Menstrual Cycle Patterns and Their Determinants during the Menopausal Transition among a Multiethnic Cohort of Women

by

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ABSTRACT

Examining menstrual cycle patterns among early and mid-reproductive aged women suggests that ethnicity, body mass index (BMI), and medical conditions influence menstrual characteristics. Little data is available on bleeding patterns and dysfunction during the menopausal transition. The few studies conducted among perimenopausal women include predominately Caucasian populations and did not examine factors that may alter bleeding patterns during the menopausal transition. The aim of this dissertation was to examine patterns of change in menstrual cycle characteristics during the menopausal transition using menstrual calendar data from a multiethnic multisite cohort study, the Study of Women's Health Across the Nation (SWAN). Monthly menstrual calendars were recorded between 1996 -2006.

This dissertation found that staging the menopausal transition by menstrual calendars identified the start of each menopausal stage than with estimates from annual interviews. Increase in menstrual cycle length occurred predominately in the right tail of the distribution, with greater variability in extreme lengths occurring during the 2 years prior to the final menstrual period (FMP). Menses of 10 or more days, menses with at least 6 days of spotting, and menses with at least 3 days of heavy bleeding occurred at least once during the menopausal transition in the majority of women. Menses of 15 or more days were less common. Obese women had longer menstrual cycle lengths and were more likely to report menses with at least 3 days of heavy bleeding. After adjusting

for body size, Chinese and Japanese women had longer menstrual cycle lengths and Japanese women were less likely to report menses with at least 3 days of heavy bleeding. African-American women were less likely to report menses of 10 or more days or menses with at least 6 days of spotting. Menstrual characteristics were not associated with diabetes, thyroid conditions, or uterine fibroids after adjustment.

The normative patterns of menstrual cycle characteristics as women progress through the menopausal transition include increased propensity for longer menstrual cycles, longer-lighter menses, and episodes of heavy menstrual bleeding. The results of this work will help define abnormal uterine bleeding in perimenopausal women.

CHAPTER I

Introduction

The menopause transition (MT) is critical time for women and has been linked to future health consequences. In the United States, the median age of menopause has been reported to be 51-52 years.[1, 2] Yet women who reach the age of 50 in the US are expected to live on average another 32.5 years.[3] Prior research has linked the age at final menstrual period (FMP) to future disease risk. Younger age at menopause has been linked to a greater risk of mortality in several countries.[4-7] Younger age at menopause has also been linked to cardiovascular disease risk and risk of osteoporosis.[8] Older age at menopause has been linked to an increased risk of breast cancer.[9]

While factors associated with the timing of FMP have been investigated, gaps of knowledge regarding the MT still exist. Prior studies have shown that menstrual cycle length and menstrual cycle variability increase prior to the FMP. Clarity is needed on how the overall distribution of menstrual length and menstrual variability changes during the MT. It has been suggested that menses duration and flow change during the MT, however a study has yet to evaluate changes in menstrual duration and flow throughout the whole MT. It is unknown which demographic, lifestyle, or medical conditions influence menstrual cycle length, menses duration, or menstrual flow during the MT.

One aspect of the MT which has been recently defined is the stages of the MT. In 2001, the Stages of Reproductive Aging Workshop (STRAW) defined the MT as having two distinct stages, early and late.[10] The starts of these two stages were defined by

changes in menstrual cycle length. Among women over 40 years old, the start of the MT occurs when a persistent difference in consecutive menstrual cycles of at least 7 days is observed. The start of the late MT occurs when a menstrual cycle of at least 60 days is observed. These definitions proposed by the first STRAW workshop were recently validated by the ReSTAGE collaboration [11-13] and adopted by the STRAW +10 guidelines [14-17].

While the stages of the MT have now been defined, little is known about the patterns of menstrual cycle characteristics during the MT. Most studies have examined time to the final menstrual period, and only a few have had the ability to examine menstrual cycle characteristics. Prospectively collected menstrual calendars are the preferred method of examining menstrual cycle characteristics and few studies have had the resources to collect this information, since they are more labor intensive and therefore more costly than studies that only use questionnaires. Several cohort studies of midlife women have used annual interviews to classify women's menopausal status, yet few studies have assessed the agreement between information obtained from annual interviews and menstrual calendars in midlife women. The Melbourne Women's Midlife Health Project (MWMHP) found that the interview questions used in their study had low sensitivity for picking up menstrual cycle variability and menses flow variability.[18] The Seattle Midlife Women's Health Study (SMWHS) compared interview questions inquiring about menstrual cycle irregularity to menstrual calendars and reported weak agreement.[19] Neither of these two studies examined factors that influence agreement.

In the 20th century, four cohort studies utilized menstrual diaries to describe menstrual cycle length during the reproductive life span. In 1955, Vollman published his

analysis of menstrual diaries from 592 Swiss women, who were followed for 20 years. In 1967, Treloar published 30 years of menstrual cycle data from the TREMIN Research Program on Women's Health Study.[20] This study enrolled a cohort of female students from the University of Minnesota from 1934-1939. A second cohort was also enrolled from 1961-1963. The women were followed until they reached their final menstrual period. During the study, daughters of the women were also enrolled, so that for some women their whole reproductive life-span was documented. The TREMIN study is probably the best known cohort, and analysis using data from this study continues today. While the Vollman study and the TREMIN study followed women for long periods of time, two other studies followed women across a large age-span for two years. Matsumoto published data collected from the diaries of 701 Japanese women.[21] Chiazze collected diary data from 2,316 American and Canadian women.[22] These four classic studies demonstrated that menstrual cycle length had the highest variability right after menarche and then again before menopause. Cycle lengths for 20 to 40 year olds were shown to be less variable. Except for the Japanese study, the studies were conducted in Caucasian populations.

In the last few decades, menstrual calendar studies have been conducted in late reproductive and perimenopausal women. The Massachusetts Women's Health Study (MWHS), collected diary data for 352 women, aged 50-60, for three years in the late 1980's.[23] MWHS found that short cycle lengths and short bleeding/spotting episodes are most frequent during early to middle perimenopause and long cycle lengths were less frequent and occurred later during the transition. MWMHP, which began in 1991, published results from 121 women aged 45-53 years who had diary information for at

least 10 consecutive menstrual cycles.[24] MWMHP examined their data in groups, the first 10 cycles of the study and at least 10 cycles prior to the FMP. Cycle length varied little in the first 10 cycles of the study, but increased variability was seen in the menstrual cycles prior to the FMP. SMWHS published results from 184 women aged 35-54 years who had at least four years of menstrual calendar data.[25] SMWHS characterized the MT as having three stages. The first stage was characterized by menstrual flow changes, the second stage was characterized by menstrual irregularity, and the last stage was skipped periods. A Danish cohort study, using data from the first year of their menstrual calendars, published results from 592 women aged 45-54 years. This study examined menstrual cycle length, menses duration, and heaviness of flow. The study found that women who were consider perimenopausal had longer median menstrual cycle length and longer median menses duration than women who were considered premenopausal. They also reported that women who were perimenopausal had less heavy bleeding episodes than premenopausal women.

While these recent studies have given some insight into patterns of menstrual cycle characteristics, they have major limitations. The small sample size of most of these cohorts prohibited these studies from examining patterns fully. Except for the Danish cohort, these studies did not examine which demographic, lifestyle, or medical characteristics influence menstrual cycle characteristics. The Danish cohort examined age, body mass index (BMI), smoking, and health status, but only presented unadjusted associations. Another major limitation of these studies was the short duration of follow-up, which did not allow for characterization of the full MT in the study subjects. Another drawback of these studies was the study participants were predominately Caucasian.

Studies from the World Health Organization have suggested that ethnic and regional differences exist in menstrual cycle characteristics.[26-29] These reports compared women in different world regions without adjusting for other health, lifestyle or medical history characteristics. US based menstrual calendars studies have reported ethnic differences in menstrual characteristics in both postmenarcheal [30, 31] and reproductive age women [32, 33]. These differences may be due to differences in body size, medical conditions, or other demographic and lifestyle factors. Prior work in postmenarcheal and reproductive age women have shown BMI to be associated with menstrual cycle length [33-39], menstrual bleeding duration [30, 34, 40, 41, , 42, 43], and heaviness of flow [30]. Some studies have also found that diabetes [38, 44], thyroid disorders [45, 46], and uterine fibroids [47-49] influence menstrual cycle characteristics.

Dissertation Aims

The goal of this dissertation was to describe the patterns of change in menstrual cycle characteristics as women progress through the MT and to identify biological, demographical, and behavioral characteristics that influence these patterns. To achieve this goal menstrual calendar data collected from 1996 through 2006 from 1320 participants of the Study of Women's Health Across the Nation (SWAN) were utilized.

Aim 1: To assess the agreement between MT stages as defined by the annual interview or annual follicle-stimulating hormone (FSH) levels and MT stages defined by the menstrual calendar, and to examine demographic and lifestyle factors that influence agreement.

Aim 2: To examine the pattern of menstrual cycle length during the MT, and to assess the association between menstrual cycle length and ethnicity, BMI, diabetes,

thyroid conditions, and uterine fibroids after adjustment for other demographic and lifestyle characteristics.

Aim 3: To describe the distribution of menses duration and heaviness of flow, and to assess the association between these menstrual characteristics and ethnicity, BMI, diabetes, thyroid conditions and uterine fibroids after adjustment for other demographic and lifestyle characteristics.

Background

Physiology of the Menstrual Cycle

The normal menstrual cycle can be grouped into two components: the ovarian and the endometrial. The ovarian component is characterized by changes in the ovarian follicle, with ovulation as the major event. The endometrial component describes changes in the uterine lining. Both the ovarian and endometrial components are driven by changes in the endocrine system.

Ovaries and Follicle Development

In the human female, the ovaries are paired organs that are responsible for storing ova, which are female germ cells, and producing female sex hormones. A normal adult ovary is usually 3 to 5 cm in length, 1.5 to 3 cm in width and up to 1.5 cm thick.[50] The size of the ovary is dependent on menstrual cycle phase, as well as the age of the female. The ovary consists of two areas, the cortex and the medulla. The cortex is the outer area and is covered by the surface epithelium. The surface epithelium is made up of the *tunica albuginea*, a strip of connective tissue, and follicles.[51] A follicle is composed of an outer layer of theca cells, separated by a basement membrane from an inner layer of granulosa cells which surround an ooycte.[39] Follicles are present in the adult ovary in various stages of development. Resting follicles are located in a nonvascular layer of the

cortex beneath the *tunica albuginea*. The cortical medullary border, a highly vascular area of the cortex, contains growing follicles, follicles which are undergoing atresia, and corpora lutea.[51] The cortex also consists of stromal cells, vasculature, and elements of the autonomic nervous system. Stromal cells are cells that lend structural support to the ovary and are made up of undifferentiated mesenchymal cells.[52] Stromal cells are thought to differentiate into theca and luteal cells.[52] The medulla section of the ovary contains connective tissue, stromal cells, blood vessels, and lymphatics.[51]

In human females, ooycte production occurs before birth. A human female is born with all the oocytes she will have in her lifetime. Starting at approximately the 4th week of embryonic development, primordial germ cells begin the process of becoming oogonia.[51] The peak number of oogonia is around 7 million and occurs around the 20th week of gestation.[53] Oogonia that enter meiotic prophase I are called oocytes. The oogonia that do not enter meiosis are lost through atresia, by apoptosis or programmed cell death. Primary oocytes are arrested in the diplotene stage of meiotic. A layer of epithelial pregranulosa cells surround the oocytes to form primordial follicles.[51] Primordial follicles stay in the arrested diplotene stage until development, or they undergo atresia.

Folliculogenesis is the process of follicular development and has two important pathways, initial recruitment and cyclic recruitment.[39] Initial recruitment is the process where primordial follicles are activated and begin to grow. This process starts occurring from the 20th week of gestation and continues through menopause. The factors that stimulate initial recruitment are unknown.[39] Primordial follicles that are selected to grow are recruited into the primary follicular pool. Primary follicles develop by

proliferating their granulosa cell layers and by increasing the size of the ooycte.[51] Once there are 2 or more complete layers of granulosa cells, the follicle is considered a secondary follicle. In the secondary follicle stage, the theca layer of the follicle develops. The theca layer stratifies into the theca externa and the theca interna. In the theca interna, epitheloid cells begin to develop; these cells become the steroid-secreting cells. Once the epitheloid cells develop the secondary follicle is defined as a preantral follicle.[51] Once the follicle begins to form a small fluid-filled cavity, called the antrum, it is called an antral follicle. Before puberty, these antral follicles undergo atresia.

After the onset of menarche, the first menstrual period, some antral follicles enter cyclic recruitment. In this process, a group of 6 to 10 antral follicles are selected to become preovulatory follicles. These selected follicles are referred to as Graafian follicles.[39] Among the Graafian follicles, one follicle becomes dominant during the late follicular phase of the menstrual cycle and the others undergo atresia. As the dominant follicle grows, it increases the number of granulosa cells and the theca becomes highly vascular.[50] Once the follicle reaches maturation, the ooycte is released from the follicle into the fallopian tube; this process is ovulation. After the follicle has extruded the ooycte, it collapses and becomes the corpus luteum, which starts the luteal phase of the menstrual cycle. If fertilization of the ooycte occurs, the corpus luteum remains for about 3 months and provides hormonal support for the pregnancy. However, if fertilization does not occur, the corpus luteum atrophies and becomes the corpus albicans, which is white scar tissue.[50]

Hormonal Control

The ovarian component is regulated both by hormones that are secreted by the ovaries as well as by hormones that are secreted in other organs. Hormonal control of the menstrual cycle is determined by the interaction between the central nervous system, primarily the hypothalamus and pituitary, and the ovaries, referred to as the hypothalamic-pituitary-ovarian axis. The hypothalamus secretes gonadotrophin-releasing hormone (GnRH). GnRH is secreted in a pulsating fashion and has a short half-life of less than three minutes, which makes peripheral serum measurements unreliable as they do not reflect central levels.[54] GnRH triggers the pituitary to synthesize, store, and secrete the gonadotrophins, FSH and luteinizing hormone (LH). FSH and LH stimulate the growth and development of Graafian follicles.[50] FSH triggers granulosa cell growth within the follicle. LH stimulates theca cells to produce androgens. The androgens are transferred to the granulosa cells where FSH triggers their aromatization into estradiol. [53] In the follicular phase of the menstrual cycle, as follicles grow the granulosa cells produce estradiol. FSH and LH act on cells in the ovaries to produce several other hormones, some of which have positive and negative feedback on gonadotrophin secretion. FSH and LH levels peak in the follicular phase, just prior to ovulation. Estrogen reaches its highest level during the follicular phase as well. Once levels of estrogen reach a high level, estrogen exerts a negative feedback on FSH, inhibiting the growth of multiple follicles and causing LH to surge. The surge of LH stimulates ovulation.[50] During the luteal phase of the menstrual cycle, the corpus luteum secretes progesterone. Progesterone inhibits follicular growth during the luteal phase.[55]

Recently research has established the role of additional hormones that are involved in the control of the menstrual cycle. Inhibin B is produced in the granulosa cells of antral follicles.[56] Inhibin B participates in the negative feedback loop of the hypothalamic-pituitary-ovarian axis by down-regulating the secretion of FSH. Inhibin B levels peak at two times during the follicular phase, once during the early to mid follicular phase and again at ovulation.[56] Anti-Müllerian hormone (AMH), which is produced by primary, secondary, and early antral follicles [57], inhibits the initiation of primordial follicle growth.[53] During the luteal phase of the menstrual cycle, the corpus luteum also secretes inhibin A [56], which also helps suppress FSH [55].

Endometrial Component

The endometrium is the tissue that lines the uterus. It is composed of two zones. The *decidua functionalis* is the outermost zone and comprises two thirds of the endometrium.[53] It is made up of two layers, the stratum spongiousum and the stratum compactum. The *decidua functionalis* is the layer of the endometrium that undergoes changes during the menstrual cycle and is shed during menses. The *decidua basalis* is the innermost zone that comprises one third of the endometrium, and does not undergo significant change during the menstrual cycle.[53]

The endometrial component consists of three phases, the proliferative, the secretory, and menstrual. The purpose of the endometrial component is to provide a hospitable environment for embryo implantation. The increased estrogen production that occurs during the follicular phase causes mitotic growth of the *decidua functionalis*.[53] Estrogen stimulates the rapid growth of the glands and the stromal of the functional layers of the endometrium during the proliferative phase of the endometrial component

Progesterone, produced during the luteal phase of the ovarian component, causes the endometrium to become increasingly vascular and causes the secretion of glycogen and lipids, which defines the secretory phase.[50] When the corpus luteum atrophies, estrogen and progesterone levels plummet and the superficial layers of the endometrium that were built during the proliferative phase are sloughed off. This begins the menstrual phase of the endometrial component.

