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Executive summary: Stages of Reproductive Aging Workshop (STRAW) Park City, Utah, July, 2001

The Stages of Reproductive Aging Workshop (STRAW) was held in Park City, Utah, July 23 and 24, 2001. There were 27 invited participants, most of whom had extensive clinical and/or research experience in reproductive aging in women. The sponsors were the American Society for Reproductive Medicine (ASRM), the National Institute on Aging (NIA), the National Institute of Child Health and Human Development (NICHD), and the North American Menopause Society (NAMS). The purpose of the workshop was to address the absence of a relevant staging system for female reproductive aging, as well as the frustration with the current nomenclature.

The workshop consisted of focused presentations on menstrual cyclicity, endocrinology, pelvic anatomy, symptoms in other organ systems, nomenclature, fertility, and both clinical and basic research gaps in relation to reproductive aging. After each presentation there was a panel discussion followed by a group discussion. Later there were breakout groups that sought agreement on the practical utility of using different signs and symptoms for a staging system. Subsequently, the leaders from each of the breakout groups presented to all the participants their recommendations which were then melded into a combined staging system (Figure 1). Each point in the proposed staging system was accepted by at least a super majority (70%) of the participants. There was unanimity on most points.

Women do not begin reproductive function (puberty) nor end it (menopause) at a particular chronologic age. Both puberty and the menopausal transition are dynamic periods for the reproductive axis, during which development or senescence occurs in a relatively rapid fashion. While there is a useful staging system for puberty (the Tanner/Marshall system),[1] heretofore there has been no similar staging system for late reproductive function. The need and demand for a staging system have been most apparent to the biomedical research community, but the intended audience of the workshop also included two secondary groups, health practitioners and the public. The specific goals of the reproductive aging workshop were to:

- develop a relevant and useful staging system.
- revise the nomenclature.
- identify knowledge gaps (both clinical and basic) that should be addressed by the research community.

BACKGROUND AND SIGNIFICANCE

Aging can be defined as the natural progression of changes in structure and function that occur with the passage of time in the absence of known disease. The female reproductive axis is essentially composed of the hypothalamic-pituitary-ovarian axis and the mullerian-derived structures (e.g., uterus). The reproductive axis ages to a non-functional state (menopause) much earlier than the other organ systems at a time when a woman is otherwise healthy. The basis of reproductive senescence in women is oocyte depletion in the ovary. A woman is endowed at birth with a finite number of oocytes that are arrested in prophase I of meiosis. Reproductive aging consists of a steady loss of oocytes from atresia or ovulation, which does not necessarily occur at a constant rate. The relatively wide age range (42 to 58 years) for reproductive failure (menopause) in normal women would seem to indicate that females are endowed with a highly variable number of oocytes and/or lose them at a highly variable rate.

Reproductive aging is a natural process that begins at birth and proceeds as a continuum. Clearly it is a *process* and not an *event*, and the end (menopause) is much easier to identify than the beginning. With the realization that chronologic age is a very poor indicator, the purpose of a staging system would be the identification of where a given woman was in the process of reproductive aging.

SUBJECTS

Until recently, there has been a paucity of interest and studies in reproductive aging. An understanding of the pattern of reproductive senescence in normal healthy women is just now emerging. Most of the current medical information in this field has come from

