Hormonal algorithm lay in its ability to identify perimenopausal women, with a kappa = 0.90. When combining the women with and without hysterectomy (data not shown), the highest kappa measure of agreement was 0.49 (postmenopausal) for the Menstrual algorithm and 0.62 (postmenopausal) for the Historical algorithm, indicating that agreement with the expert consensus adjudications was good. For the Hormonal algorithm, the kappa statistics exceeded 0.90 for all menopausal statuses. The specific shifts are illustrated in Figure 4. A woman classified as premenopausal by the Menstrual algorithm continued to be premenopausal by the Historical algorithm. Women

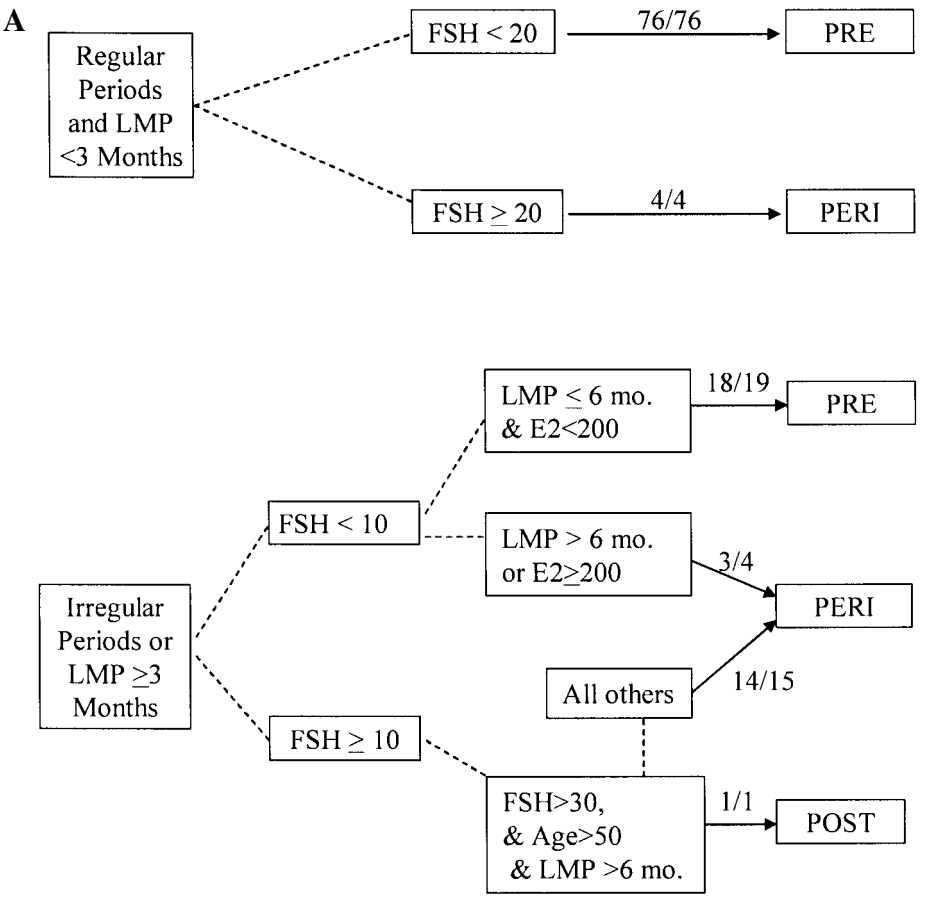

FIG. 3. (**A**) WISE Hormone algorithm for women who are not currently on HT or OCs. Women with menstrual period < 12 months. PRE, premenopausal; PERI, perimenopausal; POST, postmenopausal; E_2, estradiol; FSH, follicle-stimulating hormone; LMP, time since last menstrual period. Numerator, number of women assigned to status by WISE Hormone algorithm; denominator, number of women assigned to status by expert consensus adjudication.

classified as postmenopausal by the Menstrual algorithm were more likely to be reassigned to premenopausal by the Historical algorithm. About 75% of the classifications by the Historical algorithm retained their status when reclassified by the WISE Hormone algorithm.