Menstrual Cycle Length

Menstruation is the most easily observed event of the menstrual cycle. By convention, the first day of menstruation is considered the first day of a menstrual cycle. Duration of menstruation typically lasts 2-6 days.[53] In most descriptions of the human menstrual cycle, the cycle length is characterized as 28 days. However, the range of normal menstrual cycle length is somewhat variable. Treloar and colleagues found that during the ages 20 to 40, there was less variability in menstrual cycle length as compared to the years following menarche and the years preceding menopause.[20] For example, for women age 27 the median menstrual cycle length was 27.5 years and the 25-75% range was 25.7-29.9.[20] Several studies have found similar results. A study of 2316 American and Canadian women aged 15-44 years found mean cycle length of 28.1 ±3.95 days.[22] A study of New York women age 34-45 years, reported the mean menstrual cycle length to be 27.8.[37] A recent study of 161 US women age 21-41 found the mean menstrual cycle length to be 28.9 days.[58] A recent study of New Mexican women age 18-36 reported a mean menstrual cycle length of 27.7± 2.7 days.[59]

Follicular phase length and luteal phase length have also been studied. Studies by Lenton and colleagues in the early 1980's observed follicular phase length to range from

8.2 to 20.5 days [60] and luteal phase length to range from 9-20 days [61]. The New Mexican study found a follicular phase length range of 10-20 days and luteal phase length of 9-17 days.[59] Both studies observed that the phase with the most between-women variation is the follicular phase.[59]

Changes Due to Aging

Ovarian Aging

A human female is born with the total number of follicles she will have in her lifetime. The total number of primordial follicles are called the ovarian reserve.[62] At birth, the total number of follicles in the ovarian reserve is about one million.[53] Since primordial follicles are constantly being recruited to initiate either growth or apoptosis, the ovarian reserve diminishes as a woman ages. Approximately 75% of the ovarian reserve is lost from birth until puberty.[54] The rate of loss from the ovarian reserve is not constant.[62] It was once believed that once the number of follicles in the ovarian reserve reach approximately 25,000, the rate of loss begins to accelerate [62], approximately around age 37.5 years [54]. However, recent work by Hansen and colleagues has demonstrated that the rate of loss does not abruptly accelerate, but is constantly accelerating.[63] The number of follicles left in the ovarian reserve when a woman reaches menopause (end of menstrual cycles) ranges from 100 to 1000, and occurs at the mean age of 51 years old.[51] Although mean ages are given above, the number of follicles at each chronological age differs among women, therefore chronologic age and ovarian age are not the same across women. Another important characteristic of ovarian aging is the increased number of anovulatory cycles (menstrual cycles where ovulation fails to occur), presumably due to functional aging of the

remaining oocytes. Women who are in the menopausal transition, have more anovulatory cycles than when they were premenopausal.[64]

Hormone Levels and Aging

As the follicle pool diminishes changes in hormone levels are seen. The drop in the number of antral follicles cause the secretion of inhibin B to decrease.[65] The decline in inhibin B reaches an undetectable level approximately 4 years before the FMP.[66] Since inhibin B is a major regulator of FSH secretion, the drop in inhibin B levels allow FSH levels to rise.[66] The rate of FSH increase is not constant as a woman ages. Data from the Michigan Bone Health and Metabolism Study (MBHMS), found that FSH levels rise slightly at a constant rate from 10 to 7 years before the FMP. From 7 to 2 years before the FMP, the rate of change increases more rapidly. From 2 years to the FMP to 1 year after the FMP the rate of change dramatically increases. One year after the FMP, FSH levels begin to plateau.[67] Increases in LH levels are also seen in women as they age. LH levels begin to increase approximately 5 years before the FMP and the levels plateau approximately 6 months to a year after the FMP.[68]

AMH, like inhibin B, is a hormone that is thought to be a biomarker of ovarian reserve. AMH levels are an indicator of the number follicles in the follicular pool with declining levels suggesting advancing ovarian age.[69] One reason AMH is thought to be an attractive candidate for a biomarker for the MT is that its measurement, unlike inhibin B, is not dependent on menstrual cycle phase.[70] Two studies have examined AMH during the MT and have found that AMH levels decline to undetectable levels approximately 4 to 5 years before the FMP.[57, 66]

As ovarian aging advances, estradiol (E2) levels are the last hormone to change with relation to the FMP.[71] E2 levels do not gradually decrease during the MT. Three studies have shown that approximately 2 years before the FMP, the level of E2 drops dramatically. In a 1999 study by Burger et al., mean E2 were approximately 250 pmol/L at 1 ½ years before the FMP and dropped to about 50 pmol/L at 1 year after the FMP.[72] Both the MBHMS and SWAN have demonstrated increased rates of change of E2 levels during 2 years before and after the FMP.[73, 74] The rapid changes in E2 levels may be the reason for some perimenopausal symptoms, like hot flashes.[75]

Other hormones change during the MT. Testosterone levels have been shown to be decreased in menopausal women.[55] However, in a longitudinal study that measured testosterone levels starting from 10 years prior to the FMP to 10 years after the FMP, testosterone levels increased gradually.[76] The same study found that sex hormone binding globulin (SHBG) levels gradually decreased.[76] Dehydroepiandrosterone sulfate (DHEA) has been shown to rise at the beginning of the MT before declining afterwards.[77, 78]

Menstrual Cycle Characteristics and Aging

As stated above, limited information on menstrual characteristics during the MT exists and the purpose of this dissertation is to examine menstrual characteristics as they change during the MT. However, some studies have documented increased variability of menstrual cycle length the closer a woman is to her final menstrual period. The Treloar analysis found increased menstrual cycle variability approximately 7 years before the FMP.[20] However, his initial analysis had some bias due to misidentified menopause dates and exclusion of menstrual cycles that overlapped calendar years.[79] A reanalysis

of the Treloar data found that in the 4 years before the FMP, menstrual cycle length variability was increased, especially during the last year before the FMP.[79] The MWMHP found that menstrual cycle length increased in the last 20 menstrual cycles before the FMP as compared to earlier menstrual cycles.[24] In SWAN, reporting longer menstrual cycle lengths as well as more variable menstrual cycles was associated with a shorter time to the FMP.[80] Increased duration of menstruation as well as heaviness of bleeding episodes have also been demonstrated by the Danish cohort during the menopause transition.[81]

Questionnaires vs. Menstrual Diaries

Prospectively collecting data on menstrual cycles characteristics using menstrual calendar data is considered to be the preferred data collection method because it is not subject to recall bias.[82] However, data collection using menstrual calendars is more costly and more labor intensive than questionnaires. Other benefits associated with using questionnaires to assess menstrual cycle characteristics include the ease of administration to a large group of women, the decreased likelihood that they reflect non response bias, and the ready incorporation into studies where reproductive stage is of interest but not a primary aim. Several studies including SWAN have used annual interviews to classify women's menopausal status, yet few studies have assessed the agreement between information obtained from an annual interview and menstrual calendars in perimenopausal women, and even fewer have assessed the factors impact that agreement. Staging women based on their menstrual characteristics also provides an opportunity to assess how recent recommendations regarding bleeding criteria for staging reproductive aging [10, 12, 13] might classify women differently than the classification upon which

SWAN staging is based (e.g. 60 versus 90 days of amenorrhea, respectively, for defining the late transition). The information gained can also be used to refine questionnaires for future studies.

Studies have examined reliability of self-reported menstrual cycle lengths among reproductive age women. A WHO study demonstrated that most women were able to accurately recall the duration of their last menses and predict the duration of their next menses, but women were less able to predict the length of their next bleed-free episode or when their next menses would start.[27] One US study found only 43% of women were able to accurately predict their next cycle length within 2 days [83], while another study demonstrated that women had longer menstrual cycle lengths than what was retrospectively reported[84]. The agreement between reported and observed menstrual cycle length has been shown to be poor to moderate. [85, 86]

Two of the cohort studies of midlife women have compared annual interview questions to menstrual calendar diaries. The Melbourne Women's Midlife Health Project compared questions of menstrual cycle variability and menses flow variability reported on a questionnaire to definitions derived from menstrual calendars. The researchers found that the interview questions had low sensitivity in picking up menstrual cycle variability and menses flow variability.[18] The Seattle Midlife Women's Health Project compared interview questions on cycle irregularity and skipped cycles to information obtained from menstrual calendar diaries. They found agreement for cycle irregularity to be weak (kappa=.19). Agreement on skipped cycles was good (kappa=.60) before a definition of skipped cycles was given to participants, and improved (kappa=.77) after a definition was

provided. [19] Neither the Melbourne Women's Midlife Health Project nor the Seattle Midlife Women's Health Project examined factors that affected agreement.

Factors that Influence Menstrual Cycle Characteristics

Ethnicity

Regional differences have been reported in age at menarche, with adolescent girls from industrialized countries reaching menarche sooner than adolescent girls from developing countries. In studies from WHO, earlier age at menarche was recorded in girls from Switzerland and Hong Kong, while later age at menarche was observed in girls from Nigeria and Sri Lanka.[28, 29] A 1968 study comparing Dutch school girls to Bantu (South African) school girls found that the Dutch girls reached menarche sooner and had more ovulatory cycles.[87] However, within country differences suggest minority adolescents have early age at menarche. In the US, African-American girls reached menarche sooner than Caucasian girls.[88] A similar result was shown among black South-Africans as compared to white South-Africans.[89]

In the US, ethnic differences have been seen in age at menopause. African-Americans have been reported to enter the menopause transition earlier than Caucasians. In the Harvard Study of Moods and Cycles, women of color had an earlier entry into perimenopause than white women [90]. The Penn Ovarian Aging Studies found African-American women started the menopause transition earlier than Caucasian women (OR=1.32), but no difference in ethnicity was seen in transition to later stages.[91] Among participants in the Multiethnic Cohort Study, Native Hawaiians , Latinas US born, and Latinas non-US born had an shorter time to menopause as compared to Caucasian women while Japanese-American women had a longer time to menopause.[92] The SWAN cross-sectional study also found Japanese women had a later age at

menopause.[2] A 2007 SWAN analysis, utilizing annual interview data, found the effect of older age on the time to menopause was greater in all other ethnic groups as compared to Caucasian women.[80]

Ethnic differences have also been reported in menstrual cycle length, menses duration and heaviness of flow. When compared to African-Americans or to non-Caucasians, Caucasian females have been reported to have longer menstrual cycle length and longer bleeding durations. A North Carolina study of postmenarcheal girls found Caucasian girls had slightly longer menstrual cycle lengths, longer menstrual bleeding, and had higher between-women cycle variance, but were less likely to report heavy bleeding than African-American girls.[30, 31] In The Collaborative Perinatal Project and The New York University Women's Health Study, both of which utilized questionnaires, Caucasian women had mean cycle lengths that were a half day longer than non-Caucasian women.[37, 41] Two US based studies of reproductive aged women, The Semiconductor Health Study and the Women's Reproductive Health Study, found Asian women had adjusted menstrual cycle lengths that were approximately two days longer than cycles for Caucasian women.[32, 33].

Previous SWAN analyses have found some differences by ethnicity in hormone patterns. In 2004, similar patterns of decreases in FSH and increases in estradiol were observed in each ethnic group, however serum hormone levels differed. As compared to Caucasian women, Chinese and Japanese women had lower estradiol levels. African-American women had higher FSH levels than Caucasian women.[93] In 2004, the SWAN Daily Hormone Study (DHS) reported Chinese and Japanese women had the lowest level of estrone conjugate (E1c) secretion.[94] In 2008, the DHS noted that African-American

women had greater odds of having an anovulatory non bleeding cycle than Caucasian women.[95] A recent DHS paper did not find an independent association between characteristics of menstrual bleeding episodes and ethnicity. [96]

Body Size

Ethnic differences in menstrual characteristics may be due to differences in body size. Studies that have examined the relationship between BMI and time to menopause have shown conflicting results. Higher BMI has been associated with older age at menopause in studies of women in China[97], Mexico[98], and the US [92, 99]. However, other studies have found that higher BMI was associated with younger age at menopause,[100] and some studies did not find an association [101-105]. In two population-based studies of menopausal status in the United States, one study found higher BMI to be slightly associated with being post menopausal [106] while the other study found no association between BMI and the odds of being post menopausal [107]. The Harvard Study of Moods and Cycles found the age-adjusted incidence rate of perimenopause to be 1.58 times higher among obese women as compared to normal weight women.[90] However, the Penn Ovarian Aging Study did not find an association between BMI and entry into any stage of menopause.[91] Both a 2001 report using SWAN cross-sectional survey data as well as a 2007 longitudinal SWAN analysis did not find an association between BMI and age at FMP.[2, 80]

Both low BMI and high BMI have been associated with longer menstrual cycle length. Low BMI has been associated with longer menstrual cycle length in postmenarcheal girls[31], and young adult women [34, 35]. Higher BMI has also been associated with longer menstrual cycle length.[33, 35-38] In the Michigan Bone Health

and Metabolism study, the lowest body fat mass deciles and the highest body fat mass deciles were associated with longer menstrual cycle length.[35] A few studies have found no association between cycle length and BMI.[32, 43, 108]

BMI has been associated with bleeding duration and heaviness of flow. Low BMI has been associated with longer bleeding duration [30, 40, 41] and high BMI has been associated with shorter bleeding duration [30, 34, 42, 43]. MBHS did not find an association with bleeding duration and BMI.[109] In a Danish study of premenopausal and perimenopausal women, obesity was associated with higher frequency of flooding.[81] A recent SWAN DHS paper did not show an association between BMI and menstrual cycle length, but did report that obesity was associated with increased number of heavy bleeding days.[96]

Medical Conditions

Although less frequently examined, evidence suggests medical conditions also impact menstrual function. Endocrine disorders have been linked to menstrual dysfunction. Girls with Type 1 diabetes have been reported to have later ages of menarche as compared to girls without diabetes.[110-112] Type 1 diabetes has also been reported to be associated with an earlier age at menopause.[113] Diabetes was associated with premature ovarian failure among women in the SWAN cross-sectional study [114] and women who were diabetic were more likely to be postmenopausal than women who were not diabetic [2]. One study among Puerto-Rican women did not find an association between history of diabetes and age at menopause.[115]

Diabetes has been associated with longer menstrual cycle lengths, longer bleeding duration, and heavier bleeding episodes. Women with diabetes have been shown to have

longer menstrual cycles than non-diabetic women [38, 44], including women in the SWAN DHS/menstrual calendar study [96]. An Italian study found high triglyceride levels, which is commonly seen in women with hyperinsulinemia, were associated with longer menstrual cycle lengths.[116] One study found women with diabetes had longer and heavier menstrual bleeding than non-diabetic women [44], but this association was not found in the SWAN DHS/menstrual calendar study [96]. Menstrual cycle irregularity and longer cycle lengths have been reported to increase the risk of diabetes.[117-119] However, the TREMIN study did not find an association between menstrual cycle length at age 25-29 and the subsequent risk of diabetes.[120]

Abnormal thyroid function has been linked with menstrual dysfunction. Abnormal menstruation has been linked to both hypothyroidism and hyperthyroidism in small studies of women in Greece [45, 46] and India[121]. An early descriptive study of women with hyperthyroidism found that more severe the disease was associated with less menstrual blood flow; the same study found that women with hypothyroidism had higher frequencies of menorrhagia.[122] One US based study of young adult women found that women with Grave's disease were more likely to report long cycle lengths.[38] In the SWAN study of baseline thyroid stimulating hormone (TSH) levels, increasing TSH levels were associated with increasing menstrual bleeding duration.[123] In the SWAN DHS/menstrual calendar study, thyroid conditions were not associated with menstrual cycle length, duration of menstrual bleeding, or heavier bleeding episodes.[96]

Some evidence suggests that uterine leiomyomas, commonly referred to as fibroids, impact menstrual function. Studies that examined the association between uterine leiomyomas and menstrual bleeding characteristics have been mixed. Several

studies that used ultrasound to detect fibroids have reported an association with abnormal bleeding.[47-49] However, other studies that also used ultrasound to detect fibroids have not reported an association.[124, 125] One study reported that women with uterine fibroids were more likely to have longer cycle lengths.[49] However, two other studies did not report an association between cycle length and the presence of fibroids.[33, 125] In the SWAN DHS/menstrual calendar study, fibroids were associated with shorter menstrual cycle length, but also associated with longer bleeding duration and heavier bleeding episodes.[96]

Cigarette Smoking

An important factor which contributes to medical conditions and which also influences menstrual cycle characteristics is smoking. Ethnic differences in menstrual characteristics may be due to differences in smoking prevalence. Among countries with a higher female smoking prevalence, including the US, cigarette smoking has been linked to an earlier age at menopause [97, 99-101, 103, 126-128] and shortened duration of the transition [91, 129]. In countries where there is a lower female smoking prevalence, cigarette smoking has not been associated with age at menopause[130, 131]. One study of Mexican women did not report cigarette smoking to be associated with age at menopause [132], but in another study conducted 10 years later cigarette smoking was associated with younger age at menopause [98]. The SWAN cross-sectional study found a higher percentage of current smokers were post menopausal, with a dose-response seen with increasing number of cigarettes.[2] The SWAN longitudinal study found that cigarette smoking was associated with a shorter time to menopause.[80]

A few US studies have reported shorter menstrual cycle lengths among women who smoke, [37, 38, 133] but several other studies have not found an association between cigarette smoking and menstrual cycle length.[32, 34, 109, 134] Two studies have found that cigarette smoking shortens the duration of menstrual bleeding,[133, 134] while one study found that cigarette smoking increases bleeding duration[109]. Another study found that cigarette smoking increases the daily amount of bleeding.[134] In the SWAN DHS/ menstrual calendar study, smoking history was not independently associated with cycle length, bleeding duration, or heavy bleeding.[96]

Physical Activity

Ethnic differences or differences seen in BMI and menstrual characteristics may be due to different rates of physical activity. In some studies, physical activity has been found to been associated with older age at menopause.[97, 100, 107] Other studies did not find an association between physical activity and age at menopause.[99, 103] The SWAN longitudinal study found that physical activity was associated with a longer time until menopause.[80]

Physical activity has been associated with menstrual cycle frequency and menstrual cycle length. Among athletes, less frequent menstrual cycles have been reported [135, 136]. Among post menarcheal girls and young adult women, physical activity was associated with longer cycle lengths.[31, 34, 36, 109] One study did not find an association between physical activity and menstrual cycle length.[32] Physical activity has been associated with both longer bleeding duration [109] and shorter bleeding duration.[34, 40]

Socio-economic Status

Ethnic difference in menstrual characteristics may be partially explained by differences in socio-economic status. Indicators of socio-economic status (SES) have been linked to age at menopause. Low education attainment has been associated with an earlier age at menopause in some studies [97, 98, 132], but not in several other studies[99, 126, 129, 131]. In the US, less than a high school education was associated with postmenopausal status in one population based study [106], but not in another population based study [107]. Both the SWAN cross-sectional survey and the SWAN longitudinal study found that women with less than a high school education had a shorter time to menopausal.[2, 80] Low family income and economic distresses have been associated with early entry into the menopause transition [90] as well as younger age at menopause[97]. The SWAN longitudinal study found that women who had a harder time paying for basics had a shorter time to menopause.[80]

Only a couple of studies have reported an association between socio-economic status (SES) and menstrual cycle length. A Danish study found that women with a lower social class had a higher frequency of cycle variability.[137] One US based study found that women who had not attained a high school education or who did graduate from high school had mean cycle lengths that were approximately a day shorter than women who had some post high school education.[33]

Summary and Chapter Overview

Very few menstrual calendar studies have focused on menstrual cycle characteristics among perimenopausal women. Studies among postmenarcheal and young reproductive aged women have demonstrated that demographic, lifestyle, and medical factors influence menstrual cycle characteristics. The purpose of this dissertation is to

provide a deeper understanding of how menstrual cycle characteristics change during the MT and how ethnicity, BMI, diabetes, thyroid conditions, and uterine fibroids affect menstrual cycle patterns. In Chapter 2 of this dissertation, the agreement between MT staging using annual interviews or FSH levels and MT staging using menstrual calendars is evaluated. Factors that influence this agreement are also explored. The overall change in menstrual cycle length during the MT is assessed and the association between menstrual cycle length and ethnicity, BMI, diabetes, thyroid conditions and uterine fibroids is evaluated in Chapter 3. Chapter 4 examines the distribution of menstrual bleeding characteristics, potential abnormal bleeding events, and examines the association with ethnicity, BMI, diabetes, thyroid conditions, and uterine fibroids. A summary of results is given in Chapter 5, along with clinical and public health implications and future directions.

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CHAPTER II

Poor Agreement Found Between Staging the Menopausal Transition Using Annual Interview Questions or Annual Follicle-Stimulating Hormone Measures and Menstrual Calendars

Introduction

In the past decade, the stages of women's reproductive life have become more clearly defined. The 2001 Stages of Reproductive Aging Workshop (STRAW) defined the menopausal transition (MT) as having two distinct perimenopausal stages, early and late. The start of the early MT was defined by increased variability in menstrual cycle length, defined as a change in consecutive cycle lengths of at least 7 days, while the start of the late MT was defined by amenorrhea of at least 60 days[1]. These definitions have since been validated by the ReSTAGE collaboration.[2-4] STRAW also noted that serum follicle-stimulating hormone (FSH) increases during the MT. Since STRAW, studies have demonstrated that the mean levels of FSH differ between the different stages of the MT[5] and the rates of change in FSH level also differ.[6, 7]

The data that were used to validate the menstrual bleeding markers for early and late MT stages came from prospectively collected menstrual calendars, the preferred method of data collection[8]. However, data collection using menstrual calendars is more labor intensive and therefore more costly than studies that use questionnaires. Several cohort studies of midlife women have used annual interviews to classify women's

menopausal status, yet few studies have assessed the agreement between information obtained from an annual interview and menstrual calendars in midlife women. The Melbourne Women's Midlife Health Project (MWMHP) found that the interview questions used in their study had low sensitivity for picking up menstrual cycle variability and menses flow variability.[9] The Seattle Midlife Women's Health Study (SMWHS) compared interview questions inquiring about menstrual cycle irregularity to menstrual calendars and reported weak agreement.[10] Neither of these two studies examined factors that influence agreement. The purpose of this paper was to assess the agreement between MT stages as defined by the annual interview or annual FSH level and MT stages defined by the monthly menstrual calendar in the Study of Women's Health Across the Nation (SWAN) and to examine demographic and lifestyle factors that may influence this agreement.

