The menopause transition and the aging process: A population perspective

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ABSTRACT. The menopause transition period, extending from active reproductive capacity with well-characterized hormone profiles through reproductive senescence, has been less well studied than any other period of the life span except extreme old age. Yet, for the gerontologist, this is an important period to understand for at least two reasons. First, during this period changes in the neuroendocrine system and ovary may provide a model for the study of other aging-related processes. Second, specific characteristics of this transitional period (including duration, intensity, and age at menopause) may be considered aging, and influence short-term health and quality-of-life status, as well as life expectancy. In addition to discussing the menopause transition in terms of age and culture, we include some of the theories and conceptual models that can influence the nature and interpretation of information from this time period, and its ultimate impact on health and health practice.

INTRODUCTION

The menopausal transition period extends from active reproductive capacity with well-characterized hormone profiles through reproductive senescence and the absence of an ovarian contribution to hormone profiles. This transitional period is complex because ovarian change, with its alterations in bleeding patterns and hormone patterns, includes the overlay of physical, neurological and psychological characteristics associated with the aging process. Yet, for the gerontologist, this is an important period to understand for at least two reasons. First, during this period changes in the neuroendocrine system and ovary may represent a biological system that is aging in a more compressed time period than other systems such as liver, heart or kidneys. This system is influenced by both social and biological influences; therefore, ovarian senescence may provide a model for the study of aging-related processes. Second, specific characteristics of this transitional period (including duration, intensity, and age at menopause) may influence short-term health and quality-of-life status, as well as life expectancy, all factors that are considered “aging”.

This paper will include the operational definition of the menopause, and consider aspects of the transition in terms of age and culture. For example, are chronologically older women expected to have a different frequency of hot flashes from chronologically younger women, or are women who consume diets rich in plant sterols with estrogen-like activity less likely to have hot flashes? We will characterize the current understanding of the relationship between bleeding characteristics and the attending hormonal variation. We include some of the theories and conceptual models that can influence the nature and interpretation of information from this time period, and its ultimate impact on health and health practice.

DEFINITION OF THE MENOPAUSE

The most frequently used definition of the menopause was developed by a World Health Organization (WHO) consensus panel (1). The MENOPAUSE is defined as the permanent cessation of menstruation resulting from loss of ovarian follicular activity. This attribution is made in retrospect following 12 months of amenorrhea not associated with other factors such as pregnancy or lactation. The PERIMENOPAUSE (or climacteric) includes the period prior to the menopause when endocrinological, clinical, and biological changes associated with the menopause are occurring, as well as the first year following the menopause. The POSTMENOPAUSE is defined as the period after the menopause and begins following 12 months of spontaneous

Key words: Aging, hormones, life expectancy, menopause.

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Received and accepted December 5, 1999.
involved clinical studies conducted in a limited number of Caucasian women over a relatively brief period of time relative to the length of the transition. Based on animal studies and a very limited number of human studies, a three-phase working paradigm of hormonal events associated with the menopause transition has been developed. This is a working paradigm, and more refinement is required before hormone concentrations and varied hormone or bleeding patterns become an integral part of the operational definition of the menopause transition. Indeed, Prior (2) has proposed a five-stage paradigm to reflect the interplay of ovarian, menstrual, and neuroendocrine variation.

In the first phase of menopause transition, there is an increase in FSH secretion, without concomitant increase in the luteinizing hormone (LH) level (3). Research indicates a reduction in the secretion of inhibin and follistatin, peptides that inhibit the release of FSH from the pituitary gland in a closed feedback system with FSH. There is an increasing likelihood of premature ovulation, more frequently decreased progesterone production with luteal insufficiency (3-5), hyperestrogenism in ovulatory cycles (6, 7), and an excess of estrogen relative to progesterone. Characteristics of the perimenopause include a decline in the number of ovarian follicles to a depleted state in the postmenopause, and a decrease in the proportion of ovulatory cycles (8).

The second phase of the menopausal transition is characterized by an even greater instability in estrogen levels, and an increasing probability of anovulatory cycles (9), with an apparent failure to mount an LH surge in response to an estrogen stimulus (4). Abnormalities of the GnRH pulse generator, including rapid follicular (8) and luteal phase (10), as well as premature pulsatile LH secretion have also been reported. Gonadal hormone levels are erratic with hyperestrogenism relative to progesterone (11), and altered presentation of menstrual cycle lengths and bleeding patterns (9, 12-14). This may include an increased frequency of dysfunctional uterine bleeding attributable to anovulation.

In the third phase of the menopausal transition, the ovarian follicles no longer respond to FSH and LH. Plasma estradiol concentrations drop below 20 pg/mL, and progesterone concentrations are non-measurable. Menstrual bleeding ceases. FSH and LH levels are consistently elevated, remaining so for an extended period of time (11, 15, 16). It is important to recognize that these events are on a poorly defined continuum. There may not be discernible discrete phases with a well-defined onset or specific points in time in every woman. An area of active

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**Figure 1 - Employing World Health Organization definitions related to the menopause (reproduced with permission).**

amennorhea. The transitional period, in its entirety, is probably 4-10 years in duration (Fig. 1).

While there is much merit in standardizing the vocabulary associated with this developmental stage, there are deficiencies evident with these definitions. With the WHO definition, conceptually, menopause becomes characterized almost as a yes-no phenomenon, rather than a developmental stage or process. On one day, the woman may be perimenopausal, and the next day she is postmenopausal, which is rather like crossing the equator from the Northern to the Southern Hemisphere. Just as the distance from the equator makes a difference in weather, so distance from the menopause makes a difference in functional status or health. However, the WHO definition of menopause cannot be assigned until a year has transpired without menstrual bleeding, making the simultaneous assessment of physical and psychological status more complex. There are other limitations. While the WHO definitions consider when the “perimenopause” ends, there are no well accepted measures of when the “perimenopause” commences. Though health care providers have attempted to use level of follicle-stimulating hormone (FSH) concentration as the indicator of the onset of the perimenopause, the variation in FSH concentrations generated by minute-to-minute, daily and monthly cyclicity, as we now know it, precludes having the sensitivity and specificity necessary for use as an appropriate measurement tool.

**HORMONAL EVENTS AND THE MENOPAUSAL TRANSITION**

Hormone studies of ovarian aging have generally