Comparison of algorithms with expert consensus individual menopausal classification

Sensitivities, specificities, and predictive values for each algorithm are shown in Table 3. The Menstrual algorithm performed relatively well with the premenopausal classification, the most common classification in this population, but was notably inaccurate in classifying women as perimenopausal, with a sensitivity of 6%. The postmenopausal classification had a sensitivity of 94% and predictive value of 45%, indicating that although at least 9 of 10 truly postmenopausal women were correctly identified, a postmenopausal classification was accurate in less than half of the women, producing a high percentage of false negatives. The Historical algorithm did not perform much better for either the premenopausal or postmenopausal women but had a slightly better overall predictive accuracy than the Menstrual algorithm (74% vs. 68%). The WISE Hormonal algorithm was able to correctly classify 96% of all women. Of the remaining 4% (8 women), 4 were misclassified and 4 fell into the hand-code category of the algorithm. The following is a summary of these misclassifications (or lack of agreement between expert adjudication and Hormonal algorithm):

Woman 1. Age 45, no hysterectomy, irregular cycles (the last was 10 days ago), not a smoker, BMI 41.2, classified by all three algorithms as premenopausal. E_2 = 28, E_1 = 58, FSH = 7.6, LH =

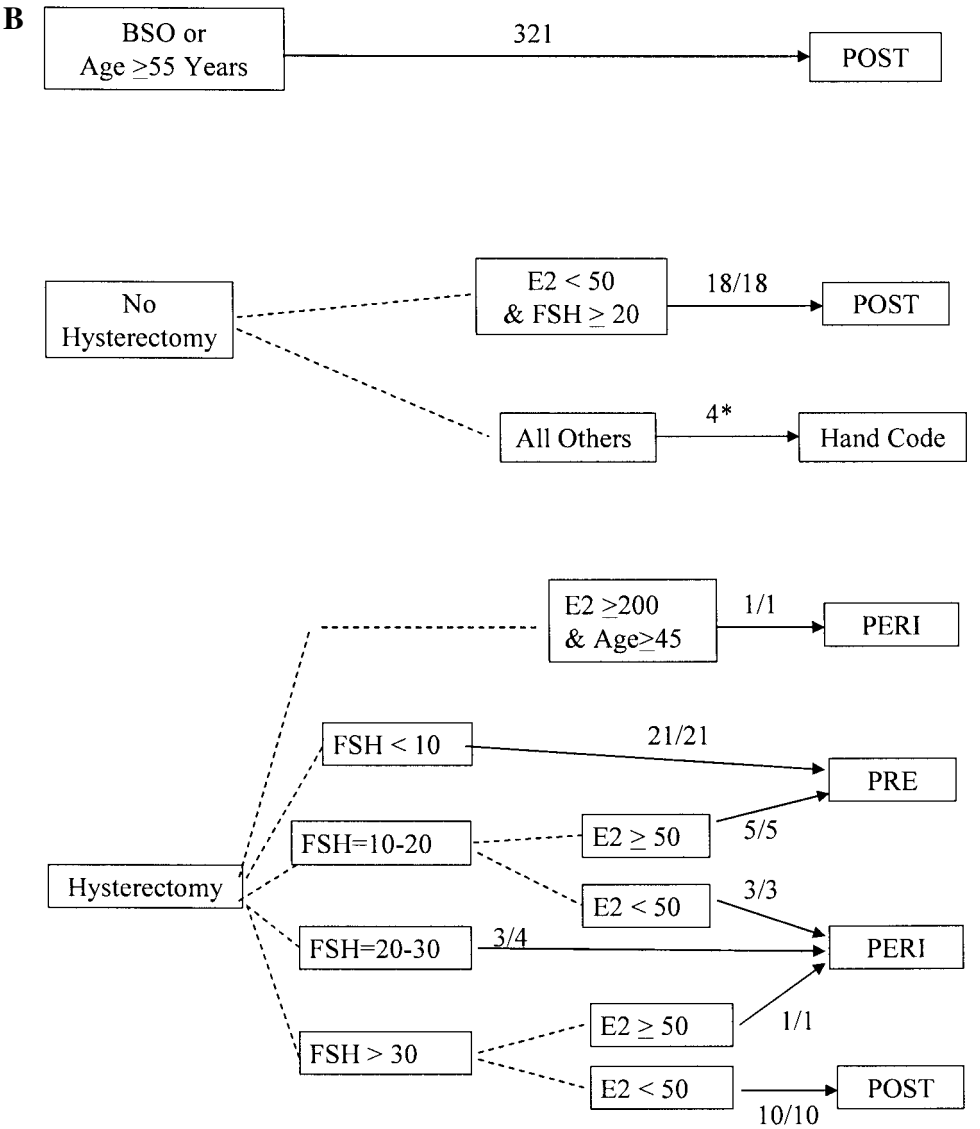

FIG. 3. (**B**) WISE Hormone algorithm for women who are not currently on HT or OCs. Women with no menstrual period < 12 months. Three of the women were either premenopausal or perimenopausal. Their amenorrhea was due to other physical causes (e.g., hypothalamic amenorrhea). PRE, premenopausal; PERI, perimeno-pausal; POST, postmenopausal; E_2, estradiol; FSH, follicle-stimulating hormone; LMP, time since last menstrual period; BSO, bilateral salpingo-oophorectomy. Numerator, number of women assigned to status by WISE Hormone algorithm; denominator, number of women assigned to status by expert consensus adjudication.

4.4, PO = 1.03. The hormone committee classified her as perimenopausal. The combined age, history of irregular cycles, and hormone profile suggested oligoovulation or an inadequate luteal phase, which can occur during the perimenopause.