Methods

SWAN is a multiethnic, multi-site cohort study of middle-aged women. The design of the study has been previously described.[11] Briefly, a cross-sectional screening survey was administered to 16,065 women at seven sites between 1995 and 1997 to assess eligibility for enrollment into the cohort study. Eligibility criteria for the survey included women, age 40-55 years old, self-designation as a member of the targeted racial/ethnic group and residence in the geographic area of one of the seven clinic sites, the ability to speak English, Cantonese, Japanese, or Spanish, and the ability to give verbal consent. Each site recruited Caucasian women and women from one specified minority group (African Americans in Pittsburgh, Boston, southeastern Michigan, and Chicago; Japanese in Los Angeles; Chinese in Oakland; and Hispanic women in Newark). A total of 3302 women were enrolled into the cohort study.

Eligibility for the cohort study included age 42-52 years, an intact uterus, at least one menstrual period and no use of reproductive hormones in the previous 3 months. Institutional Review Boards at each study site approved the protocol.

The cohort study began in 1996 and annual follow-up visits have been conducted since that time. This paper includes data through annual visit 10. Each visit consisted of both interviewer-administered and self-administered questionnaires that inquired into a broad range of topics including information on menstrual experience as well as socio-demographic experience, lifestyle, and medical history. The participants also underwent physical assessments that included a blood draw.

A self-administered monthly menstrual calendar component began in 1996 and continued through 2006. Participants filled out the monthly menstrual calendars daily to capture days where any spotting or bleeding occurred. Heaviness of flow was recorded as spotting, light to moderate bleeding, or heavy bleeding. On the last day of the month women indicated whether no bleeding occurred that month by checking the appropriate box and answered questions about oral contraceptive or hormone therapy use as well as gynecological procedures which could affect bleeding. Women were asked to continuing filling out and returning the monthly calendar for 2 years after their last menstrual bleed.

Women's menstrual experience was assessed by examining their sequence of menstrual cycle lengths. A menstrual cycle consists of a bleeding episode and a subsequent bleed free interval of at least 3 days. Menstrual cycle length was calculated using bleeding definitions originally developed by the World Health Organization[8] and previously utilized in ReSTAGE analyses [2, 4].

A serum sample was obtained at each annual interview, in the morning following an overnight fast, on days 2-5 (days 2-7 from January 1996 through May 1996) of a spontaneous menstrual cycle. Two attempts were made to obtain a day 2-5 sample. If a timed sample could not be obtained, a random fasting sample was taken within 90 days of the anniversary of the baseline visit. FSH assays were conducted using an ACS-180 automated analyzer (Bayer Diagnostics Corp., Norwood, MA). FSH concentrations were measured with a two-site chemiluminometric immunoassay. The interassay coefficient of variation was 12.0%, the intraassay coefficient of variation was 6.0%, and the lower limit of detection was 1.1 IU/liter.

Classification of Reproductive Stage

Menstrual calendar

Bleeding criteria for the onset of early and late MT stages were defined from the calendar data using definitions developed by STRAW/ReSTAGE[1-4]. We defined the bleeding marker of the early MT as a persistent difference of ≥7 days in the menstrual cycle length of consecutive cycles. Persistence is defined as recurrence within 10 cycles of the first variable length cycle. The start date of early MT was then defined as the first day of the first variable length cycle. We defined two bleeding markers for late MT. The first definition, consistent with the SWAN annual interview algorithm, was the first day of the first occurrence of a cycle length of 90 days or greater. The second definition, consistent with the STRAW/ReSTAGE definition, used the first occurrence of a cycle length of 60 days or greater. The final menstrual period (FMP) was defined as the first day of a bleeding segment which was followed by at least 12 months of amenorrhea. For women who had missing calendars during the 12 months of amenorrhea, we accepted the

potential FMP in the menstrual calendar if the date was less than 31 days different from the FMP date identified in the annual interview. We also accepted the potential FMP calendar date if there were only 2 missing calendars during the 12 months of amenorrhea.

Annual Interview

The annual interview ascertained information on menstrual bleeding since the last study visit which was used to define a women's menopause status. The questions, based on the Massachusetts Women's Health Study (MWHS),[12] included the following four questions: "Did you have any menstrual bleeding since your last study visit? Did you have any menstrual bleeding in the last 3 months? What was the date that you started your most recent menstrual bleeding? Which of the following best describes your menstrual periods since your last study visit: have they become farther apart, become closer together, occurred at more variable intervals, stayed the same, become more regular, or don't know?" Early MT stage was defined as the first visit where a woman who had had a menstrual period within the last 3 months reported that the variability of her menstrual periods had increased (either became farther apart, closer together, or with more variable intervals). Late MT stage was defined as the first visit where a woman reported that she had a menstrual period in the last year but had not had a menstrual period in the last three months at the time of the interview. Final Menstrual Period (FMP) was defined retrospectively as the self-reported date of the last menstrual period after at least 12 months of amenorrhea, not due to pregnancy or lactation.

FSH Based on previous analyses of FSH trajectories using the SWAN population [6], we defined the early MT by FSH level as the first annual visit with a

serum FSH concentration between 15 and 29.9 IU/liter. We defined late MT by FSH level as the first annual visit with a serum FSH concentration of 30.0 IU/liter or greater.

Covariates

Ethnicity was self-defined and categorized as African American, Chinese, Japanese, or Caucasian. Highest education (high school graduate /GED or less than high school versus at least some college) and marital status (single, married, or separated, widowed, or divorced) were assessed at baseline. Economic strain was assessed during the initial screening survey with the question "how hard is it to pay for basics?" and was categorized as very hard, somewhat hard, or not hard. Prior use of female hormone therapy (not oral contraceptives) was assessed during the initial screening survey as well.

Height was measured without shoes using either a metric folding wooden ruler or measuring tape (home and some clinic visits), or a fixed stadiometer (clinic visits). Weight was measured without shoes, and in light indoor clothing, using a portable digital scale (home and some clinic visits) or either a digital or balance beam scale in the clinic. Body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, was categorized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m$^{2)}$, overweight (25.0-29.9 kg/m^2), or obese (≥ 30.0 kg/m^2).

Statistical analyses

For this analysis cleaned calendar data were available from four study sites (Boston, southern Michigan, Oakland, and Los Angeles). Analyses were restricted to women who had at least 10 consecutive untreated (i.e. not using hormones) menstrual cycles recorded in the menstrual calendar. We assessed agreement between MT stage based on menstrual calendar and MT stage based on the annual interview and on MT

stage based on annual FSH level in all eligible women and in women who had a documented FMP in the menstrual calendar. Since failure to observe transition stages was common among women not observed through the FMP, and the analyses were consistent (see Appendix A), we present results only for analyses among women with a documented FMP. Women were censored at the time of hysterectomy or bilateral oophorectomy. Women who started hormone therapy were excluded. Women who were already in early MT at the baseline interview were excluded from the assessment of early MT as it was not possible to assess the time of onset of early MT in these women. Similarly, women who had serum FSH concentrations of 15.0 IU/liter or greater at baseline were excluded from assessment of early MT in the comparison with FSH, and women who had serum FSH concentration of 30.0 IU/liter or greater at baseline were excluded from comparisons of early and late MT in analyses comparing FSH defined MT with MT stage by menstrual calendar.

Data were analyzed using SAS v. 9.2 (SAS Institute Inc., Carey, NC.). To compare baseline characteristics of eligible women and other participants, Pearson's chi-square or Fisher's exact tests were used to compare proportions, and Student's *t* tests were used to compare means.

To examine agreement between the MT stage by annual interview and MT stage by menstrual calendar, the date of entry into each MT stage was determined in the calendar and compared to the MT stage at the next annual interview. If the annual interview MT stage indicated a change in stage from the prior visit, then the annual interview MT stage and the calendar MT stage were determined to have occurred at the same time. If the annual interview MT stage changed at an earlier visit, then the annual

interview MT stage was determined to have occurred before the menstrual calendar MT stage. If the annual interview MT stage changed at a later visit then it was determined to have occurred after the menstrual calendar MT stage. If an annual interview MT stage, menstrual calendar MT stage, or both were not observed this was also characterized. The percent in each of these agreement categories was calculated. An example is shown in Figure 2.1. In this example, the early MT bleeding marker was observed in the menstrual calendar between annual visit 2 and visit 3. If the annual interview at visit 3 observed a change in MT stage from pre MT stage to early MT stage, then the two methods occurred at same time (0). If the annual interview observed a change at visit 4, then the early MT stage by menstrual calendar is defined as having occurred 1 visit before the annual interview (-1). If the annual interview observed the change at visit 2, then the early MT stage by menstrual calendar is defined as having occurred 1 visit after the annual interview (+1).

Agreement was defined as concordant when either the annual interview MT stage and the menstrual calendar MT stage occurred at the same time or both the annual interview MT stage and the menstrual calendar MT stage were not observed. Discordance was defined when the timing of the annual interview MT stage and timing of the menstrual calendar MT stage did not match, or if either the annual interview MT stage or the menstrual calendar MT stage were not observed. Cohen's Kappa statistics were calculated for 2 by 2 tables (Figure 2.2). Muliple logistic regression was used to examine factors that influenced discordance. The same approach was used to compare the annual FSH MT stage with the menstrual calendar MT stage.

Results

Among the 1950 participants from the four study sites, 1852 (95.0%) enrolled in the SWAN calendar study. Participation rates were as follows: Boston 94.0%, south-eastern Michigan 90.8%, Oakland 98.0%, and Los Angeles 97.6%. Of these women, 1339 (72.3%) recorded at least 10 consecutive untreated non-missing cycles and were eligible for this analysis. At baseline, eligible women were more likely to be from the Oakland and Los Angeles study sites and thus more likely to be Chinese or Japanese than non-eligible participants. Women included in this analysis were younger, more educated, and more likely to be married than other study women. Eligible women were also less likely to report economic strain and less likely to be overweight or obese than other study women, but did not differ in history of having used female hormones at baseline. (Table 2.1a)

Of the 1339 eligible women, 379 (28.3%) had their FMP recorded in the calendar study, 23 (1.7%) had a hysterectomy, 381 (28.5%) started taking female hormones, 435 (32.5%) women did not complete the calendar study through FMP or hysterectomy, and 121 (9.0%) were still recording menstrual bleeding at the end of the study. Women who had their FMP recorded were older at study enrollment, and were more likely to be from the Oakland and Los Angeles study sites, thus Chinese or Japanese, than other eligible women. Education, marital status, economic strain, BMI, and history of female hormone use did not differ at baseline between women whose FMP was and was not recorded. (Table 2.1b)

Comparison of MT stage by menstrual calendar to MT stage by annual interview.

For 42.8% of women, the early MT stage by menstrual calendar occurred at the same time as the early MT stage by annual interview.(Table 2.2) However, a large

percentage of women had their early MT stage by menstrual calendar occur more than a year before the onset of early MT stage by the annual interview, with 12% having had their early MT stage by menstrual calendar occur at one visit before and 17.2% having had their early MT stage by menstrual calendar occur two or more visits before the early MT stage was assigned by the annual interview. A smaller percentage had onset of early MT stage reported in the annual interview before the occurrence of the early MT stage by annual interview. The early MT stage by menstrual calendar occurred one visit after the early MT stage by annual interview in 6.8% and two or more visits later in 4.4% of women. An early MT stage by annual interview, early MT stage by menstrual calendar, or both was not observed in 16.8% of women. Thus, agreement was poor between the early MT stage by menstrual calendar and the early MT stage by annual interview (Kappa = -0.13, 95% confidence interval= - 0.25, -0.02).

Women from the Boston study site were more likely to be discordant (OR=2.17, 95%CI= 1.03, 4.53) than women from Los Angeles. Race/ethnicity, education, age, marital status, economic strain, BMI, and history of female hormone use were not associated with discordance.

In order to compare similar definitions of late MT stage, the late MT stage by menstrual calendar, defined as first cycle length of at least 90 days , was compared to the late MT stage by annual interview. (Table 2.2) The two classifications were concurrent in 13.5% of women. The late MT stage by menstrual calendar tended to occur earlier with 29.0% occurring one visit prior and 12.2% occurring at least two visits prior to the late MT stage by annual interview. Only 1.9% of late MT stage by menstrual calendar occurred after the late MT stage by annual interview. A large percentage of

women (21.4%) did not have the late MT stage identified by annual interview but had a late MT stage identified in the calendar, while 12.1% of women did not have their late MT stage identified by either method. Similar to the analysis of agreement of early transition, poor agreement was found between the late MT stage by menstrual calendar and the late MT stage by annual interview (Kappa= -0.18, 95%CI= -0.26, -0.11).

We next examined agreement between the STRAW/ReSTAGE preferred definition for the late MT stage by menstrual calendar (cycle length of at least 60 days) and the late MT stage by the annual interview. The two classifications were concurrent in 6.1% of the women. Similar to analysis of the 90 day definition, most women had their late MT stage by menstrual calendar occur before the late MT stage by annual interview, with 21.9% occurring one visit prior and 34.3% occurring at least two visits prior. A very small number of women (0.6%) had their late MT stage by menstrual calendar occur after being classified as in late MT stage by the annual interview. The percent of women who did not have late MT stage by annual interview but had a late MT stage by menstrual calendar was 26.6%, while 3.7% had late MT stage by annual interview but no late MT stage observed in the calendar. A small number of women (6.9%) did not have the late MT stage identified by either classification method. Similar to the results for the 90 day definition, poor agreement was found between the 60 day late MT stage by menstrual calendar and the late MT stage by the annual interview (Kappa =-0.08, 95%CI= -0.12, -0.03).

When we examined factors that influence discordance in classification between late MT stage by menstrual calendar and late MT stage by annual interview for the 90 day definition, women from Oakland were more likely to be discordant than women from

Los Angeles (OR=2.15, 95%CI= 1.18, 3.93), and a similar relationship was seen in the discordant analysis for the late MT stage by menstrual calendar 60 day definition (OR=2.33, 95%CI= 1.04, 5.26). In both discordant analyses, Chinese women were more likely to be discordant as compared to Caucasian women (late MT definition of 90 days: OR=2.09, 95%CI= 1.04, 4.23; late MT definition of 60 days: OR=2.71, 95%CI= 1.00, 7.36). African-American women were more likely to be discordant as compared to Caucasian women for the 90 day definition (OR=2.39, 95%CI= 1.00, 5.71), but not for the 60 day definition (OR=1.70, 95%CI=0.62, 4.69). Women with a high school education or less were more likely to be discordant in both analyses (the late MT stage of 90 days: OR=2.16, 95%CI= 1.08, 4.30; late MT stage of 60 days: OR=2.92, 95%CI=1.02, 8.40). Age, marital status, economic strain, BMI, and history of female hormone were not associated with discordance in either analyses of discordance.

Comparison of MT stage by menstrual calendar to MT stage by FSH

A comparison of the early MT stage by menstrual calendar with the early MT stage as defined by the FSH level at the annual visit is shown in Table 2.3. For 20.8% of the women, the classification of early MT stage by FSH level occurred at the same time as the classification of early MT stage by menstrual calendar. A similar percentage of women (16.1%) had their early MT stage by menstrual calendar occur either before their classification of early MT stage by FSH level or after (15.4%). A large percentage of women (32.2%) had an early MT stage observed in the menstrual calendar but no early MT stage by FSH level, while 10.1% of women had early MT stage by FSH level but no early MT stage by menstrual calendar. A small percentage of women (5.4%) women did not have their early MT stage classified by either method. Poor agreement was found

between the early MT stage by menstrual calendar and the early MT stage by FSH level (Kappa= -0.44, 95% CI= -0.57,-0.30). None of the factors examined (study site, race/ethnicity, age, education, marital status, economic strain, BMI, and history of female hormone use) were associated with discordance.

When we compared onset of the late MT based on the menstrual calendar (90 day definition) to onset of the late MT stage by FSH level (Table 2.3), we observed that many (43.1%) women had their late MT stage by menstrual calendar occur after their classification of late MT stage by FSH level. Only 12.7% of women had their late MT stage by menstrual calendar before their classification of late MT stage by FSH level. Unlike the early MT stage by FSH level comparison, a small proportion of women (3.3%) had a late MT stage observed in the menstrual calendar but no late MT stage by FSH level, while 20.3% of women had a late MT stage by FSH level but no late MT stage by annual interview. For a very small percentage of women (2.0%), their late MT stage was not identified by either method. Poor agreement was found between the late MT stage (90 day definition) in the menstrual calendar and the late MT stage by FSH level (Kappa= -0.32, 95%CI= -0.42,-0.23). In this analysis, obese women were less likely to be discordant as compared to women with normal BMI (OR=0.39 95%CI= 0.20, 0.77). Study site, race/ethnicity, age, education, marital status, economic strain, and history of female hormone use were not associated with discordance.

In contrast, when we compared the late MT stage by menstrual calendar (60 days definition) to the late MT stage by FSH level (Table 2.3), for 21.0% of women the late MT stage occurred at the same time by both measures. A similar percentage had their late MT stage by menstrual calendar occur either before (32.0%) or after (36.1%) their

late MT stage by FSH level. A small proportion of women (4.2%) had a late MT stage by menstrual calendar observed but no late MT stage by FSH level, while only 5.6% of women had a late MT stage by FSH level but no late MT stage by menstrual calendar observed. Again a very small percentage of women (1.3%) did not have their late MT stage identified by either method. Poor agreement was seen in the comparison of the late MT stage (60 days definition) with the late MT stage by FSH level (Kappa= -0.63, 95%CI= -0.70,-0.56). Unlike the comparison for the 90 days definition, BMI was not associated with discordance nor were any of the other factors.

Discussion

This study assessed agreement between MT stage as defined by a menstrual calendar compared to status defined by annual interview and by annual FSH level in SWAN. Poor agreement was found between the menstrual calendars and the annual interviews. Menstrual calendars identified the start of early and late MT earlier than the annual interviews. For the early MT, 29.2 % of women had their status change in the menstrual calendar occur before it was reported in the annual interview. The late MT stage by menstrual calendar 90 days definition occurred earlier in 41.2% of the women and the late MT stage by menstrual calendar 60 days definition occurred earlier in 56.2% of women. Poor agreement was also found between the menstrual calendar and the annual FSH level.