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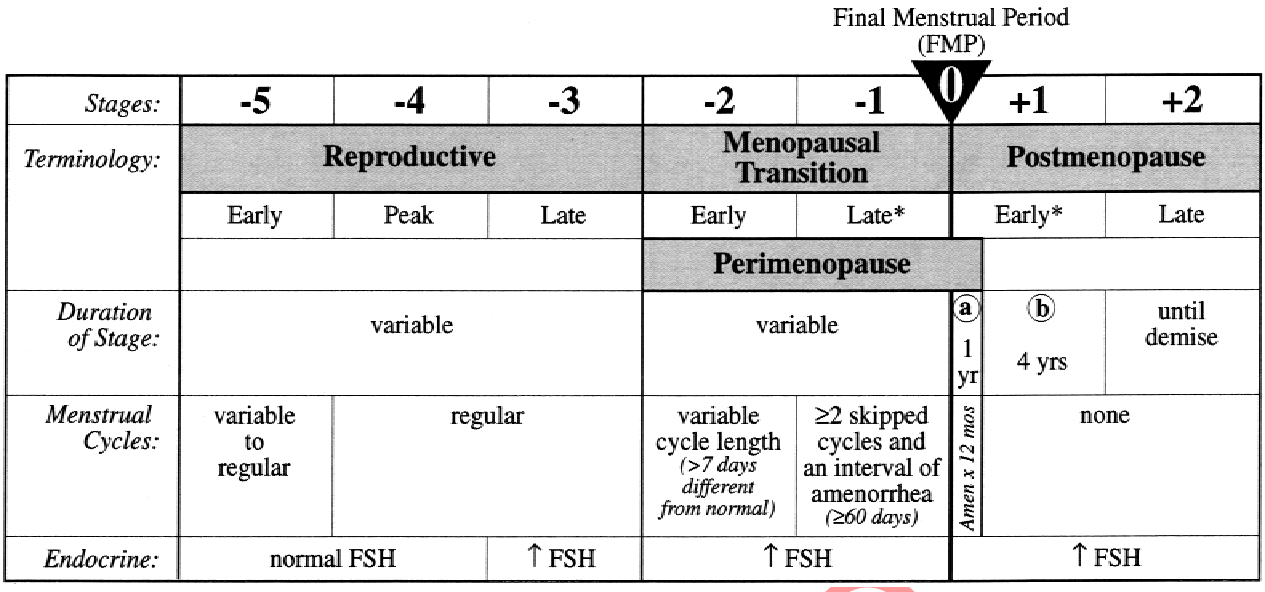

FIG. 1. Stages/nomenclature of normal reproductive aging in women.
***Stages most likely to be characterized by vasomotor symptoms.**

studies of a rather narrow segment of the population (Caucasian women of mid to upper socioeconomic means). There appears to be racial, ethnic, cultural, geographic, and socioeconomic diversity in the signs and symptoms of reproductive aging. Given these considerations, the workshop concentrated on developing a staging system for healthy women who age spontaneously to a natural menopause. While all women would likely experience similar signs and symptoms as they develop ovarian failure, we recommend not applying this staging system in the following circumstances:

- Cigarette smoking
- Extremes of body weight (BMI <18 or >30 kg/m^2)
- Heavy exercise (>10 h/wk of aerobic exercise)
- Chronic menstrual cycle irregularity
- Prior hysterectomy
- Abnormal uterine anatomy (e.g., fibroids)
- Abnormal ovarian anatomy (e.g., endometrioma)

CRITERIA FOR AN IDEAL STAGING SYSTEM

An ideal staging system would adhere to the following criteria:

- Use only objective data because symptoms are inherently subjective.
- Employ only reliable tests that are relatively inexpensive and readily available.
- Allow women to be classified in the appropriate stage prospectively.
- Inclusion in one stage precludes placement in another stage.

THE STAGING SYSTEM

A dominant pattern for reproductive senescence has been identified that is the basis for the recommended staging system. However, it must be recognized that not all healthy women will follow this pattern. While most normal women will progress from one stage to the next, there will be individuals who "see-saw" back and forth between stages or skip a stage altogether.

The workshop participants considered a number of potential components of a staging system: menstrual cycles, endocrine/biochemical factors, fertility, signs/symptoms in other organ systems, and uterine/ovarian anatomy. Each component was discussed separately. The anchor for the staging system is the final menstrual period (FMP). Prior to the FMP there are five stages (Fig. 1); the age range and duration for each of these five stages is variable.