Woman 2. Age 31, no hysterectomy, irregular cycles, not a smoker, BMI 21.5, classified by Menstrual and Historical algorithms as premenopausal and by Hormonal algorithm as perimenopausal. E_2 = 390, E_1 = 264, FSH = 1.6, LH = 22.2, PO = 3.77. The hormone committee adjudicated that the hormone profile was more consistent with premenopausal and follicular (ovulating).

Woman 3. Age 53, hysterectomy with ovaries intact, not a smoker, BMI 32.3, classified by the Menstrual algorithm as postmenopausal, by Historical algorithm as premenopausal, and by Hormoneal algorithm as perimenopausal. E_2 = 4.0, E_1 = 20, FSH = 28, LH = 54.1, PO = 0.16. The hormone committee adjudicated that the hormone profile was more consistent with postmenopausal status.

Table 1. Demographic, Clinical, and Reproductive Variables of Overall Population and Study Population

Variable	*Overall population* n = *515*	*Women classified by algorithms* n = *186*
Age in years (range)	58 (21–86)	45 (21–<55)
Race (% minority)	21	28
≥2 cardiac risk factors,[a] %	78	69
Obesity (BMI ≥30),[b] %	42	50
Current smoker, %	21	30
CAD (≥50% stenosis in ≥1 coronary artery), %	41	27
Reproductive history		
BSO	97 (19%)	0
No menses within 12 months and age ≥55 years (no BSO)	224 (43%)	0
All others	194 (38%)	—
Missing information[c]	8 (4%)	—
To be adjudicated by algorithm	186 (96%)	186
Hysterectomy	—	45 (24%)
Chronic menstrual irregularity	—	32 (17%)
Menstrual period(s) within last 12 months:		
Regular (%)	—	80 (43)
Irregular (%)	—	39 (21)
None (%)	—	67 (36)

[a]Risk factors include history of hypertension, dyslipidemia, diabetes mellitus, family history of CAD, current smoking.

[b]BMI, body mass index, calculated as (kg/m^2); CAD, coronary artery disease; BSO, bilateral salpingo-oophorectomy; SD, standard deviation.

[c]Missing information on HT use, current cycling, BSO, or hysterectomy.

Woman 4. Age 52, no hysterectomy, last menstrual period 5 months ago, smoker for 20 years, BMI 30.9, classified by Menstrual and Hormonal algorithms as perimenopausal and by Historical algorithm as premenopausal. $E_2 = 36$, $E_1 = 79$, FSH = 32.2, LH = 29.7, PO = 0.22. The hormone committee adjudicated that the hormone profile was more consistent with postmenopausal status and that the woman had experienced her final menstrual period.

Although they could not be automatically coded by the algorithm, an additional 8 women with missing reproductive historical information but complete hormone profiles were hand-coded. By evaluating reproductive hormone levels, the WISE expert consensus hormone committee was able to resolve all but 1 of these cases and assign them to a menopausal status group.