Increasing variability in menstrual cycle frequency has been a hallmark description of the onset of the MT.[4, 13] Using this definition to mark the start of the early MT, our study found poor agreement between the menstrual calendar and the annual interview as the annual interview frequently identified early MT 1-3 years later than the menstrual calendar. Other studies of midlife women have found poor agreement

between menstrual calendars and interviews when defining menstrual cycle variability. The MWMHP reported that annual interviews had low sensitivity in detecting menstrual cycle irregularity, defined as change in menstrual cycle frequency.[9] The SMWHS reported poor agreement between annual interviews and menstrual calendars in detecting menstrual cycle irregularity (Cohen's kappa= .19).[10]

The reasons for poor agreement for the early MT may be due to differences in women's versus researchers' interpretation of menstrual cycle variability. The annual interview question used to define the start of the early MT in SWAN asked a woman to decide if her menstrual periods were farther apart, closer together, or more variable since her last visit. No definition of what farther apart, closer together, or more variable was provided. Therefore, women might not all use the same definition nor use the same definition as researchers. They might only note increased cycle variability when the difference in cycle length is greater than seven days or when differences start to occur more frequently. Our data suggests this may be true given that for approximately one-third of the women the menstrual calendars identified the start of the early MT stage earlier than the annual interviews.

In this study we also found poor agreement between menstrual calendars and annual interviews regarding onset of the late MT stage. We used two definitions for the start of the late MT in the menstrual calendars, a cycle length of at least 90 days and a cycle length of at least 60 days. The 90 days definition gained prominence in the 1990's[14] and was easily applied in the clinical setting. Recently, the 60 days definition has been found to be a better marker for the late MT stage, since 9.0% to 21.4% of women have passed their FMP before experiencing 90 days of amenorrhea. [2] In this

analysis, women were more likely to have experienced the late MT bleeding marker of at least 60 days (89.4%) than the late MT bleeding marker of at least 90 days (77.8%).

As with the early MT, the menstrual calendars place the start of the late MT earlier than the annual interview. This finding is not surprising given the structure of the annual interview questions used to identify late MT. The questions were based on the MWHS[15] which were designed to capture women who were currently experiencing 3 to 11 months of amenorrhea and were thus likely to be classified as post-menopausal at their subsequent visit[14]. The annual interview failed to detect a late MT stage in 33.5% of the women. All of these women were classified as having changed from early MT directly to being post-menopausal. The annual interview questions ascertained only whether a woman currently had not bleed for three months, not whether she had experienced an episode of amenorrhea lasting 90 days or longer in the past year. If in the past year, a woman had had a menstrual cycle that was 90 days or greater but also had a menstrual cycle in the three months preceding the annual interview, she would be classified as being in the early MT by the annual interview definition. However, she would be staged as late MT by the menstrual calendar. A better interview approach to identify the start of the late MT would be to ask about the occurrence of any cycle that was 60 days or greater since the last study visit. This approach was used in the SMWHS, which found good agreement (Cohen's kappa =.71) between their interview and their menstrual calendar status classification, especially once a definition of skipped period was given to study participants. [10]

We found the agreement for staging the late MT was influenced by study site, ethnicity, and educational attainment. Chinese women were most likely to have their

menstrual calendars and annual interview be discordant. One US study found that Asian women were less likely to accurately recall their last menstrual cycle length; however, the association disappeared once other factors were taken into account including education and income[16]. Our study found women with a high school education or less were more likely to be discordant. Two studies have found that women with a lower educational attainment were less likely to recall their last menstrual cycle length, however the associations were not statistically significant.[16, 17] Both of these studies also reported that women with lower incomes were less likely to accurately recall their last menstrual cycle.

This study also found poor agreement between menstrual calendars and MT classification by annual FSH levels. Although definitive FSH staging criteria have not been established[18], recent publications give guidance on appropriate values in the SWAN population[6]. However, for the early MT, one-third of the women did not have an early MT identified by annual FSH levels suggesting that single annual measurements of FSH levels frequently miss the rise of FSH, and more frequent measurements may be necessary. For the late MT stage of 90 days, we found obese women were less likely to be discordant, consistent with the evidence that obesity affects FSH levels.[6]

This study has some limitations. Since women were enrolled into the study between the ages of 42-52 years, left censoring likely occurred such that women may have started the MT before entry into the study. It is possible that the women we determined to be pre-menopausal at baseline interview were already in early MT at the time the study began. Selection bias could also have been a factor. Women who were eligible for this analysis were more likely to be younger, Chinese or Japanese, and to be

married as compared to other SWAN participants. Eligible participants were also less likely to be overweight or obese and were less likely to experience economic strain, which could reduce power to detect associations.

In conclusion, we found poor agreement between menstrual calendars and annual interviews when staging women during the MT. Accurately identifying MT stage has implications for interventions and healthcare. Bone loss is accelerated in the last couple of years prior to the FMP [19], as well as adverse changes in lipid profiles [20]. Treatment and lifestyle intervention should optimally begin before this time period. Since menstrual calendars are considered the gold standard when measuring menstrual cycle characteristics, these results suggest the need to improve questionnaire based approaches to classification of MT stage. Currently available instruments do not adequately capture the start of the early MT. For the late MT stage, questions that are similar to the skipped periods question used in SMWHS are suggested and need to be validated in a multiethnic population. Increasing the frequency of interviews and blood draws may also be warranted. These results also suggest that misclassification of stage may be an important concern in studies that assess change in health status by MT stage based on annual interview classification. Re-analysis of major findings using menstrual calendar based classifications is likely warranted.

Figure 2.1 An Example of the Comparison Between the Annual Interviews (Baseline and Visits) to the Menstrual Calendar. The early menopausal transition (MT) bleeding marker occurs in the menstrual calendar between annual visits 2 and 3. If the annual interview notes a change in menopausal status from premenopausal to early perimenopausal at visit 3 then the two methods are in agreement (0). Instead, if the annual interview notes a change in menopausal status at visit 4, then the early MT stage by menstrual calendar occurs 1 visit prior to the annual interview (-1). If the annual interview notes a change in menopausal status at visit 2, then the early MT stage by menstrual calendar occurs 1 visit after the annual interview (+1).

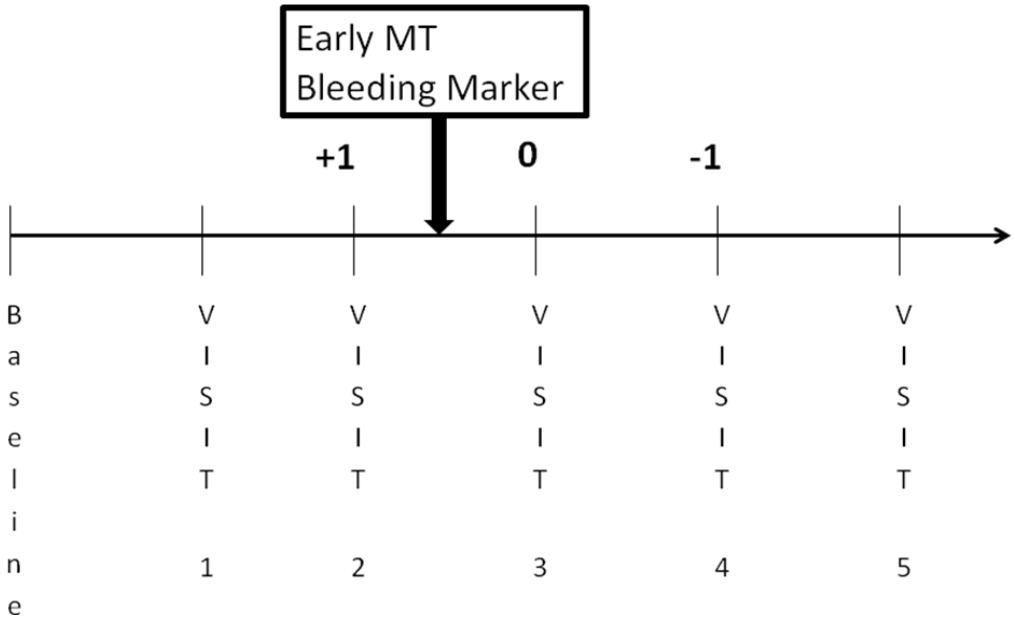

Figure 2.2 The 2 by 2 Table for Calculation of Cohen's Kappa Statistic

		Menstrual Calendar	
		Yes	**No**
Annual Interview	**Yes**	Same time	Interview stage before calendar stage + Interview stage but no calendar stage
	No	Calendar stage before interview stage + Calendar stage but no interview stage	Neither interview stage nor calendar stage observed

Table 2.1a Baseline Demographics of Women Participating in the SWAN Menstrual Calendar Study

	Eligible Participants[1] n=1339	All Others n=611	P-value[2]
Age at Screener in years, Mean (SD)	45.5 (±2.6)	46.5 (±2.9)	<.01
	n (%)	n (%)	
Study Site			
Michigan	301 (22.5)	242 (39.6)	<.01
Boston	290 (21.7)	162 (26.5)	
Oakland	350 (26.1)	109 (17.8)	
Los Angeles	398 (29.7)	98 (16.0)	
Race/Ethnicity			
African-American	263 (19.6)	261 (42.7)	<.01
Chinese	202 (15.1)	48 (7.9)	
Japanese	226 (16.9)	55 (9.0)	
Caucasian	648 (48.4)	247 (40.4)	
Language of Baseline Interview			
English	1168 (87.2)	561 (91.8)	.01
Cantonese	86 (6.4)	23 (3.8)	
Japanese	85 (6.4)	27 (4.4)	
Education			
Less than High School	51 (3.8)	40 (6.7)	<.01
High School Grad	202 (15.2)	120 (20.0)	
Some College/Vocation	421 (31.6)	220 (36.6)	
College Graduate	319 (24.0)	114 (19.0)	
Post College	339 (25.5)	107 (17.8)	
Missing	7	10	
Marital Status			
Single	204 (15.4)	96 (15.9)	<.01
Married	902 (68.0)	349 (57.8)	
Separated	40 (3.0)	37 (6.1)	
Widowed	17 (1.3)	21 (3.5)	
Divorced	163	101 (16.7)	
Missing	13		
How Hard Is It To Pay For Basics			
Very Hard	89 (6.7%)	68 (11.3)	<.01
Somewhat Hard	341 (25.8)	199 (22.1)	
Not Hard	891 (67.5)	335 (55.7)	
Missing	18	9	
Body Mass Index, kg/m^2			
Underweight (<18.5)	33 (2.5)	16 (2.7)	<.01
Normal (18.5-24.9)	727 (55.1)	238 (39.8)	
Overweight (25.0 -29.9)	275 (20.9)	153 (25.6)	
Obese(≥ 30.0)	284 (21.5)	191 (31.9)	
Missing	20	13	
Ever taken hormones at screener	150 (11.3)	73 (12.1)	.61
Missing	17	10	

[1]At least 10 consecutive untreated non-missing cycles observed in calendar

[2]Missing not included in P-[2]value calculation.

Table 2.1b Baseline Demographics of Women Participating in the SWAN Menstrual Calendar Study with at least 10 Consecutive Untreated Non-Missing Cycles Observed by FMP Status

	FMP observed N=379	NO FMP observed N=960	P-value[1]
Age at Screener in years , Mean (SD)	46.3 (±2.5)	45.2 (±2.5)	<.01
	n (%)	n (%)	
Study Site			
Michigan	60 (15.8)	241 (25.1)	. <.01
Boston	76 (20.1)	214 (22.3)	
Oakland	107 (28.2)	243 (25.3)	
Los Angeles	136 (35.9)	262 (27.3)	
Race/Ethnicity			
African-American	47 (12.4)	216 (22.5)	<.01
Chinese	72 (19.0)	130 (13.5)	
Japanese	94 (24.8)	132 (13.8)	
Caucasian	166 (43.8)	482 (50.2)	
Language of Baseline Interview			
English	305 (80.5)	863 (89.9)	<.01
Cantonese	32 (8.4)	54 (5.6)	
Japanese	42 (11.1)	43 (4.5)	
Education			
Less than High School	15 (4.0)	36 (3.8)	.99
High School Grad	57 (15.0)	145 (15.2)	
Some College/Vocation	119 (31.4)	302 (31.7)	
College Graduate	91 (24.0)	228 (23.9)	
Post College	97 (25.6)	242 (25.4)	
Missing	0	7	
Marital Status			
Single	62 (16.5)	142 (15.0)	.16
Married	267 (71.0)	635 (66.8)	
Separated	8 (2.1)	32 (3.4)	
Widowed	3 (0.8)	14 (1.5)	
Divorced	36 (9.6)	127 (13.4)	
Missing	3	10	
How Hard Is It To Pay For Basics			
Very Hard	16 (4.3)	73 (7.7)	.08
Somewhat Hard	98 (26.3)	243 (25.6)	
Not Hard	259 (69.4)	632 (66.7)	
Missing	6	12	
Body Mass Index, kg/m^2			
Underweight (<18.5)	13 (3.5)	20 (2.1)	.12
Normal (18.5 -24.9)	219 (58.7)	508 (53.7)	
Overweight (25.0 -29.9)	69 (18.5)	206 (21.8)	
Obese(≥ 30.0)	72 (19.3)	212 (22.4)	
Missing	6	14	
Ever taken hormones at screener	35 (9.4)	115 (12.1)	.16

[1]Missing not included in P-value calculation

Table 2.2 Menopausal Transition (MT) Stage by Menstrual Calendar Compared to MT Stage by Annual Interview among Those with Observed FMP in the Menstrual Calendar

	Early MT Stage[1] n=250		Late MT Stage (≥ 90 days) n=379		Late MT Stage of (≥ 60days) n=379	
	n	**%**	**n**	**%**	**n**	**%**
No Interview MT stage	7	2.8	81	21.4	101	26.6
3+ visits before Interview (-3)	18	7.2	18	4.8	52	13.7
2 visits before Interview (-2)	25	10.0	28	7.4	78	20.6
1 Visit before Interview (-1)	30	12.0	110	29.0	83	21.9
Markers at Same Time (0)	107	42.8	51	13.5	23	6.1
1 visit after Interview (+1)	17	6.8	6	1.6	1	0.3
2 visits after Interview (+2)	9	3.6	0	0.0	0	0.0
3+ visits after Interview (+3)	2	0.8	1	0.3	1	0.3
No Calendar Marker	18	7.2	38	10.0	14	3.7
Neither Marker nor Interview	17	6.8	46	12.1	26	6.9
% Agreement	124	49.6	97	25.6	49	12.9
Kappa (95% Confidence Interval)	-0.13 (-0.25, -0.02)		-0.18 (-0.26, -0.11)		-0.08 (-0.12,-0.03)	

[1]Note for comparison of early MT stage by menstrual calendar to early MT stage by annual interview, women who determined to be in early MT stage by baseline interview were excluded. If early MT stage by menstrual calendar occurred at same time or after the late MT stage by menstrual calendar than then early MT stage by menstrual calendar was set to missing.

Table 2.3 MT Stage by Menstrual Calendar Compared to MT Stage by FSH Level among Those with Observed FMP in the Menstrual Calendar

	Early MT Stage[1] n=149		Late MT Stage (≥ 90 days)[2] n=300		Late MT Stage (≥ 60days)[2] n=300	
	n	%	n	%	n	%
No MT stage by FSH	48	32.2	10	3.3	12	4.0
3 visits before FSH (-3)	6	4.0	7	2.3	17	5.7
2 visits before FSH (-2)	6	4.0	8	2.7	23	7.7
1 Visit before FSH (-1)	12	8.1	23	7.7	52	17.3
Markers at Same Time (0)	31	20.8	56	18.7	63	21.0
1 visit after FSH (+1)	13	8.7	59	19.7	49	16.3
2 visits after FSH (+2)	6	4.0	23	7.7	26	8.7
3 visits after FSH (+3)	4	2.7	47	15.7	29	9.7
No Calendar Marker	15	10.1	61	20.3	25	8.3
Neither Marker nor FSH	8	5.4	6	2.0	4	1.3
% Agreement	39	26.1	62	20.7	67	22.3
Kappa and 95%Confidence Interval	-0.44 (-0.57,-0.30)		-0.32 (-0.42,-0.23)		-0.60 (-0.68,-0.53)	

[1]For comparison of early MT stage by menstrual calendar to early MT stage by FSH, women who determined to have an FSH level at baseline of 15.0 IU/liter or greater were excluded. If early MT stage by menstrual calendar occurred at same time or after the late MT stage by menstrual calendar then the early MT stage by menstrual calendar was set to missing.

[2]For comparisons of late MT stage by menstrual calendar to late MT by FSH, women who determined to have an FSH level at baseline of 30.0 IU/liter or greater were excluded.

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CHAPTER III

Quantile Regression Models of Factors Associated with Menstrual Cycle Length During the Menopausal Transition

Introduction

The Stages of Reproductive Aging Workshop (STRAW) criteria for staging reproductive age in women were recently updated (STRAW+10) to clarify the stages of late reproductive life and the post menopause as well as the menstrual bleeding criteria for the early and late menopausal transition (MT) [1-4]. While the menstrual criteria for defining the onset of each stage of the MT have been identified, little is still known about population differences in menstrual cycle characteristics during the MT. Of interest is not only how menstrual cycle length changes during the MT, but which factors influence menstrual cycle length and their pattern of change as women move through the transition. Prior studies of younger women have found ethnic differences in menstrual cycle length [5-7] as well as differences in menstrual cycle length by body mass index (BMI) [7-11]. BMI has also been shown to influence the levels and trajectories of change of the reproductive hormones follicle-stimulating hormone (FSH) and estradiol.[12] The few studies in the age group of women [13-16] that are based on prospectively collected menstrual diaries, the preferred method in evaluating menstrual cycle length [17], were conducted in Caucasian populations.

Studies that have examined factors that influence menstrual cycle length have mostly focused on factors that influence the mean. The distribution of menstrual cycle

length in perimenopausal women is often skewed [18], so that the median is much more informative about central tendency than the mean. Quantile regression allows for examining factors that influence the median as well as factors that influence different parts of the distribution.[19] The purpose of the present study was to utilize quantile regression to examine the pattern of menstrual cycle length during the MT and to assess the association of ethnicity, BMI, and medical conditions with menstrual cycle length among a multiethnic cohort of midlife women in the Study of Women's Health Across the Nation (SWAN).

Methods

Study design and population

This analysis includes women from three SWAN sites: southeastern Michigan, Los Angeles, and Oakland which participated in the menstrual calendar substudy. The design of the main cohort study has been previously described.[20] Briefly, a cross-sectional screening survey was administered to 6,345 women at the three of study sites between 1995 and 1997 to assess eligibility for enrollment into the cohort study. Eligibility for the cohort study included age 43-52 years, self-designation as a member of the targeted racial/ethnic group, residence in the geographic area of one of the three clinic sites, the ability to speak English, Cantonese, Japanese, the ability to give verbal consents, an intact uterus, at least one menstrual period and no use of reproductive hormones in the previous 3 months. Each site recruited Caucasian women and women from one specified minority group (African Americans in southeastern Michigan, Japanese in Los Angeles, and Chinese in Oakland). A total of 1498 women were enrolled into the cohort study from the three study sites. Institutional Review Boards at each study site approved the protocol.

The SWAN cohort study began in 1996 and annual follow-up visits have been conducted since that time. Each visit consisted of both interviewer administered and self administered questionnaires that inquired into a broad range of topics including information on menstrual experience as well as socio-demographic characteristics, lifestyle, and medical history. The participants also underwent physical assessments which included a blood draw.

A self-administered menstrual calendar component began in 1996 and continued through 2006, corresponding to the tenth annual follow-up visit. Participants filled out the menstrual calendars daily to capture days where any spotting or bleeding occurred. On the last day of the month women indicated whether no bleeding occurred that month by checking the appropriate box and answered questions about oral contraceptive or hormone therapy use as well as gynecological procedures which could affect bleeding. Women were asked to continuing filling out and returning the monthly calendar for two years after their last menstrual bleed. The menstrual calendar substudy included additional end of the month questions which included information on cigarette use and physical exercise.