The staging system that was developed at the workshop has seven stages; five precede and two follow the FMP. Stages −5 to −3 encompass the Reproductive Interval; −2 to −1 the Menopausal Transition; and +1 to +2 the Postmenopause (Fig. 1).

Menstrual Cyclicity

After menarche (and entry into Stage −5), it usually takes several years to assume regular menstrual cycles which should then occur every 21 to 35 days for a num-

ber of years (Stages −4 and −3). There is no clear demarcation from Stages −5 to 3 because there is a gradual and imperceptible rise and decline in fertility over a number of years. This change in the length of regular cycles is usually preceded by variation in cycle length. A woman's menstrual cycles remain regular in Stage −2 (early menopausal transition), but the length changes by seven days or more (e.g., her regular cycles are now every 24 instead of 31 days). Stage −1 (late menopausal transition) is characterized by two or more skipped menstrual cycles and at least one intermenstrual interval of 60 days or more. While duration and/or amount of menstrual flow often changes during the menopausal transition, these changes were considered to be highly variable and therefore not included in the staging system. Several prospective longitudinal studies of menstrual cyclicity have documented that many women are poor historians in relation to even their recent menstrual history; it is recommended that investigators and clinicians confirm menstrual histories by asking women to keep prospective menstrual calendars. A sonogram or other imaging modality of the uterus should be employed at baseline and periodically (every two to three years) to document that uterine bleeding is due to hormonal changes and not uterine pathology (e.g., leiomyoma, adenomyosis).

Endocrine

Rudimentary knowledge of the endocrinology of the menstrual cycle is all that is necessary to use the staging system. An FSH elevation is the first measurable sign of reproductive aging. This initial FSH elevation is most prominent in the early follicular phase of the cycle; a single venous blood sample should be obtained between cycle days two and five (the first day of flow is day one) and subsequently assayed for FSH and estradiol. Serum FSH immunoassays are readily available and relatively inexpensive. The initial elevation in the late reproductive Stage −3 is subtle; while clinicians often use 10 mIU/ml as the cutoff value, in the research setting it would be best to determine the actual level for a particular laboratory in a young control population from Stage −4 (peak reproductive). An FSH elevation would be an early follicular phase level that exceeds two standard deviations of the mean level for a population of normal women of peak reproductive age (e.g., age 25 to 30 years). In the late reproductive stage, the estradiol level in the early follicular phase is either normal or elevated; if it is elevated, it can suppress what otherwise would be an FSH elevation and, therefore, the FSH level should only be interpreted in the context of a simultaneous estradiol level. An estradiol level >80 pg/ml is often considered to be elevated. An elevated FSH level in a single cycle is significant, sufficient to place a woman in Stage −3, and does not need to be repeated. However, a normal FSH level in a 40- to 45-year-old woman with regular cycles will be elevated in a preceding or subsequent cycle about 30% of the time. Therefore, it is recommended that a second FSH level be obtained if the first is normal. It is recognized that FSH levels gradually increase throughout the menopausal transition but the variability is high and it would be exceedingly difficult to identify meaningful cut-off levels for Stages −3 to +1.

There are significant and predictable changes in other reproductive hormones during the menopausal transition: estradiol levels eventually fall, luteinizing hormone (LH) levels change later than FSH but gradually increase, and progesterone levels decrease as ovulation ceases. However, the variability of each of these hormone changes is high, thus diminishing their utility for a staging system. Serum hormone assays are more readily available and validated, but urinary hormone assays provide a more integrated picture of hormone secretion over a period of time. In the research setting, it may be useful to use serum assays when cycles are regular and urine assays in the late menopausal transition (Stage −1), when cycles are irregular. Normative data are not as readily available for urinary assays as they are for serum assays.