Verification

Table 4 gives the median age, reproductive hormone levels, time since last period, and expert consensus hormone committee menopausal status classifications of women with (1) self-reported regular cycles, or (2) irregular cycles, (3) amenorrheic, aged <55, without reproductive surgery, (4) BSO, and (5) amenorrheic, aged ≥55, without reproductive surgery. Groups 3 and 4 were very similar on all characteristics, except for a small difference in FSH. Only 1 woman with BSO had an FSH <20, and her surgical status was unavailable for verification. Of the women in group 5, 12 (5%) had an FSH <20, suggesting possible residual ovarian function beyond the natural cessation of menses. Although there was a trend indicating decreasing ovarian function for women with irregular cycles, both regulary and irregularly cycling women displayed wide variation in their reproductive hormone levels, confirming the assertion that cycling history or hormone levels, by themselves, are not sufficient for menopausal status classification.

Six-week and 1-year follow-up information was available for 69% and 77% of the women, respectively (Table 5). The 6-week data showed high test-retest reproducibility of self-reported menstrual cycling. Among premenopausal women, 98% of those reporting regular cycles at baseline continued to report regular cycles within 3 months follow-up, and 86% of those reporting irregular cycles at baseline continued to report ir-

TABLE 2. CROSS-CLASSIFICATION OF "MENSTRUAL," "HISTORICAL," AND "HORMONAL" ALGORITHM RESULTS VS. EXPERT CONSENSUS: DATA FOR WOMEN WITHOUT HYSTERECTOMY ONLY (n = 141)

	Expert consensus		*Expert consensus*		*Expert consensus*	
Algorithm	*PRE*[a] n = *97* *(+)*[b]	*Not PRE* n = *44* *(−)*	*PERI* n = *23* *(+)*	*Not PERI* n = *118* *(−)*	*POST* n = *21* *(+)*	*Not POST* n = *120* *(−)*
Menstrual						
(+)	95 (98%)	21 (48%)	1 (4%)	2 (2%)	19 (90%)	3 (2%)
(−)	2 (2%)	23 (52%)	22 (96%)	116 (98%)	2 (10%)	117 (98%)
Kappa[c]	0.57		0.04		0.86	
Historical						
(+)	95 (98%)	24 (55%)			19 (90%)	3 (2%)
(−)	2 (2%)	20 (45%)		[d]	2 (10%)	117 (98%)
Kappa	0.50				0.86	
Hormonal						
(+)	94 (97%)	1 (2%)	21 (91%)	2 (2%)	19 (90%)	0 (0%)
(−)	3 (3%)	43 (98%)	2 (9%)	116 (98%)	2 (10%)	120 (100%)
Kappa	0.93		0.90		0.94	

[a]PRE, premenopausal; PERI, perimenopausal; POST, postmenopausal.
[b](+), Classification (e.g., premenopausal) positive; (−), classification (e.g., premenopausal) negative.
[c]Kappa measure of agreement with expert consensus adjudications: 0.40–0.75, good agreement; 0.76–0.90, very good agreement; >0.90, excellent agreement.
[d]Perimenopausal status could not be ascertained by the WISE Historical algorithm.

regular cycles. Test-retest reproducibility was at 100% among perimenopausal and postmenopausal women. At 1-year follow-up, of the 57 premenopausal women with originally regular cycles, 10 (18%) became irregular and 2 (3%) reported no menstrual period within 1 year (an additional 2 women had hysterectomies). Of the 14 premenopausal women with originally irregular cycles, 4 (28%) claimed to resume regular cycling, and 2 (14%) reported no menstrual period within 1 year. Among the 20 total perimenopausal women, 13 (65%) had irregular cycles at 1-year follow-up, and 5 (25%) reported no menstrual period within 1 year. None of the 14 postmenopausal women with 1 year of follow-up resumed cycling. Our available prospective data thus demonstrate good test-retest reproducibility and overall consistency with menopausal status classification.