Women's menstrual experience was assessed by examining their sequence of menstrual cycle lengths. Menstrual cycle length was calculated using bleeding definitions originally developed by the World Health Organization[17] and previously utilized in ReSTAGE analyses[21-23]. A menstrual cycle consists of a bleeding episode and a subsequent bleed free interval of at least 3 days. Onset of the early MT was defined from the calendar data using definitions developed by the STRAW[24] and refined by the ReSTAGE collaboration[21-23] and adapted by STRAW+10[1-4]. The

start of the early transition is defined by the persistent difference of at least 7 days in the length of consecutive menstrual cycles. Persistence is defined as recurrence within 10 cycles of the first variable length cycle. The start date of the early transition is the date of the first variable length cycle.

The final menstrual period (FMP) was defined as the first day of a bleeding segment which was followed by at least 12 months of amenorrhea. For women who had missing calendars during the 12 months of amenorrhea, we accepted the potential FMP in the menstrual calendar if no more than 2 calendars were missing or if the date was less than 31 days different from the FMP date identified by the annual interviews.

Hormone therapy use, which included hormone replacement therapy, oral contraceptives, or chemotherapy, was assessed monthly. For months with missing hormone information, menstrual cycles were coded as untreated if a woman never reported hormone therapy use in the study, if the menstrual cycle occurred before the first report of hormone therapy use, or if the menstrual cycle occurred in a year where no hormone therapy use was reported in the monthly calendars or annual interview.

Height was measured without shoes using either a metric folding wooden ruler or measuring tape (home and some clinic visits), or a fixed stadiometer (clinic visits). Weight was measured at each annual visit without shoes, and in light indoor clothing, using a portable digital scale or either a digital or balance beam. For each menstrual cycle, weight was linearly interpolated between the last annual visit and the next annual visit. BMI, calculated as weight in kilograms divided by height in meters squared, was categorized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m$^{2)}$ overweight (25.0-29.9 kg/m^2), or obese (≥ 30.0 kg/m^2).

At each annual interview women were asked whether they were diagnosed with diabetes since the last visit or were taking any medications for diabetes (high blood sugar). Serum glucose levels were also measured at each of the first seven annual visits. A woman was considered diabetic if she indicated she was diagnosed with diabetes, was taking diabetes medication, or had a serum glucose level of ≥126 mg/dl. Women were also asked if they were diagnosed with a thyroid condition or were taking medication for a thyroid condition, and if they had been diagnosed with uterine fibroids. For each of the three medical conditions above, six months was subtracted from the annual visit date a woman first indicated she had the condition and all menstrual cycles on or after this date were considered to have the condition.

Women were asked to indicate whether they smoked at least one cigarette a day or a total of 30 cigarettes in the last month and positive responses were considered current cigarette use for that month. If a woman never indicated she was a smoker, all her menstrual cycles were considered non-smoking. Women were asked if they participated in moderate to vigorous physical activity, the average times a week they participated and the average minutes they participated each time. Average total hours of physical activity per week were calculated for each month. For menstrual cycles that covered more than one month, the highest average total hours of physical activity per week was used.

Ethnicity was self-defined and categorized as African American, Chinese or Chinese American, Japanese or Japanese, or Caucasian. Highest education (high school graduate /GED or less than high school versus at least some college) and marital status (single, married, or separated, widowed, or divorced) were assessed at baseline. Economic strain was assessed at baseline with the question “how hard is it to pay for

basics?" and was categorized as very hard, somewhat hard, or not hard. Prior use of female hormones (yes/no), which did not include oral contraceptives, was also assessed at baseline.

Data Analysis

Of the 1498 women who were enrolled, 1320 (88.2%) were eligible for this analysis. An eligible woman had a least one untreated menstrual cycle recorded in the menstrual calendars with menstrual cycle-level covariate information available. Menstrual cycles were excluded if women were on hormones or hormone use could not be ruled out. Menstrual cycles observed after periods of hormone use were included and identified by an indicator variable. Women were censored at time of hysterectomy, bilateral oophorectomy, or chemotherapy. Pregnancy and post pregnancy cycles were excluded as were cycles which had missing covariate information. The number of menstrual cycles for each set of models by exclusion criteria is given in Table 3.1.

Baseline demographics were compared for eligible women and non-eligible women. Pearson's chi-square or Fisher's exact tests were used to compare proportions, and Student's *t* tests were used to compare means between groups. The distribution of menstrual cycle length is not normal; it is right-skewed (Figure 3.1). Therefore, the median is more informative than the mean. Quantile regression permits evaluation of factors affecting cycle length at the center of the distribution as wells as the tails. In order to examine central tendency and variance, quantile regression was used to model menstrual cycle length at the 25th, 50th, 75th, and 90th percentiles. The regression coefficients of a quantile regression are interpreted similarly to regression coefficients of a linear regression. For example, the regression coefficients of a categorical predictor

represent the difference in menstrual cycle length for the relevant percentile between one category and the reference group, adjusted for all other covariates in the model. To better reflect the standard error in our data which included repeated measures, bootstrap sampling with 500 repetitions was conducted to construct 95% confidence intervals (CI). The bootstrap sampling was based on samples of women and not menstrual cycles. If a woman was selected then all of her eligible menstrual cycles were included.

Two sets of quantile regression models were evaluated. First we included women who were identified as having started the MT during the calendar substudy (n=963) and examined correlates of cycle length occurring after the onset of the transition, including time since the start of the transition. Only menstrual cycles after the start of the MT were included. For univariate analysis, the potential list of correlates was chosen as factors that have been shown to be associated with menstrual cycle length in younger reproductive aged women (results shown in Appendix B). Covariates were included in the adjusted model if there was evidence of an adjusted association with the right-tail. The same adjusted model was used for each of the four percentiles of interest. Time since the start of the MT was added to the multivariate model using a natural cubic spline. Initially, knots were placed at years 1-9. The figure was inspected visually, and knots that did not contribute to the fit were deleted. The final natural cubic spline contained knots at 2, 3, 4, 5, and 6 years. Statistical interaction between time since the start of the MT and the other covariates was examined graphically.

Our second set of models included women who had a defined final menstrual period (FMP) in the menstrual calendar data (n=431). All cycles prior to FMP were included and time until FMP was included as a covariate. In order to compare the FMP

adjusted models with the start of the MT adjusted models, the same covariates were included in the models, except for above median age at the start of transition. No association was seen with the variable above median age at the FMP. Time until the FMP was added to the models using a natural cubic spline, with knots at -5, -4,-3,-2, and -1 years until the FMP.

Data programming and analysis of baseline demographics was done using SAS 9.2 (Cary, NC). Quantile regression was conducted using the quantreg package in R 2.13.1, developed by Roger Koenker[19].

Results

Of the 1320 eligible women, 963 (73.0%) had the onset of the early MT observed in the menstrual calendar while 431 (32.7%) had their FMP identified. Additionally 19 (1.4%) had a hysterectomy, 233 (17.7%) began using hormones and had no further untreated menstrual cycles observed, and 637(48.3%) withdrew from the study before their FMP was identified. Baseline demographics of women who participated in the SWAN by eligibility for each set of analyses are shown in Table 3.2. Women who had eligible calendar data for this analysis were younger, had higher educational attainment, were more likely to be married, had less economic strain, and had smaller BMI. Eligible women were less likely to be from Michigan, African-American, or current smokers. Women eligible for the analysis since the onset of early MT were also were also less likely to ever be diagnosed with diabetes or fibroids. In contrast women who had their FMP observed were older, but were more likely to ever be diagnosed with diabetes, have diabetes during substudy participation, ever diagnosed with fibroids, and have fibroids during substudy participation.

The relationship between menstrual cycle length and time since the start of the MT is displayed in Figure 3.2 and is for women in the reference categories based in the models shown in Table 3.3. That is, estimated cycle lengths are for women who were Caucasian, normal or underweight, had an age at the start of the transition <46.25 years, did not smoke, had at least some post high school education, and did not have any moderate or physical activity during the average week. At approximately 2 years after the start of the MT, the menstrual cycle length distribution begins to widen. as seen by increases in the 75^{th} and 90^{th} percentiles. From 2 to 8 years, menstrual cycle lengths at the 90^{th} percentile increased sharply. At approximately 7.5 years after the start of the MT, the variance of estimated menstrual cycle length increased for each of the four percentiles, suggesting greater variability of menstrual cycle length as the FMP approaches.

The quantile regression models for the 25^{th}, 50^{th}, 75^{th}, and 90^{th} percentile of menstrual cycle lengths among women since the start of the MT are given in Table 3.3. Associations were adjusted for all factors listed in the table as well as time since the start of the MT. The intercepts are the estimated menstrual cycle length for women in the reference category at the start of the MT. Women whose age at the start of the MT was above 46.25 years had longer cycle lengths at the 50^{th}, 75^{th}, and 90^{th} percentiles as compared to women with a younger age at the start of the MT. Chinese and Japanese women had longer menstrual cycle lengths than Caucasian women at each of the four percentiles. Obese women had longer menstrual cycle lengths than normal/underweight women at each of the four percentiles. Overweight women had longer menstrual cycle lengths than normal/underweight women at the 25^{th} and 50^{th} percentiles. Current smoking and high school education or less was associated with longer menstrual cycle lengths at

the 75th and 90th percentiles. Hours of moderate or vigorous physical activity per week was associated with longer menstrual cycle lengths at the 90th percentile. Diabetes was associated with longer menstrual cycle length at the 50th percentile (0.70 days, 95% CI: 0.03, 1.36). Uterine fibroids, thyroid disorders, or previous hormone use during the study were not associated with menstrual cycle length. We found no evidence of statistical interaction between time since the start of the MT and the other covariates.

The relationship between menstrual cycle length and time until the FMP is shown in Figure 3.3, for women in the reference categories of the models displayed in Table 3.4. Estimated cycle lengths are for women who were Caucasian, normal or underweight, did not smoke, had at least some post high school education, and did not have any moderate or physical activity during the average week. At approximately 7.5 years prior to the FMP, the distribution of menstrual cycle lengths begins to increase as shown by the increase in the 90th percentile. The steepest increase in menstrual cycle length is seen between 4 and 1.5 years prior to the FMP. In the last 2 years prior to the FMP, the variance of estimated menstrual cycle length increased for each of the four percentiles.

African-American women had longer menstrual cycle lengths than Caucasian women at the 50th and 75th percentile in the time until the FMP models (Table 3.4). Chinese women had longer menstrual cycle lengths than Caucasian women at each of the four percentiles. Japanese women had longer menstrual cycle lengths than Caucasian women at the 25th, 50th, 75th percentile. The relationship between BMI and menstrual cycle length in the time until the FMP models were similar to those observed in the time since the start of the MT models. Obese women had longer menstrual cycle lengths at each of the four percentiles while overweight women had longer menstrual cycle lengths

at the 25th and 50th percentiles. Hours of moderate or vigorous physical activity per week was associated with longer menstrual cycle lengths at the 75th and the 90th percentile. . In the time until the FMP models, above the median age at FMP, current smoking, education, medications, and hormone use were not associated with menstrual cycle lengths. No evidence to suggest statistical interaction was observed between time until the FMP and the other covariates.

Discussion

This paper is one of the first to assess whether factors that have been identified as influencing menstrual characteristics in adolescent and young adult women also influence menstrual cycle length as women transition through the menopause. Quantile regression facilitated understanding of how factors influence the median and the tails of the distribution. Chinese and Japanese women had longer menstrual cycle lengths throughout the distribution as compared to Caucasian women, as did obese women compared to normal weight women. Increased moderate to vigorous physical activity lengthened the menstrual cycle only at the right tail of the distribution. There was some evidence to suggest that current cigarette smoking also increased menstrual cycle length at the right tail.

The relationship between time since the onset of the MT or time until the FMP and menstrual cycle length is not uniform. Increases in menstrual cycle length, as women progress through the transition, are mostly limited to the upper percentiles of the distribution, with the median unaffected until 3 years prior to the FMP, when a small increase is seen. In our population, menstrual cycle length in the right tail began to increase approximately 2 years after the start of the MT or 7 years prior to the FMP. In a prior analysis from the same cohort [12], FSH levels were observed to rise in a similar

timeframe indexed to the FMP. In an analysis of the TREMIN Trust data, the average menstrual cycle length began to rapidly increase starting at four years prior to the FMP.[25] Two years prior to the FMP, menstrual cycles become highly variable as seen by the increase in the 95% CI for all four percentiles. The Melbourne Midlife Women's Health Project found a similar result; menstrual cycle length variability was the highest during the last 17 menstrual cycles prior to the FMP [15] , as was the rate of FSH increase in SWAN.[12]

Prior studies have suggested that menstrual cycle characteristics differ by ethnicity. The Semiconductor Health Study in California and Utah found that Asian women had menstrual cycle lengths that were approximately two days longer than Caucasian women.[6] A similar result was reported by the Women's Reproductive Health Study.[7] In the present study, Chinese and Japanese women had longer menstrual cycle lengths than Caucasian women, suggesting that Asian women have longer menstrual cycle lengths throughout the reproductive lifespan. One North Carolina study among adolescents found African-American adolescents had shorter menstrual cycles than Caucasians.[5] In the current study, African-American women had longer menstrual cycle length as compared to Caucasians at both the 50^{th} and 75^{th} percentiles, when indexed to the FMP.

We found obese women had longer menstrual cycle length than normal weight women across the distribution of menstrual cycle length. Prior studies have found a similar association. Higher BMI has been shown to be associated with longer menstrual cycle lengths in women aged 17-19 [8] and women aged 20-40 [7, 9-11]. However, not all studies have found an association between menstrual cycle length and BMI.[6, 26, 27]

Obesity is associated with circulating levels of the hormones FSH and estradiol in SWAN and other studies of the MT.[12, 28-30]

Several studies have demonstrated an association between physical activity and longer menstrual cycle length. In athletes, less frequent menstrual cycles have been reported. [31, 32] Among adolescent girls [5] and young adult women [8, 33, 34], physical activity increased mean menstrual cycle length. In the present study, physical activity was associated with longer menstrual cycle length at the right tail of the distribution, but not at the median.

In this study, current cigarette smoking was associated with longer menstrual cycle length in the upper percentiles for women indexed to the start of the transition. A similar association was not seen in the models indexed to the FMP. Prior studies examining cigarette use have not found an association [6, 33-35], or have found that smoking is associated with shorter menstrual cycle lengths[9, 10, 36]. Smokers have been shown to have an earlier age at menopause than non-smokers in the population from which the SWAN cohort was selected [37] as well as other populations [38-43]. Smokers have also been shown to have a shorter duration of perimenopause [44, 45], thus the longer cycles exhibited by smokers, when indexed to the start of the MT, may reflect the shorter duration of perimenopause in these women.

This study has some important limitations. The mean age of women eligible for this study was 45.7 years. It is possible that the start of the MT occurred earlier than enrollment into the study. Age-eligible women who were in the late stage of the MT or who had already experienced their FMP were excluded. Women with younger ages at FMP may have different patterns of menstrual cycle characteristics [46]. The ethnic

differences we observed could reflect study site differences. In the cross-sectional study, from which the SWAN cohort study was selected, African-American women were more likely to have had a hysterectomy than other women and thus less likely to be enrolled into the cohort study [37]. In the current analysis, African-American women were less likely to have either the start of the MT observed or their FMP observed. Women with diabetes and women with fibroids were also less likely to be included in this analysis, which may have affected our ability to detect an association for either of these diseases.

In conclusion, we found increases in menstrual cycle length during the MT to occur mostly in the right tail, reflecting a greater propensity for longer menstrual cycles. Greater variability in extreme menstrual cycle length was seen during the 2 years prior to the FMP. Chinese, Japanese, and obese women had longer menstrual cycle lengths during the MT. An important next step would be to examine how patterns of menstrual cycle length influence the duration of the MT. Women with longer mean menstrual cycles during their reproductive years have been shown to have a later age at menopause [18, 47], and those women with shorter mean menstrual cycle lengths have demonstrated an earlier age at menopause [41, 48]. If certain patterns of menstrual cycle length are associated with age at menopause, physicians could then use this information to help women predict when their final menses is likely to occur.

Figure 3.1 Kernel Density Plot of Menstrual Cycle Length

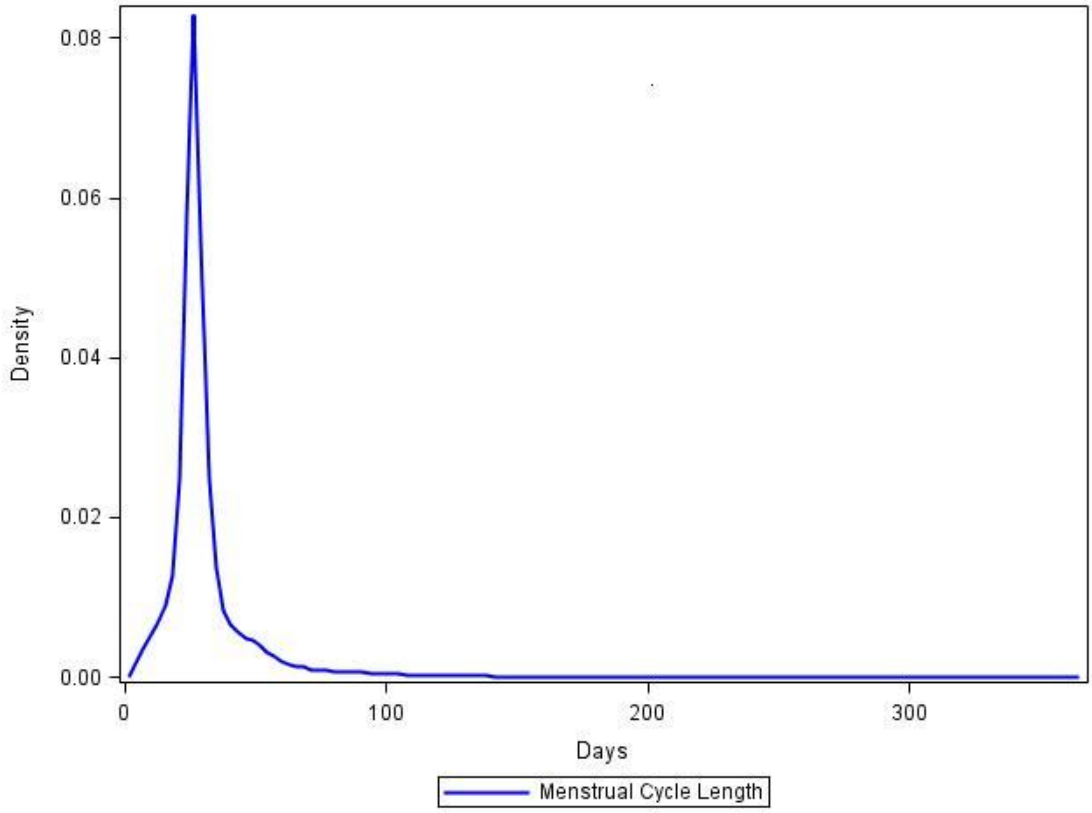
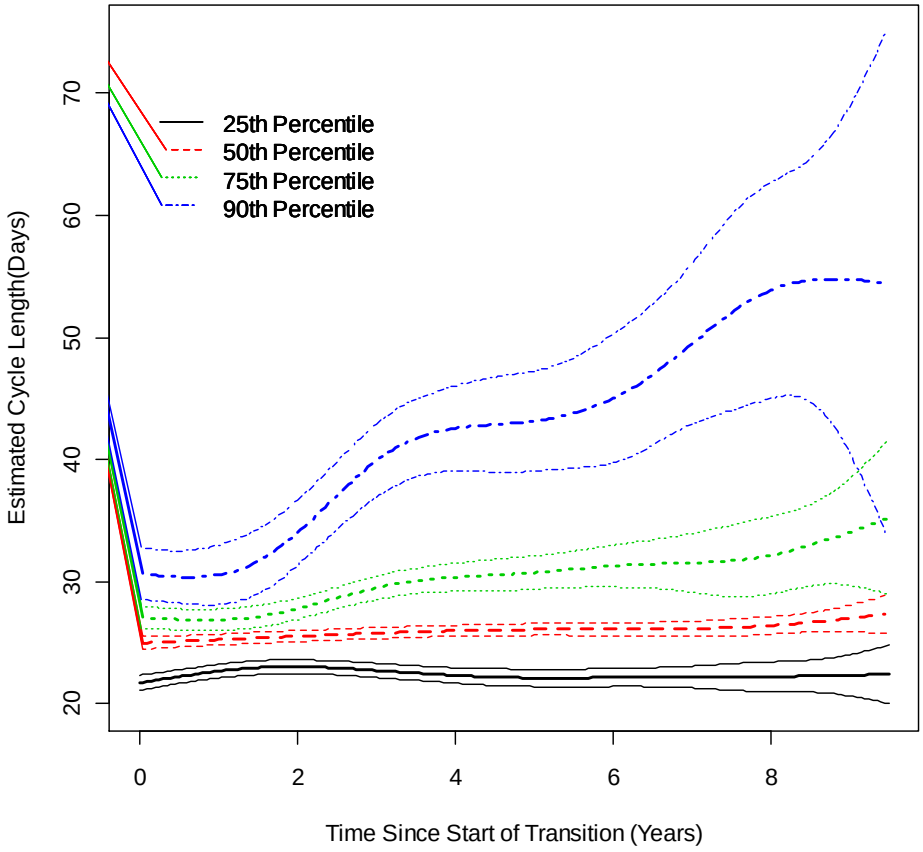


Figure 3.2 Estimated Cycle Length by Time since the Start of Transition from Multivariate Quantile Regressions for Four Percentiles: 25th, 50th, 75th and 90th. Natural cubic spline of time since the start of transition contained 5 knots at 2, 3, 4, 5, and 6 years. Estimated cycle lengths are for women who were Caucasian, normal or underweight, had an age at the start of the transition <46.25 years, did not smoke, had at least some post high school education, and did not have any moderate or physical activity during the average week.