Symptoms

Some women start to experience various symptoms, including vasomotor symptoms, breast tenderness, insomnia, migraines, and premenstrual dysphoria, during late reproduction (Stage −3). Also, in the late menopausal transition and beyond, genital atrophic symptoms and problems in sexual function can occur as well. Not all women have symptoms as they transition to the menopause, and women with symptoms experience them in different combinations and levels of intensity. These symptoms are subjective by their nature, which makes quantification difficult. It has been observed that symptomatology varies markedly between ethnic groups, cultures, socioeconomic groups, and even in different climates. Furthermore, these symptoms do not track closely with the menstrual cycle nor endocrine changes during the menopausal transition. Vasomotor symptoms are the most frequent and prominent of the menopausal symptoms; women in Stages −1 and +1 frequently experience the onset or increased intensity of vasomotor symptoms.

Fertility

A woman's peak fertility occurs in her mid- to late twenties and progressively decreases until menopause (Stage −4 to −1). The loss of fertility is the first sign of reproductive aging that precedes the monotropic FSH rise and changes in menstrual cyclicity. However, fertility was not included in the staging system because relative fertility in an individual is nearly impossible to measure and is codependent on the fertility of the male partner.

Imaging

The workshop considered imaging of the pelvic organs by various modalities (e.g., ultrasound, MRI, CT) for their potential to contribute to a staging system. For practical purposes, the best imaging modality is sonography. Uterine sonography did not seem applicable to a staging system per se, but may be used to rule out uterine pathology as a cause of uterine bleeding. Ovarian pathology (e.g., dermoid) may be ruled out with ultrasound as well because it could also affect reproductive aging. Ovarian sonography, specifically antral follicle (2–10 mm) counts, appears to be very promising for use in a future revision of the staging system. The number of antral follicles in the ovary do not vary over the menstrual cycle, correlate well with chronologic age, and probably reflect the size of the reserve pool of primordial follicles. However, there is currently a paucity of studies of antral follicle counts in women during the menopausal transition.

NOMENCLATURE

The workshop participants recognized the current confusion and duplication in the nomenclature as applied to female reproductive senescence. The World Health Organization (WHO) has attempted to address these concerns on several occasions (most recently in 1996).[2] The Council of Affiliated Menopause Societies (CAMS) convened a working group to further define the terminology in 1999.[3] The WHO and CAMS definitions generally have vague starting points and use terms such as premenopause, perimenopause, menopausal transition, and climacteric, which overlap.

Our recommendations for a revision in the nomenclature appear in Figure 1.

Menopause

Menopause is the anchor point that is defined after 12 months of amenorrhea following the final menstrual period (FMP), which reflects a near complete but natural diminution of ovarian hormone secretion.

Menopausal Transition

Stage −2 (early) and −1 (late) encompass the menopausal transition and are defined by menstrual cycle and endocrine changes. The menopausal transition begins with variation in menstrual cycle length in a woman who has a monotropic FSH rise and ends with the FMP (not able to be recognized until after 12 months of amenorrhea).

Postmenopause

Stage +1 (early) and Stage +2 (late) encompass the postmenopause. The early postmenopause is defined as 5 years since the FMP. The participants agreed this time period is relevant, as it encompasses a further dampening of ovarian hormone function to a permanent level as well as the period of accelerated bone loss. Stage +1 was further subdivided in segment "a," or the first 12 months after the FMP, and "b," or the next four years. Stage +2 has a definite beginning, but the duration is variable because it ends with the woman's death. Further divisions may be warranted as women live longer and more information is accumulated.

Perimenopause

Perimenopause literally means "about or around the menopause." It begins with Stage −2 and ends 12 months after the FMP. The *climacteric* is a popular but vague term that we recommend be used synonymously with perimenopause. Generally speaking, the terms perimenopause and climacteric should not be used in scientific papers but only with patients and in the lay press.

The success of the workshop will depend on whether investigators, clinicians, and others find this staging system/nomenclature useful. We recommend it as a distinct improvement over the current situation, which is a non-existent staging system and confusing nomenclature. However, the participants recognized that this is a "work in progress" and expect to make revisions in the future as more knowledge becomes available.

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APPENDIX

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