DISCUSSION

These results demonstrate that a relatively simple hormone algorithm that includes a one-time measurement of reproductive blood hormone

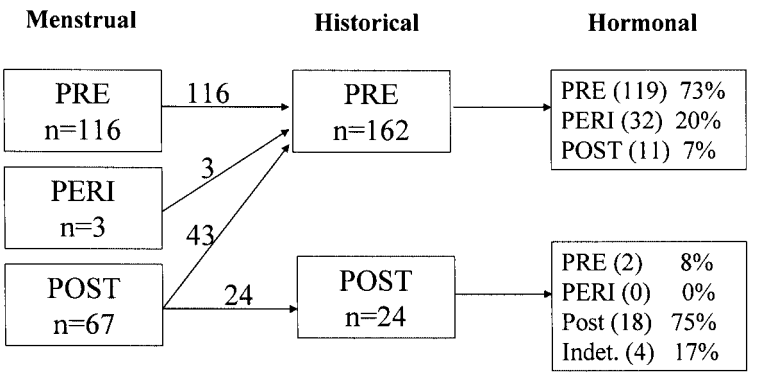

FIG. 4. Classification by algorithm. PRE, premenopausal; PERI, perimenopausal; POST, postmenopausal; Indet, indeterminate.

Table 3. Sensitivity, Predictive Value, and Predictive Accuracy (%) of Algorithms for Various Classifications. All Women Classified by Algorithms (n = 186)

	Simple Menstrual algorithm	*WISE Historical algorithm*	*WISE Hormonal algorithm*
Premenopausal			
Sensitivity	77**	97	97
Specificity	67**	32**	97
Predictive value	82**	73**	98
Perimenopausal			
Sensitivity	6**		88
Specificity	99		97
Predictive value	67		88
Postmenopausal			
Sensitivity	94	59**	85*
Specificity	76**	97	99
Predictive value	45**	79**	97
Predictive accuracy	68**	74**	96

[a]Perimenopausal status could not be ascertained by the WISE Historical algorithm.
Difference from perfect agreement with expert consensus: *$p < 0.01$; **$p < 0.0001$.

levels is practical and substantially enhances menopausal status classification compared with self-report algorithms. Application of the WISE Hormonal algorithm should be most useful in investigations in which repeated blood or urine measures, timed on specific days of the menstrual cycle, are not feasible. Most WISE women made only one clinic visit for completing in-person baseline questionnaires, diagnostic tests for ischemia, clinical measures, and a fasting blood draw, and our relatively simplified Hormonal algorithm produced a 96% accuracy overall compared with expert consensus individualized menopause determination. Although our one-time measure of blood hormones per woman necessarily provides only a snapshot measure of her true menopausal status, the WISE Hormonal algorithm is a probabilistic estimate that appears to be reasonably accurate and practical to use. Although the WISE data include fasting blood samples, it is likely that blood sampling could occur at any time for this purpose. Blood hormone levels are

Table 4. Age and Blood Reproductive Hormone Level Distribution across Selected Groups of Women, by Menstrual History

	Regular cycles n = *80*	*Irregular cycles* n = *39*	*No cycles, no hysterectomy, age <55*[b] n = *19*	*BSO, age <55* n = *30*	*No BSO or hysterectomy, no cycles, age ≥55* n = *224*
Age, years	44 (21–54)[a]	48 (31–55)	51 (43–54)	50 (40–54)	68 (55–85)
FSH[c] (mIU/ml)	4.8 (1.0–69.2)	5.6 (0.5–97.0)	47.3 (15.5–106.0)	52.2 (4.6–111.2)	48.5 (1.0–136.2)
LH (mIU/ml)	3.2 (0.2–22.2)	5.0 (0.2–35.5)	20.2 (7.3–39.0)	23.5 (9.8–55.1)	15.5 (0.2–64.8)
E_2 (pg/ml)	68 (2–292)	36 (7–390)	13 (3–34)	11 (4–30)	11 (1–65)
E_1 (pg/ml)	82 (29–344)	59 (12–274)	40 (14–70)	42 (3–96)	38 (4–244)
Bioavailable E_2 (pg/ml)	43 (1–160)	23 (3–158)	7 (2–16)	7 (1–23)	7 (1–42)
Progesterone (ng/ml)	0.54 (0.06–15.89)	0.36 (0.10–11.68)	0.24 (0.09–0.73)	0.25 (0.06–0.59)	0.21 (0.08–1.11)
Time since LMP	12 days (0–64)	24 days (0–249)	71 months (20–235)	182 months (17–458)	274 months (23–609)
Premenopausal[d]	95%	49%	0%	0%	0%
Perimenopausal[d]	5%	46%	0%	0%	0%
Postmenopausal[d]	0%	5%	100%	100%	100%

[a]Median (range).
[b]Excludes 3 women who were amenorrheic due to hypothalamic hypoestrogenemia.
[c]FSH, follicle-stimulating hormone; LH, luteinizing hormone; E_2, estradiol; E_1, estrone; LMP, last menstrual period.
[d]Menopausal status as determined by WISE hormone committee.