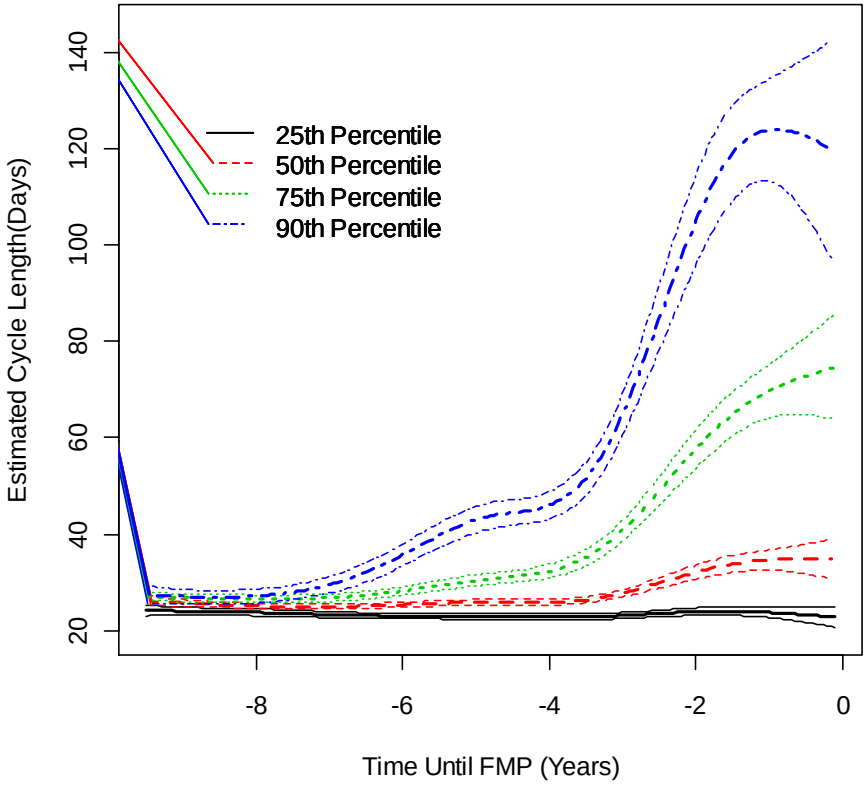


Number of women at each year

		Time in Years Since Start of Transition							
	[0,1]	(1, 2]	(2, 3]	(3, 4]	(4, 5]	(5, 6]	(6, 7]	(7, 8]	(8, 9.5]
Total Women	963	849	710	539	383	251	173	120	69
Ethnicity									
African-American	129 (13.4%)	103 (12.1%)	75 (10.6%)	59 (11.0%)	47 (12.3%)	32 (12.8%)	25 (14.5%)	11 (9.2%)	6 (8.7%)
Chinese	184 (19.1%)	173 (20.4%)	154 (21.7%)	119 (22.1%)	82 (21.4%)	54 (21.5%)	34 (19.6%)	20 (16.7%)	8 (11.6%)
Japanese	212 (22.0%)	198 (23.3%)	172 (24.2%)	132 (24.5%)	95 (24.8%)	61 (24.3%)	42 (24.3%)	34 (28.3%)	18 (26.1%)
Caucasian	438 (45.5%)	375 (44.2%)	309 (43.5%)	229 (42.5%)	159 (41.5%)	104 (41.4%)	72 (41.6%)	55 (45.8%)	37 (53.6%)
BMI									
Underweight/ Normal	515 (53.5%)	442 (52.1%)	383 (53.9%)	287 (53.3%)	200 (52.2%)	129 (51.4%)	80 (46.2%)	61 (50.8%)	34 (49.3%)
Overweight	213 (22.1%)	199 (23.4%)	150 (21.1%)	120 (22.3%)	86 (22.5%)	65 (25.9%)	43 (24.8%)	31 (25.8%)	19 (27.5%)
Obese	235 (24.4%)	208 (24.5%)	177 (24.9%)	132 (24.4%)	97 (25.3%)	57 (22.7%)	50 (28.9%)	28 (23.3%)	16 (23.2%)

Figure 3.3 Estimated Cycle Length by Time until FMP from Multivariable Quantile Regressions for Four Percentiles: 25th, 50th, 75th and 90th.

Natural cubic spline of time until FMP contained 5 knots at -5, -4,-3,-2, and -1 years. FMP is at time 0. Estimated cycle lengths are for women who were Caucasian, normal or underweight, did not smoke, had at least some post high school education, and did not have any moderate or physical activity during the average week.



Number of women at each year

		Time Until FMP								
	[-9.5, -8)	[-8,-7)	[-7,-6)	[-6,-5)	[-5,-4)	[-4,-3)	[-3,-2)	[-2,-1)	[-1,0)
Total Women	61	96	137	190	242	306	361	379	431
Ethnicity									
African-American	2 (3.3%)	8 (8.3%)	8 (5.8%)	16 (8.4%)	18 (7.4%)	25 (8.2%)	28 (7.8%)	32 (8.4%)	40 (9.3%)
Chinese	14 (23.0%)	20 (20.8%)	27 (19.7%)	43 (22.6%)	58 (24.0%)	70 (22.9%)	79 (21.9%)	83 (21.9%)	94 (21.8%)
Japanese	14 (23.0%)	29 (30.2%)	44 (32.1%)	61 (32.1%)	72 (29.8%)	89 (29.1%)	109 (30.2%)	115 (30.3%)	123 (28.5%)
Caucasian	31 (50.8%)	39 (40.6%)	58 (42.3%)	70 (36.8%)	94 (38.8%)	122 (39.9%)	145 (40.2%)	149 (39.3%)	173 (40.4%)
BMI									
Underweight/ Normal	42 (68.9%)	59 (61.5%)	86 (62.8%)	115 (60.5%)	149 (61.6%)	174 (56.9%)	204 (56.5%)	210 (55.4%)	234 (54.3%)
Overweight	7 (11.5%)	15 (15.6%)	22 (16.1%)	33 (17.4%)	38 (15.7%)	59 (19.3%)	73 (20.2%)	81 (21.4%)	89 (20.7%)
Obese	12 (19.7%)	22 (22.9%)	29 (21.2%)	42 (22.1%)	55 (22.7%)	73 (23.9%)	84 (23.3%)	88 (23.2%)	108 (25.1%)

Table 3.1 Number of Cycles for the Start of the Menopausal Transition Models and the FMP Models by Exclusion Criteria.

	Start of the Menopausal Transition Models 963 women		FMP Models 431 women	
	n	**(%)**	**n**	**(%)**
Pregnancy/post pregnancy	29	0.1%	13	0.1%
Hormone use	2,709	6.4%	1,143	5.5%
Missing covariates	2,026	4.8%	1,302	6.3%
In Analysis	37,288	88.7%	18,305	88.1%
Total	42,052		20,763	

Table 3.2 Baseline Demographics of Women in SWAN by Eligibility

	Eligible Women n=1320	Not Eligible Women n=178	P value	Start of Transition Observed n=963	NO Start Observed n=357	P value	FMP Observed n=431	NO FMP Observed n=889	P value
Age at Screener years , Mean (STD)	45.7 (2.7)	46.3 (3.0)	0.02	45.6 (2.6)	46.0 (2.9)	0.01	46.4 (2.6)	45.4 (2.7)	<0.01
	n (%)	n(%)		n (%)	n(%)		n (%)	n(%)	
Study Site									
Michigan	430 (32.6)	113 (63.5)	<0.01	256 (26.6)	174 (48.7)	<0.01	89 (20.7)	341 (38.4)	<0.01
Oakland	432 (32.7)	27 (15.2)		331 (34.4)	101 (28.3)		153 (35.5)	279 (31.4)	
Los Angeles	458 (34.7)	38 (21.3)		376 (39.0)	82 (23.0)		189 (43.9)	269 (20.2)	
Race/Ethnicity									
African-American	236 (17.9)	89 (50.0)	<0.01	129 (13.4)	107 (30.0)	<0.01	40 (9.3)	196 (22.1)	<0.01
Chinese	232 (17.6)	18 (10.1)		184 (19.1)	48 (13.4)		94 (21.8)	138 (15.5)	
Japanese	262 (19.8)	19 (10.7)		212 (22.0)	50 (14.0)		123 (28.5)	139 (15.6)	
Caucasian	590 (44.7)	52 (29.2)		438 (45.5)	152 (42.6)		173 (40.4)	416 (46.8)	
Education									
Less than High School	66 (5.0)	14 (8.6)	0.01	39 (4.1)	27 (7.6)	<0.01	23 (5.3)	43 (4.8)	0.37
High School Grad	219 (16.6)	35 (21.6)		151 (15.7)	68 (19.0)		74 (17.2)	145 (16.3)	
Some College/Vocation	455 (34.5)	60 (37.1)		319 (33.1)	136 (38.1)		132 (30.6)	323 (36.3)	
College Graduate	296 (22.4)	35 (21.6)		240 (24.9)	56 (15.7)		104 (24.1)	192 (21.6)	
Post College	284 (21.5)	18 (11.1)		214 (22.2)	70 (19.6)		98 (22.7)	186 (20.9)	
Marital Status									
Single	172 (13.0)	22 (12.6)	0.02	125 (13.0)	47 (13.2)	<0.01	58 (13.5)	114 (12.8)	0.06
Married	911 (69.1)	103 (58.9)		690 (71.7)	221 (62.1)		314 (72.9)	597 (67.2)	
Separated	44 (3.3)	10 (5.7)		27 (2.8)	17 (4.8)		9 (2.1)	35 (3.9)	
Widowed	24 (1.8)	6 (3.4)		15 (1.6)	9(2.5)		8 (1.9)	16 (1.8)	
Divorced	168 (12.7)	34 (19.4)		106 (11.0)	62 (17.4)		42 (9.7)	126 (14.2)	

[1] Does not include oral contraceptive pills. [2] Diagnosed during the first 10 annual visits. [3] Diagnosed while still in menstrual calendar substudy.

Table3.2 Cont' Baseline Demographics of Women in SWAN by Eligibility

	Eligible Women n=1320 n (%)	Not Eligible Women n=178 n(%)	P value	Started Transition n=963 n (%)	NO Start Identified n=357 n(%)	P value	FMP Observed n=431 n (%)	NO FMP Observed n=889 n(%)	P value
How Hard Is It To Pay For Basics									
Very Hard	91 (6.9)	15 (8.8)	0.01	55 (5.7)	36 (10.1)	<0.01	15 (3.5)	76 (8.6)	<0.01
Somewhat Hard	349 (26.4)	63 (36.8)		243 (25.2)	106 (29.7)		110 (25.5)	239 (26.9)	
Not Hard	880 (66.7)	93 (54.4)		665 (69.1)	215 (60.2)		306 (71.0)	574 (64.6)	
Body Mass Index, kg/m^2									
Underweight (<18.5)	42 (3.2)	5 (2.9)	0.01	32 (3.4)	10 (2.9)	<0.01	18 (4.3)	24 (2.7)	0.01
Normal (18.5 -24.9)	717 (55.2)	62 (35.4)		554 (58.3)	163 (46.7)		254 (60.2)	463 (52.7)	
Overweight (25.0 -29.9)	251 (19.3)	54 (30.9)		184 (19.4)	67 (19.2)		72 (17.1)	179 (20.4)	
Obese(≥ 30.0)	290 (22.3)	54 (30.9)		181 (19.0)	109 (31.2)		78 (18.5)	212 (24.2)	
Baseline Smoking Status									
Never	836 (64.1)	104 (59.8)	0.03	639 (67.2)	197 (55.8)	<.01	281 (67.1)	555 (62.7)	0.05
Past	277 (21.2)	31 (17.8)		194 (20.4)	83 (23.5)		91 (21.7)	186 (21.0)	
Current	191 (14.7)	39 (22.4)		118 (12.4)	73 (20.7)		47 (11.2)	144 (16.3)	
Ever Taken Hormones Prior to Study[1]	154 (11.7)	17 (9.7)	0.43	118 (12.3)	36 (10.1)	0.28	42 (9.8)	112 (12.6)	0.14
Ever Diabetes During Study[2]	211 (16.0)	33 (18.5)	0.39	139 (14.4)	72 (20.2)	0.01	57 (13.2)	154 (17.3)	0.06
Ever Diabetes Cycle[3]	n/a	n/a		97 (10.1)	39 (10.9)	0.65	34 (7.9)	102 (11.5)	0.04
Ever Fibroids During Study[2]	417 (31.6)	47 (26.4)	0.17	285 (29.6)	132 (37.0)	0.01	106 (24.6)	311 (35.0)	<0.01
Ever Fibroids Cycle[3]	n/a	n/a		246 (25.6)	90 (25.2)	0.90	93 (21.6)	243 (27.3)	0.02
Ever Thyroid Disorder During Study[2]	252 (19.1)	33 (18.5)	0.86	173 (18.0)	79 (22.1)	0.09	94 (21.8)		0.08
Ever Thyroid Disorder Cycle[3]	n/a	n/a		138 (14.3)	58 (16.3)	0.38	75 (17.4)	121 (13.6)	0.07

[1] Does not include oral contraceptive pills .[2] Diagnosed during the first 10 annual visits. [3] Diagnosed while still in menstrual calendar substudy.

Table3.3 Adjusted Menstrual Cycle Length Differences in Days among Women Since Start of the Menopausal Transition, by Percentile

Percentile	**25th**		**50th Median**		**75th**		**90th**	
Effect	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Intercept	21.69	(21.06, 22.32)	24.95	(24.42, 25.48)	27.06	(26.13, 27.98)	30.67	(28.49, 32.85)
Above Median Age at Transition (46.25 years)	0.07	(-0.35, 0.48)	**0.64**	**(0.24, 1.03)**	**3.01**	**(2.12, 3.90)**	**11.36**	**(9.11, 13.61)**
Race/Ethnicity								
African-American	0.01	(-0.74, 0.74)	0.48	(-0.19, 1.15)	1.10	(-0.40, 2.60)	0.25	(-2.77, 3.28)
Chinese	**1.81**	**(1.21, 2.41)**	**1.28**	**(0.82, 1.74)**	**2.25**	**(1.07, 3.43)**	**5.69**	**(2.34, 9.04)**
Japanese	**1.02**	**(0.41, 1.63)**	**0.82**	**(0.34, 1.31)**	**1.19**	**(0.19, 2.20)**	**3.30**	**(0.53, 6.06)**
Caucasian	Ref	-	Ref	-	Ref	-	Ref	-
Body Mass Index, kg/m^2								
Normal weight (≤24.9)	Ref	-	Ref	-	Ref	-	Ref	-
Overweight (25.0-29.9)	**0.72**	**(0.18, 1.25)**	**0.62**	**(0.16, 1.08)**	0.96	(-0.06, 1.97)	1.60	(-0.88, 4.08)
Obese (≥ 30)	**1.70**	**(1.06, 2.34)**	**1.45**	**(0.95, 1.95)**	**2.15**	**(1.07, 3.23)**	**4.94**	**(2.08, 7.80)**
Current Smoker	0.15	(-0.47, 0.77)	0.34	(-0.19, 0.88)	**1.56**	**(0.21, 2.91)**	**3.93**	**(0.88, 6.97)**
High School Graduate or Less Education	0.15	(-0.30, 0.61)	0.22	(-0.18, 0.63)	**1.27**	**(0.07, 2.48)**	**3.39**	**(0.47, 6.30)**
Every hour of moderate or vigorous physical activity per week	0.01	(-0.07, 0.08)	0.01	(-0.04, 0.06)	0.11	(-0.10, 0.32)	**0.74**	**(0.09, 1.38)**

All associations are adjusted for all factors listed, and time since the start of the menopausal transition.

Model contains 37,288 observations from 963 women.

Associations in bold are significant.