Table 5. Menstrual Cycling at 6 Weeks and 1 Year Follow-Up in Women without Hysterectomy

Baseline cycling history	At 6-week follow-up (3 weeks–3 months) n[b]	Regular cycles	Irregular cycles	No period for 12 months	At 1-year follow-up[a] (10–25 months) n[c]	Regular cycles	Irregular cycles	No period for 12 months
Premenopausal								
Regular cycles	52	98%	2%	0	57	79%	18%	3%
Irregular cycles	14	14%	86%	0	14	28%	57%	14%
Perimenopausal								
Regular cycles	4	100%	0	0	4	0	100%	0
Irregular cycles	15	0	100%	0	16	12%	56%	31%
Postmenopausal								
No cycles	12	0	0	100%	16	0	0	100%

[a]2-year follow-up was used when 1 year was not available.
[b]Number of women in each category with 6-week follow-up.
[c]Number of women in each category with 1-year follow-up.

stable in storage, and their determination is relatively economical when performed in batches for research purposes. Moreover, for practical purposes, blood hormone assays do not need to be performed for women who are clearly postmenopausal by other indicators (i.e., BSO, amenorrhea, and age ≥55 years in women without hysterectomy or age ≥60 in women with hysterectomy).

Menstrual and Historical algorithms are commonly used to classify women in large epidemiological studies. However, menstrual regularity and cycle length are not sufficient criteria for menopausal status determination. Self-reported regularity of menstruation is highly subjective[55] and subject to inaccurate recall[56] and cultural diversity.[57–58] According to recent work,[30] cycle lengths of 21–35 days are normal as long as deviations up to 14–56 days occur no more often than 1 of every 20 cycles. The onset of changes in flow during perimenopause is gradual and uneven,[35,52] and cycle length increases dramatically only just prior to the final menstrual period.[30,31] Because the final menstrual period can only be verified retrospectively (i.e., after 12 months of amenorrhea), it is possible that some women with < 12 months since their last cycle may have already experienced their final menstrual period.[59] The WISE algorithm considers this possibility highly probable if a woman is over the age of 50 and has an FSH level >30 mIU/ml. However, increased cycle length *per se* does not necessarily indicate that a woman has become perimenopausal. Other factors, such as hypoestrogenemia of hypothalamic origin, may be associa-ted with amenorrhea and irregular cycling.[20,22,26] Thus, cycle length was used to classify women only under exceptional circumstances.

Reproductive hormones alone are similarly not considered diagnostic of a woman's menopausal status.[60–63] Although FSH elevation is generally considered the first sign of reproductive aging, beginning in the late reproductive stage and occurring even in women aged ≥40 with regular cycles,[64,65] its diagnostic utility depends on the simultaneous levels of other reproductive hormones and age. FSH levels are highly variable across cycles[29] and are influenced by other factors, such as smoking and body weight.[66] A large study of women found that only 73% of women with FSH levels ≥20 mIU/ml were postmenopausal,[67] further confirming that FSH is only partially diagnostic. The predominant determinant of FSH is the E_2 level, which in turn responds to the death and growth of follicles, which are highly variable in perimenopause because of age-related decline in oocyte count.[56] Thus, E_2 levels in the perimenopause are characterized by drops and dramatic rises to levels that may greatly exceed those found in premenopausal women.[41,68] These increases are not consistent over cycles and across women.[69]

Several attempts have been made to develop a classification instrument based on symptoms[70] that occur frequently during the menopausal transition and are linked to hormone changes.[71] However, population studies have not consistently demonstrated a relationship between symptoms and menopause and show ethnic/racial differences.[72,73] Beginning during pre-

menopause, symptoms persist through perimenopause and tend to be most frequent in postmenopausal women.[74,75] Analysis of WISE data (not shown) has similarly found menopausal symptoms to be a poor indicator of menopausal status.