Table 3.4 Adjusted Menstrual Cycle Length Differences in Days among Women until the FMP by Percentile

Percentile	**25th**		**50th (Median)**		**75th**		**90th**	
Effect	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Intercept	24.47	(23.31, 25.62)	26.09	(25.12, 27.06)	26.96	(25.97, 27.95)	27.43	(25.57, 29.29)
Race/Ethnicity								
African-American	0.18	(-1.32, 1.67)	**1.58**	**(0.18, 2.97)**	**2.32**	**(0.39, 4.24)**	**3.21**	(-0.72, 7.15)
Chinese	**1.14**	**(0.42, 1.87)**	**1.18**	**(0.49, 1.86)**	**1.52**	**(0.44, 2.60)**	**3.32**	**(0.65, 6.00)**
Japanese	**1.00**	**(0.38, 1.62)**	**1.02**	**(0.46, 1.58)**	**1.29**	**(0.29, 2.28)**	2.15	(-0.25, 4.55)
Caucasian	Ref	-	Ref	-	Ref	-	Ref	-
Body Mass Index, kg/m^2								
Normal weight (≤24.9)	Ref	-	Ref	-	Ref	-	Ref	-
Overweight (25.0-29.9)	**1.00**	**(0.40, 1.60)**	**0.95**	**(0.40, 1.50)**	1.14	(-0.01, 2.28)	1.68	(-0.74, 4.10)
Obese (≥ 30)	**1.01**	**(0.35, 1.66)**	**1.13**	**(0.42, 1.85)**	**1.93**	**(0.85, 3.01)**	**3.77**	**(1.12, 6.43)**
Current Smoker	0.02	(-0.94, 0.98)	0.25	(-0.63, 1.13)	0.45	(-0.77, 1.68)	0.84	(-2.02, 3.70)
High School Graduate or Less Education	0.01	(-0.49, 0.52)	-0.08	(-0.60, 0.45)	-0.25	(-1.14, 0.63)	-0.19	(-2.20, 1.81)
Every hour of moderate or vigorous physical activity per week	0.00	(-0.08, 0.08)	0.05	(-0.04, 0.15)	**0.22**	**(0.02, 0.42)**	**0.97**	**(0.29, 1.66)**

All associations are adjusted for all factors listed and time until FMP.

Model contains 18,305 observations from 431 women.

Associations in bold are significant

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CHAPTER IV

Abnormal Uterine Bleeding Common during the Menopausal Transition

Introduction

Gynecological disorders are a major cause of inpatient hospitalization in the United States, accounting for 14% of all hospitalizations among women aged 45-54 years old from 1998 through 2005.[1] In this age group, the rate of hospitalization for menstrual disorders increased from a rate of 11.1 per 10,000 women in 1998 to 15.8 per 10,000 women in 2005.[1] Behind uterine fibroids, menstrual disorders are the second most common diagnosis associated with hysterectomy.[2] The estimated cost of treating abnormal uterine bleeding is about $1 billion annually.[3]

While the burden of abnormal uterine bleeding is significant, only recently a consensus has been reached on proper terminology and definitions. Recommendations recently put forward by the International Federation of Gynecology and Obstetrics (FIGO) Menstrual Disorders Working Group [4, 5] defined normal duration of menstrual flow to be between 4.5 and 8 days, with prolonged menstrual bleeding defined to be exceeding 8 days for mid-reproductive aged women. Previous recommendations based on data from the TREMIN Trust defined prolonged menstrual bleeding as 10 or more days,[6] while the World Health Organization (WHO) recommends a definition of prolonged menstrual bleeding to be menses exceeding 14 days.[7]

One of the classic studies on menstrual blood loss demonstrated women age 50 displayed a higher variability of menstrual blood loss then women age 23-45.[8] Although it has been reported that the first change in menstrual function noticed by women when they begin the menopausal transition (MT) is changes in menstrual bleeding [9], only a few perimenopausal cohorts have used menstrual calendar studies to examine menses duration and flow.[10-12] The Melbourne Women's Midlife Health Project did not find a change in mean heaviness of flow from the first to second year of their menstrual calendar study.[12]

The Massachusetts Women's Health Study reported a higher percentage of prolonged bleeding in perimenopausal women than premenopausal women[11], while a Danish study found the 1 year prevalence of prolonged menstrual bleeding to be 36%-49%. Drawbacks to these studies include short duration, predominately Caucasian populations.

Regional differences have been reported in studies conducted by the WHO. Women in India and Mexico had the shortest duration of menses (mean 4.0 days) while women in the United Kingdom had the longest duration of menses (mean 5.3).[13] Another study found similar results with Latin America women reporting an average duration of menses of 4.0 days while European women had an average duration of menses of 5.9 days.[14] The ethnic difference may have been due to difference in other demographical, biological, and lifestyle factors including body mass index (BMI). Studies of early and mid reproductive aged women provided evidence that BMI may also influence menses duration and flow.[15-20] Diabetes [21], thyroid disorders [22-25], and uterine fibroids [26-28] have also been associated with menses duration and flow.

The purpose of the present study was to describe the distribution of menses duration and heaviness of flow (number of heavy days, number of spotting days) and to assess the association of ethnicity, BMI, and medical conditions on these menstrual bleeding characteristics during the MT. In order to achieve this goal, we utilized data from The Study of Women's health Across the Nation (SWAN), a multiethnic cohort of midlife women.

Methods

This study includes 1498 women who participated from three sites of the SWAN menstrual calendar substudy: southeastern Michigan, Los Angeles, and Oakland. The design of the main cohort study has been previously described.[29] Briefly, a cross-sectional screening survey was administered to 6,345 women at the three of study sites between 1995 and 1997 to assess eligibility for enrollment into the cohort study. Eligibility for the cohort study included age 43-52 years, self-designation as a member of the targeted racial/ethnic group, residence in the geographic area of one of the three clinic sites, the ability to speak English, Cantonese, Japanese, the ability to give verbal consents, an intact uterus, at least one menstrual period and no use of reproductive hormones in the previous 3 months. Each site recruited Caucasian women and women from one specified minority group (African Americans in southeastern Michigan, Japanese in Los Angeles, and Chinese in Oakland). A total of 1498 women were enrolled into the cohort study from the three study sites. Institutional Review Boards at each study site approved the protocol.

The SWAN cohort study began in 1996 and annual follow-up visits have been conducted since that time. Each visit consisted of both interviewer administered and self

administered questionnaires that inquired into a broad range of topics including information on menstrual experience as well as socio-demographic characteristics, lifestyle, and medical history. The participants also underwent physical assessments which included a blood draw.

A self-administered menstrual calendar component began in 1996 and continued through 2006, corresponding to the tenth annual follow-up visit. Participants filled out the menstrual calendars daily to capture days where any spotting or bleeding occurred. Heaviness of flow for the day was recorded as spotting (bleeding not requiring the use of a sanitary product or not filling a regular-sized sanitary product), light to moderate bleeding, or very heavy bleeding (needing to change sanitary product every 1-2 hours for more than 4 hours during the day). On the last day of the month women answered questions about oral contraceptive or hormone therapy use as well as gynecological procedures which could affect bleeding, cigarette use, and physical exercise. Women were asked to continue to fill out and return the monthly calendar for 2 years after their last menstrual bleed.

Women's menstrual experience was assessed by examining their sequence of menstrual cycle lengths. Menstrual cycle length was calculated using bleeding definitions originally developed by the WHO [30] and previously utilized in ReSTAGE analyses [31-33]. A menstrual cycle consists of a bleeding episode and a subsequent bleed free interval of at least 3 days. A bleeding episode (menses) was defined as at least one day of bleeding or spotting. The duration of bleeding, total number of spotting days recorded, and total number of heavy days recorded were determined for each bleeding episode. Potential abnormal menstrual events were defined for both menses duration and heaviness of flow. Two definitions of prolonged menses were used, menses duration of 10 or more days and menses duration of 15 or more days. After examining the

distribution for the total number of spotting days and the total number heavy days, we used the cutoff of the highest 5 to 6% of values to determine the define potential abnormal events.

Onset of the early menopausal and the late MT was defined from the calendar data using definitions developed by the STRAW [34], refined by the ReSTAGE collaboration [31-33] and adopted by STRAW+10 [35-38]. The start of the early transition is defined by the persistent difference of at least 7 days in the length of consecutive menstrual cycles, with persistence defined as recurrence within 10 cycles of the first variable length cycle. The start date of the early transition is the date of the first variable length cycle. The start of the late transition is defined as the first occurrence of a menstrual cycle length of at least 60 days. Menstrual cycles before the onset of the early transition were defined as pre-transitional. Menstrual cycles after the onset of early MT but before the onset of late MT were defined as early transition and menstrual cycles after the onset of the late MT were defined as late transition. If neither the onset of the early MT nor the onset of the late MT was observed for a woman, then all her menstrual cycles were defined as undetermined.

The final menstrual period (FMP) was defined as the first day of a bleeding segment followed by at least 12 months of amenorrhea. For women who had missing calendars during the 12 months of amenorrhea, we accepted the potential FMP in the menstrual calendar if no more than 2 calendars were missing or if the date was less than 31 days different from the FMP date identified by the annual interviews.

Hormone therapy use, which included hormone replacement therapy, oral contraceptives, or chemotherapy, was assessed monthly. For months with missing

hormone information, menstrual cycles were coded as untreated if a woman never reported hormone therapy use in the study, if the menstrual cycle occurred before the first report of hormone therapy use, or if the menstrual cycle occurred in a year where no hormone therapy use was reported in the monthly calendars or annual interview. Women who ever reported hormone use during the study were identified and an indicator variable was created.

Height was measured without shoes using either a metric folding wooden ruler or measuring tape (home and some clinic visits), or a fixed stadiometer (clinic visits). Weight was measured at each annual visit without shoes, and in light indoor clothing, using a portable digital scale or either a digital or balance beam. For each menstrual cycle, weight was linearly interpolated between data recorded at the prior and subsequent annual visits. BMI, calculated as weight in kilograms divided by height in meters squared, was categorized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m$^{2)}$ overweight (25.0-29.9 kg/m^2), or obese (≥ 30.0 kg/m^2).

At each annual interview women were asked whether they were diagnosed with diabetes since the last visit or were taking any medications for diabetes (high blood sugar). Serum glucose levels were also measured at each of the first seven annual visits. A woman was considered diabetic if she indicated she was diagnosed with diabetes, was taking diabetes medication, or had a serum glucose level of ≥ 126 mg/dl. Women were also asked if they had been diagnosed with a thyroid condition or were taking medication for a thyroid condition, and if they had been diagnosed with uterine fibroids. For each of the three medical conditions above, six months was subtracted from the annual visit date

a woman first indicated she had the condition and all menstrual cycles on or after this date were considered to have the condition.

Women were asked to indicate whether they smoked at least one cigarette a day or a total of 30 cigarettes in the last month and positive responses were considered current cigarette use for that month. Women were asked if they participated in moderate to vigorous physical activity, the average times a week they participated and the average minutes they participated each time. Average total hours of physical activity per week were calculated for each month. For menstrual cycles that covered more than one month, the highest average total hours of physical activity per week was used.

Ethnicity was self-defined and categorized as African American, Chinese or Chinese American, Japanese or Japanese, or Caucasian. Highest education (high school graduate /GED or less than high school versus at least some college) and marital status (single, married, or separated, widowed, or divorced) were assessed at baseline. Economic strain was assessed at baseline with the question "how hard is it to pay for basics?" and was categorized as very hard, somewhat hard, or not hard.

Of the 1498 women, 1320 (88.2%) were eligible for this analysis. An eligible woman, had a least one untreated menstrual cycle recorded in the menstrual calendars with menstrual cycle-level covariate information available. Menstrual cycles where hormone use occurred or during a wash-out period were excluded from the analyses, as were menstrual cycles with missing covariate information.

Statistical analyses performed using SAS 9.2 (SAS Institute Inc., Cary, NC). Baseline demographics were compared for women eligible and no eligible women. Pearson's chi-square or Fisher's exact tests were used to compare proportions, and Student's *t* tests were used to compare means between groups.

To determine the frequency of abnormal menstrual events, cumulative percents were calculated using Kaplan-Meier methods for survival probabilities, which adjusted for right-censoring. Time to bleeding event was calculated as time from the start of the study until the start of the first abnormal bleeding event, second abnormal bleeding event, or the third abnormal bleeding event. For women who did not have an abnormal bleeding event, time was calculated as time from the start of the study until the start of the last menses observed. Cumulative percents of abnormal menstrual events for women during the early MT (n=963) and the late MT (n=815) were also calculated.

To examine the relationship between factors and menstrual bleeding, we first examined factors associated with median menses duration. Quantile regression was used to model the factors associated with median menses duration. To better reflect the standard error in our data which included repeated measures, bootstrap sampling with 500 repetitions was conducted to construct 95% confidence intervals (CI) for the quantile regression coefficients. The bootstrap sampling was based on samples of women and not menstrual cycles. If a woman was selected then all of her eligible menstrual cycles were included. MT stage, ethnicity, and BMI were placed into the multivariate model as well as any other covariate that showed a crude association with the median duration of menses.

We then examined factors that were associated with abnormal menstrual events. Generalized estimating equation (GEE) methods with an AR1 working correlation structure were used to model the association between menses of at least 10 days, menses with at least 3 days of heavy bleeding, or menses with at least 6 days of spotting and variables of interest. The number of events with menses exceeding 15 days was too small

to perform multivariate analysis. The working correlation structure was selected by using the quasi-likelihood information criterion (QIC). Bivariate models included only the variable of interest and were adjusted for repeated measures. Multivariable models included the major factors of interest: MT stage, ethnicity, and BMI. Additional variables were added to the multivariable model in a stepwise fashion if they exhibited a moderate association with the outcome (P<.2).

Results

Baseline demographic, social, and behavior factors for the SWAN women included in this analysis are displayed in Table 4.1. Women who did not participate in the menstrual calendar substudy were more likely to be from Michigan, African-American, report economic strain, overweight or obese, and to be a current smoker than menstrual calendar substudy participants. Women who did not participate were also less likely to be married, had lower educational attainment, and were older than menstrual calendar substudy participants.

In this analysis, 1320 women contributed 51,606 menstrual cycles. The distributions of menses duration, the total number of heavy days during menses, and the total number of spotting days during menses are reported in Table 4.2. The range for menses duration was 1 through 132 days with a mean of 5.9 days and a median of 6 days. Menses duration of 10 or more days was present in 3,401 (6.6%) menstrual cycles. Menses duration of 15 or more days was present in 838 (1.6%) menstrual cycles. The range of spotting days during menses was 0 through 82 days, with a mean of 2.6 days and a median of 2 days. Six or more days of spotting occurred in 3,181 (6.2%) menstrual cycles. The range of heavy days during menses was 0 through 19 days, with a mean of

0.7 days and a median of 0 days. Three or more days of heavy bleeding occurred in 2,746 (5.3%) menstrual cycles. Spotting of six or more days occurred in 1991 (58.5%) of the menstrual cycles with menses of 10 or more days. Among menstrual cycles with menses of 10 or more days, three or more heavy bleeding days also occurred in 561 (16.5%) menstrual cycles. Three or more heavy days of bleeding occurred in 218 (6.9%) of the menstrual cycles with spotting of six or more days, the majority of which (215) also occurred with menses of 10 or more days (Figure 4.1).

Table 4.3 presents the estimated cumulative percents of women who experienced menses of 10 or more days, menses of 15 or more days, menses with 3 or more heavy days, and menses with 6 or more spotting days during the study period. In the 10.5 years of observation, the cumulative percent of women with at least 1, 2, or 3 events of menses of 10 or more days was 91.0%, 87.5%, and 77.7% respectively and for menses of 15 or more days was 58.5%, 40.3%, and 29.8%. During the early MT, with up to 9.8 years in duration, the cumulative percent of women with at least 3 events of menses of 10 or more days was 51.6% and was 23.5% for menses of 15 or more days. During the late MT, with up to 8.4 years in duration, the cumulative percent of women with at least 3 events of menses of 10 or more days was 54.6% and was 22.8% for menses of 15 or more days.

During the study, 90.4%, 87.0%, and 66.8% of women had at least 1, 2, or 3 events of menses with 6 or more days of spotting. During the early MT, 51.2% of women have had at least 3 such events. During the late MT, 75.2% of women have had at least 3 such events.

During the study, the cumulative percent of women with at least 1, 2, or 3 events of menses with three or more days of heavy bleeding was 70.6%, 44.6%, and 34.5%.

During the early MT, 30.7% of women have had at least 3 such events. During the late MT, 34.7% of women have had at least 3 such events

The multivariable regression, modeling factors associated with median menses duration, included MT stage, ethnicity, BMI, and diagnosis of uterine fibroids. Women who were diagnosed with uterine fibroids had a 1.00 (95%CI: 0.17, 1.83) day longer median menses duration than women who were not diagnosed with uterine fibroids. Median menses duration was not associated with MT stage, ethnicity, education, economic strain, diabetes, thyroid condition, BMI, physical activity, current smoking, or ever hormone use during the study.

Adjusted and unadjusted odds ratios for factors associated with menses duration of 10 or more days are shown in Table 4.4. As compared to the pre-MT stage, women were more likely to report menses of 10 or more days in the early MT (OR= 3.15, 95%CI: 2.47, 4.02) and the late MT (OR= 4.30, 95%CI: 3.26, 5.68). African-American women were less likely to report menses of 10 or more days as compared to Caucasian women (OR = 0.64, 95%CI: 0.46, 0.89). Women with a diagnosis of uterine fibroids were 1.52 (95%CI: 1.22, 1.88) times more likely to record menses of 10 or more days than were women without a diagnosis of uterine fibroids. Women who ever used hormones during the study were more likely (OR= 1.59, 95%CI: 1.27, 2.00) to record menses of 10 or more days than were women who never used hormones during the study.

Factors associated with menses with 6 or more spotting days are shown in Table 4.5. As compared to women in the pre-MT stage, women in the early MT (OR=2.66, 95%CI: 1.98, 3.57) and women in the late MT (OR=3.95, 95%CI: 2.83, 5.52) were more likely to record 6 or more days of spotting. African-American women were less likely

(OR=0.52, 95%CI: 0.37, 0.73) to record 6 or more days of spotting than Caucasian women. Women who were diagnosed with uterine fibroids were more likely to record 6 or more days of spotting than women who were not diagnosed with uterine fibroids (OR=1.28, 95%CI: 1.04, 1.58). Women who ever used hormones during the study were more likely to record 6 or more days of spotting than women who never used hormones during the study (OR=1.32, 95%CI: 1.06, 1.64).

Factors associated with menses with 3 or more days of heavy bleeding are shown in Table 4.6. Women in the early MT (OR=1.38, 95%CI: 1.10, 1.73) and in the late MT (OR=1.75, 95%CI: 1.31, 2.34) were more likely to have had 3 or more days of heavy bleeding than women in the pre-MT stage. Japanese women were less likely (OR=0.59, 95%CI: 0.39, 0.88) to record 3 or more days of heavy bleeding than Caucasian women. Women who reported that it was very or somewhat hard to pay for basics were 1.57 (95%CI: 1.17, 2.11) times more likely to record 3 or more days of heavy bleeding than Caucasian women. Overweight women (OR=1.40, 95%CI: 1.02, 1.91) and obese women (OR=1.40, 95%CI: 1.02, 1.91) were more likely to experience 3 or more days of heavy bleeding than normal weight women. Current smokers were 1.63 (95%CI: 1.16, 2.28) times more likely to record 3 or more days of heavy bleeding than non-smokers. Women who ever used hormones during the study were more likely (OR=1.62, 95%CI: 1.21, 2.16) to record 3 or more days of heavy bleeding than women who never used hormones during the study. There was a non-significant association between uterine fibroids and menses with 3 or more days of heavy bleeding (OR=1.34, 95%CI: 0.97, 1.85). In the crude analysis, both diabetes and thyroid conditions were associated with 3 or more days of heavy bleeding, but the relationships did not persist after adjustment.

Education, economic strain, diabetes, thyroid condition, BMI, physical activity, or current smoking were not found to be associated with menses of 10 or more days or menses with 6 days of spotting. Education and physical activity were not associated with menses with 3 or more days of heavy bleeding.