Our findings demonstrate that by combining menstrual and historical with reproductive hormone information, the WISE Hormonal algorithm provides greater accuracy than currently used self-report methods for classifying menopausal status. Among the 186 women not clearly postmenopausal, the Menstrual and Historical algorithms were inaccurate compared with the expert consensus individualized menopausal status classifications by 32% and 26%, respectively, compared with 4% for the WISE Hormonal status determination. These results suggest that the various algorithms currently being used in research produce highly divergent classifications and that misclassifications may affect study outcomes. Other algorithms, such as the STRAW staging system, may not be applicable to women in various disease cohorts; 88% of the WISE women had one or more abnormalities that would render the staging system inaccurate as defined by the STRAW investigators.[29]

The WISE Hormonal algorithm is an iterative and simplified version of the processes used by the WISE expert consensus hormone committee in adjudicating individual women. As such, it is a probabilistic classification and not a diagnosis. The hormone committee took into consideration the full complexity of individual variation, including reproductive and cycling history, cycle day of blood sampling, simultaneous hormone values, age, BMI, smoking, self-reported stress, prior history of severe and chronic illness, and medication usage. Although expert consensus is not easily accommodated into an algorithm, the WISE Hormonal algorithm achieved an overall predictive accuracy of 96%.

Limitations

Endocrine systems, such as the reproductive hormone axis in women, are necessarily dynamic, characterized by fluctuations in blood hormones within as well as across cycles. Serum hormone levels are further affected by such factors as obesity and smoking. Our single measure of circulating hormones may, therefore, lead to some inaccurate classifications of menopausal status. However, the current WISE Hormonal algorithm provides the best possible probabilistic determination, given the available data, in a relatively simplified algorithm that is practical for epidemiological investigation. Prior WISE reports have documented relationships between our measure of menopausal status and biological variables of significance, such as WISE-determined arterial function,[76] suggesting that these snapshot reproductive measures have validity in cardiovascular research in women. Naturally, the more information available, the better the classification. Therefore, the WISE Hormonal algorithm is not recommended for use in clinical practice, where more rigorous measures can be obtained. At present, the algorithm is also not suitable for distinguishing between intermediate stages, such as early perimenopause vs. late perimenopause. This level of distinction would require more detailed data collection, which is not available in most large-scale epidemiological investigations. The WISE Hormonal algorithm is currently not applicable for women taking hormones, such as OC and HT use. Evidence has shown that hormone levels of women on HT (including phytoestrogens and natural progesterones) are highly variable and differentially affected by various exogenous hormone preparations, doses, and methods of administration (e.g., patch, cyclic vs. continuous).[46,47] This information was not collected in WISE.

Although the WISE hormone committee includes two reproductive endocrinologists, classifications from this panel may not constitute the best reference standard for evaluating the accuracy of the algorithms. These classifications remain subjective and difficult to verify. The accepted gold standard for determining a woman's menopausal status includes the use of menstrual calendars and repeated blood or urine sampling standardized by cycle day. Moreover, because the Hormonal algorithm was developed in conjunction with the expert consensus classifications, there is the possibility of cross-contamination, such that the algorithm classifications may have influenced the hormone committee classifications. Thus, the high correlations between the Hormonal algorithm and expert consensus classifications are not surprising and merely serve to demonstrate that a relatively simple algorithm, suitable for computerized classification, can du-

plicate the individualized classification work of experts. The possibility exists that the predictive accuracy of the algorithm may be an overestimate of the algorithm's true predictive value when used in other settings and populations. It is, therefore, important that the WISE algorithms be verified in other populations of women participating in studies that are able to implement these more rigorous methods. To address these limitations, the WISE algorithm is currently being validated in the Study of Women's Health Across the Nation (SWAN) study.[77]

CONCLUSIONS

The current study findings have potentially widespread implications for epidemiological and clinical research in women. Whereas reproductive research investigators are knowledgeable about the inaccuracies of self-reported menopausal status determination, this message is underappreciated by the general research community. Single item self-reported menopausal status can be inaccurate, yet it has been and continues to be commonly used in health research in women.[25,35,36] Adding reproductive questions and hormone levels, such as the WISE Hormonal algorithm, can achieve greater accuracy of these classifications and increase the range of women included in research, for example, women with hysterectomies or those who have undergone early natural menopause. One-time blood hormone assays are not expensive and should be done in studies in which menopausal status is of interest. Given the broad role menopausal status and hormones appear to play in health and disease in all women, accurate menopausal status determination is an important foundation for any health research endeavor.

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