Discussion

This study is one of the first to examine the frequency of bleeding events which are considered abnormal in mid-reproductive life but may not be for the MT, as well as factors associated with these potential abnormal events. A small percentage of menstrual cycles had menses of 10 or more days, yet 3 out of 4 women experienced 3 or more episodes of this bleeding event during the MT. One in 4 women experienced 3 or more episodes of menses exceeding 2 weeks. Menses with spotting of 6 or more days occurred in over half the episodes of menses of 10 or more days, suggesting a pattern of long, light bleeding. Menses with heavy bleeding of 3 or more days were less common, yet one in three women experienced 3 or more episodes. Menses of 10 or more days, menses with spotting of 6 or more days, and menses with heavy bleeding of 3 or more days were more likely to occur in the early and late MT transition. We also found that the likelihood of experiencing these menstrual events differed by ethnicity. African-American women were less likely to report menses of 10 or more days and less likely to report menses with 6 or more days of spotting, while Japanese women were less likely to report menses with heavy bleeding of 3 or more days as compared to Caucasian women. BMI was associated with prolonged heavy bleeding. Women with a diagnosis of uterine fibroids and those

who ever used hormones during the study were more likely to experience all three bleeding events.

In this study, the median duration of menses was 6 days. Other studies of perimenopausal women have found similar results with a median of 5 or 6 days.[6, 10, 11] However, one of the classic studies of menstruation conducted in Japanese women found the median duration of menses in women over 40 was 4.12 days.[39] In our study, menses of 10 or more days, menses with 6 or more days of spotting, and menses with 3 or more days of heavy bleeding were noted to occur more frequently in the early and late MT. The median duration of menses was not associated with MT stage, suggesting that it is not the median but rater the likelihood of abnormal events that changes during the MT. The Massachusetts Women's Health Study defined prolonged bleeding as menses exceeding 8 days, and found a higher percentage of prolonged bleeding in perimenopausal women than premenopausal women.[11] The Melbourne Women's Midlife Health Project did not find a change in mean heaviness of flow from the first to second year of their menstrual calendar study.[12]

We observed menses of 10 or more days to be a common event, with three-quarters of our women reporting at least three episodes during the MT. A Danish calendar-based study examined this prolonged bleeding event and found the 1 year period prevalence to be 36.4-48.7%.[10], while an English study utilizing questionnaires observed a smaller 12 month cumulative incidence of 14.7% [40]. Three or more episodes of prolonged heavy bleeding were reported by one in three women in our study. The Danish examined menstrual flooding and calculated the 1 year period prevalence to

be 10.3% to 31.0%[10], while the English cohort study observed a 1 year cumulative incidence of heavy periods to be 53.0%.[40]

The ethnic differences in menstrual bleeding observed in this study are consistent with findings in younger aged women. Besides the studies by the WHO [13, 14], only one other study, which was among postmenarcheal girls, has examined ethnic differences in menstrual bleeding. The study found the mean duration of bleeding to be a half-day less among African-American girls as compared to Caucasian girls, but African-American girls were more likely to report heavy bleeding than Caucasian girls.[18] We observed menses of 10 or more days to be less likely in African-American women as compared to Caucasian women; African-American women were more likely to report menses with 3 or more heavy days but, after adjustment, this association was attenuated. Japanese women were less likely to report menses with 3 or more heavy days.

BMI was associated with heaviness of flow but not menses duration in this study. Our results are consistent with the perimenopausal Danish study which reported that obese women were more likely to report menstrual flooding but not prolonged menstrual bleeding[10]. In the SWAN Daily Hormone Study, obesity was associated with menses with 3 or more days of heavy bleeding.[41] The Michigan Bone Health and Metabolism Study did not find an association with mean menses duration and BMI among reproductive aged women.[42] However, several studies on early and mid-reproductive aged woman have found an association between low BMI and longer menses duration [16, 18, 19] and high BMI and short menses duration [15, 17, 18, 20].

Ever being on hormones during the study was positively associated with all three bleeding events. This result is consistent with the fact that hormones are used to treat

abnormal uterine bleeding.[43] Uterine fibroids were also positively associated with all three bleeding events. This association may not be due to uterine fibroids in general, but only to uterine fibroids that cause more symptoms. In our study, women self-reported a physician diagnosis of uterine fibroids. Typically, women are only diagnosed with uterine fibroids when they present with a specific complaint and then receive an ultrasound. However, it is estimated that 50% of women with uterine fibroids are asymptomatic.[44]

This study has some limitations. Left-censoring may have biased our study results. The mean age of women eligible for this was 45.7 years, and it is possible that the start of the MT occurred prior to enrollment into the study. In an analysis using data from women 35 years and older participating in the TREMIN study, the median age of the early MT was 41.0 years.[33] Women who did not have a menstrual cycle in the last 3 months were ineligible to enroll into the SWAN cohort study, therefore women who were near the end of the MT, who experience surgical amenorrhea, or who already experienced their FMP were excluded from enrollment. In the population from which our cohort study was enrolled, African-American women were more likely to have had a hysterectomy.[45] Women who were African-American, who were less educated, were more likely to have economic strain, were overweight or obese, or were current smokers were less likely to have participated in the SWAN Menstrual Calendar Substudy.

Despite these limitations, our study has several important strengths. This is the only multiethnic cohort study to use menstrual calendar studies to examine menstrual characteristics through the MT. This study had a larger sample size and observed women for longer than many of the perimenopausal cohort studies that have utilized menstrual

calendars Our large sample size allowed us to examine adjusted associations and our long follow-up made it possible to observe the full MT in many participants.

In conclusion, we found a large majority of women experience menses duration of 10 or more days, menses with spotting of 6 or more days, and to a lesser degree menses with 3 or more days of heavy bleeding during the MT. The likelihood of experiencing these menstrual bleeding events varies by ethnicity, BMI, and uterine fibroids. This data suggest that two types of bleeding events, longer menses with more days of spotting and heavier menses, occur frequently during the MT. While these events are considered abnormal for younger aged women, the high frequencies for which these occur in perimenopausal women suggests the current FIGO definition of prolonged menstrual bleeding (menses exceeding 8 days) needs to be qualified for perimenopausal women. We recommend that prolonged menstrual bleeding for women in the MT should be defined as two or more occurrences of menses exceeding 2 weeks. Common causes for abnormal menstrual bleeding include polyps, fibroids, malignancies, coagulopathies, and ovulatory dysfunction.[5] Clinical management of abnormal menstrual bleeding includes nonsteroidal anti-inflammatory drugs, hormone therapy, and hysterectomy.[43] If a cause for abnormal bleeding is not found, and it is determined a woman is close to her FMP, then our data suggest a wait-and see approach may be warranted.

A prior study on how women perceive their changes in menstrual bleeding during the MT observed that, as a woman's menstrual pattern changed, "her focus shifted from what was normal for her to what was normal for women going through menopause."[46] While our study gives some greater understanding of the common changes in menstrual bleeding that occurs during the transition, future studies are need to replicate our results.

Figure 4.1. Venn Diagram of Potential Abnormal Bleeding Events. Shown is the number of occurances of menses of duration of 10 or more days, spotting of six or more days, and very heavy bleeding of 3 or more days, and their overlap.

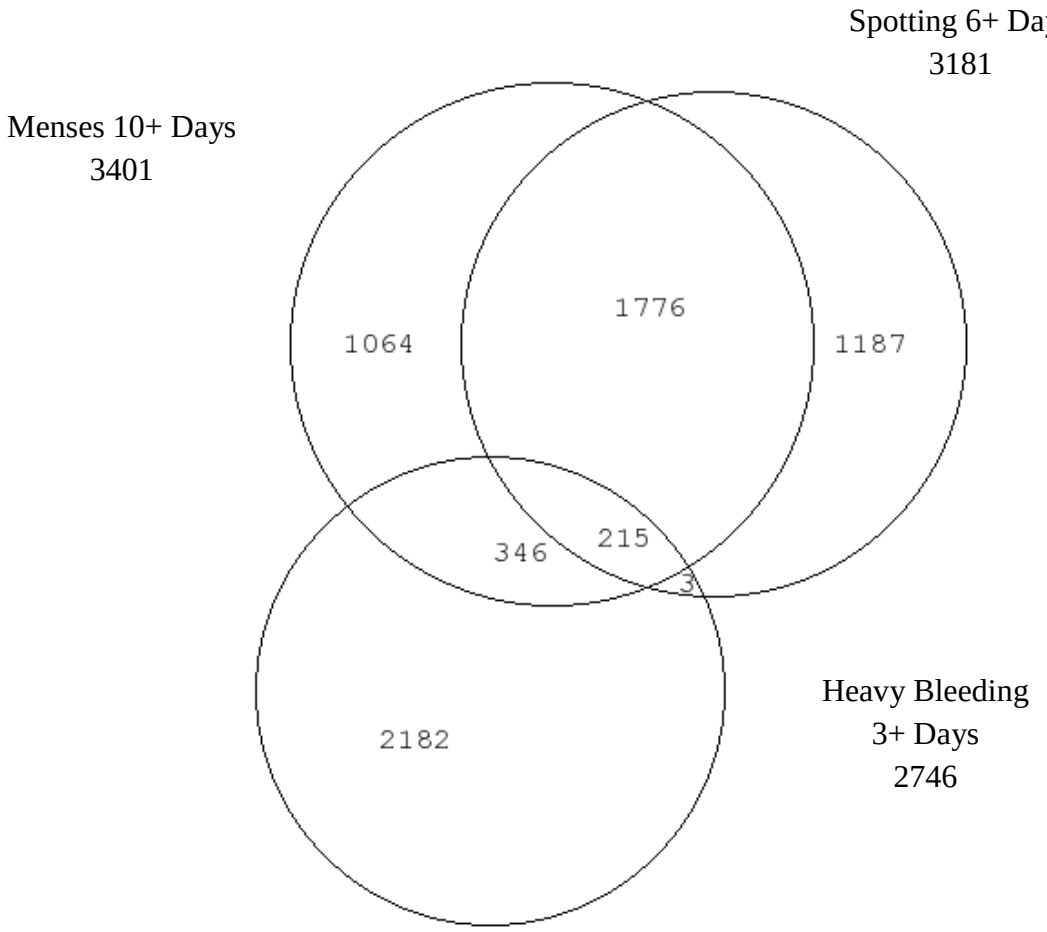

Table 4.1 Baseline Demographics of Women in SWAN by Participation in Menstrual Calendar Substudy

	Participated n=1320 n(%)	Did Not Participate n=178 n (%)	P value
Study Site			
Michigan	430 (32.6)	113 (63.5)	<0.01
Oakland	432 (32.7)	27 (15.2)	
Los Angeles	458 (34.7)	38 (21.3)	
Ethnicity			
African-American	236 (17.9)	89 (50.0)	<0.01
Chinese	232 (17.6)	18 (10.1)	
Japanese	262 (19.8)	19 (10.7)	
Caucasian	590 (44.7)	52 (29.2)	
Education			
Less than High School	66 (5.0)	14 (8.6)	0.01
High School Grad	219 (16.6)	35 (21.6)	
Some College/Vocation	455 (34.5)	60 (37.1)	
College Graduate	296 (22.4)	35 (21.6)	
Post College	284 (21.5)	18 (11.1)	
Marital Status			
Single	172 (13.0)	22 (12.6)	0.02
Married	911 (69.1)	103 (58.9)	
Separated	44 (3.3)	10 (5.7)	
Widowed	24 (1.8)	6 (3.4)	
Divorced	168 (12.7)	34 (19.4)	
How Hard Is It To Pay For Basics			
Very Hard	91 (6.9)	15 (8.8)	0.01
Somewhat Hard	349 (26.4)	63 (36.8)	
Not Hard	880 (66.7)	93 (54.4)	
Body Mass Index, kg/m^2			
Underweight (<18.5)	42 (3.2)	5 (2.9)	0.01
Normal (18.5 -24.9)	717 (55.2)	62 (35.4)	
Overweight (25.0 -29.9)	251 (19.3)	54 (30.9)	
Obese($\geq$ 30.0)	290 (22.3)	54 (30.9)	
Baseline Smoking Status			
Never	836 (64.1)	104 (59.8)	0.03
Past	277 (21.2)	31 (17.8)	
Current	191 (14.7)	39 (22.4)	
Ever Taken Hormones Prior to Study[1]	154 (11.7)	17 (9.7)	0.43
Ever Diabetes During Study[2]	211 (16.0)	33 (18.5)	0.39
Ever Fibroids During Study[2]	417 (31.6)	47 (26.4)	0.17
Ever Thyroid Disorder During Study[2]	252 (19.1)	33 (18.5)	0.86
Age at Screener years , Mean (STD)	45.7 (2.7)	46.3 (3.0)	0.02

[1] Does not include oral contraceptive pills.

[2] Diagnosed during the first 10 annual visits.

Table 4.2 Number of Menstrual Cycles (51,606) by Bleeding Characteristic

Bleeding Characteristic	Frequency	Percent
Menses Duration, Days		
1	1,992	3.9
2	1,247	2.4
3	3,320	6.4
4	6,972	13.5
5	11,780	22.8
6	10,358	20.1
7	7,005	13.6
8	3,645	7.1
9	1,886	3.6
10+	3,401	6.6
Number of Spotting Days		
0	4,990	9.7
1	10,674	20.7
2	14,177	27.4
3	10,649	20.6
4-5	7,935	15.4
6+	3,181	6.2
Number of Heavy Days		
0	32,207	62.4
1	8,352	16.2
2	8,301	16.1
3+	2,746	5.3

Table 4.3 Cumulative Percent of Women with at least 1, 2, or 3 Episodes of Bleeding Event Observed

Bleeding characteristics	Number Of Women With					
	At Least 1		At Least 2		At Least 3	
	n	%[1]	n	%[1]	n	%[1]
Menses Duration ≥10 days						
All Stages[2]	634	91.0	467	87.5	335	77.7
During Early Transition[3]	443	84.4	282	69.8	185	51.6
During Late Transition[4]	368	92.3	207	73.1	128	54.6
Menses Duration ≥15 days						
All Stages[2]	333	58.5	164	40.3	99	29.8
During Early Transition[3]	184	57.9	88	35.7	49	23.5
During Late Transition[4]	171	50.2	73	41.6	35	22.8
Menses includes ≥ 6 days of spotting						
All Stages[2]	670	90.4	458	87.0	331	66.8
During Early Transition[3]	427	87.3	272	69.0	186	51.2
During Late Transition[4]	386	90.5	215	89.0	130	75.2
Menses includes ≥3 heavy days of bleeding						
All Stages[2]	532	70.6	341	44.6	264	34.5
During Early Transition[3]	327	60.1	200	53.7	147	30.7
During Late Transition[4]	235	54.5	134	50.7	90	34.7

[1] Cumulative percent calculated by Kaplan-Meir Product Limit to adjust for right-censoring

[2] 1320 women were observed during the study

[3] 963 had the start of the early transition stage observed

[4] 815 women had the start of the late transition observed.

Table 4.4 Logistic Regression Models for Menses Duration of 10 or More Days

	Unadjusted[1]		Adjusted[2]	
	OR	**95% Confidence Interval**	**OR**	**95% Confidence Interval**
Menopausal Transition Stage				
Pre-transition	-	Referent	-	Referent
Early transition	**3.12**	**2.46, 3.96**	**3.15**	**2.47, 4.02**
Late transition	**4.20**	**3.19, 5.55**	**4.30**	**3.26, 5.68**
Unknown	1.39	0.78, 2.46	1.46	0.82, 2.59
Ethnicity				
African-American	**0.63**	**0.45, 0.88**	**0.64**	**0.46, 0.89**
Chinese	0.92	0.68, 1.23	0.97	0.72, 1.32
Japanese	0.83	0.63, 1.09	0.80	0.60, 1.07
Caucasian	-	Referent	-	Referent
High School Grad or Less	1.01	0.75, 1.36		
Very or Somewhat Hard to Pay for Basics	1.26	0.97, 1.63		
Diabetes	0.97	0.66, 1.42		
Thyroid Condition	1.21	0.89, 1.64		
Fibroids	**1.60**	**1.28, 2.01**	**1.52**	**1.22, 1.88**
Body Mass Index, kg/m^2				
Normal weight (≤24.9)	-	Referent	-	Referent
Overweight (25.0-29.9)	0.92	0.71, 1.18	0.94	0.73, 1.20
Obese (≥ 30)	0.93	0.72, 1.21	0.91	0.69, 1.19
Every 1 Hour of Moderate or Vigorous Exercise per Week	1.01	0.99, 1.03		
Current Smoker	1.00	0.74, 1.36		
Ever Hormone Use During Study	**1.71**	**1.37, 2.14**	**1.59**	**1.27, 2.00**

[1]Each univariate model contained variable listed and adjusted for repeated measures

[2]Multivariate model contains menopausal transition stage, race/ethnicity, fibroids, BMI, ever hormone use, and adjusted for repeated measures

Table 4.5 Logistic Regression Models for Menses with Spotting of 6 or More days.

	Unadjusted[1]		Adjusted[2]	
	OR	**95% Confidence Interval**	**OR**	**95% Confidence Interval**
Menopausal Transition Stage				
Pre-transition	-	Referent	-	Referent
Early transition	**2.60**	**1.93, 3.50**	**2.66**	**1.98, 3.57**
Late transition	**3.92**	**2.81, 5.46**	**3.95**	**2.83, 5.52**
Unknown	0.84	0.45, 1.59	0.94	0.50, 1.77
Ethnicity				
African-American	**0.52**	**0.37, 0.72**	**0.52**	**0.37, 0.73**
Chinese	1.27	0.95, 1.71	1.23	0.90, 1.69
Japanese	1.09	0.84, 1.42	1.01	0.76, 1.34
Caucasian	-	Referent	-	Referent
High School Grad or Less	1.12	0.85, 1.48		
Very or Somewhat Hard to Pay for Basics	1.18	0.92, 1.51	1.24	0.96, 1.60
Diabetes	1.06	0.70, 1.58		
Thyroid Condition	1.00	0.72, 1.38		
Fibroids	**1.29**	**1.03, 1.60**	**1.28**	**1.04, 1.58**
Body Mass Index, kg/m^2				
Normal weight (18.5-24.9)	-	Referent	-	Referent
Overweight (25.0-29.9)	0.81	0.64, 1.01	0.88	0.70, 1.11
Obese ($\geq$ 30)	**0.72**	**0.54, 0.96**	0.80	0.58, 1.10
Every 1 Hour of Moderate or Vigorous Exercise per Week	1.01	0.99, 1.04		
Current Smoker	0.79	0.56, 1.10		
Ever Hormone Use During Study	**1.33**	**1.07, 1.66**	**1.32**	**1.06, 1.64**

[1]Each univariate model contained variable listed and adjusted for repeated measures

[2]Multivariate model contained menopausal transition stage, race/ethnicity, hard to pay for basics, fibroids, BMI, ever hormone use, and adjusted for repeated measures

Table 4.6 Logistic Regression Models for Menses with Heavy bleeding of 3 or More Days

	Unadjusted[1]		Adjusted[2]	
	OR	**95% Confidence Interval**	**OR**	**95% Confidence Interval**
Menopausal Transition Stage				
Pre-transition	-	Referent	-	Referent
Early transition	**1.48**	**1.17, 1.87**	**1.38**	**1.10, 1.73**
Late transition	**1.90**	**1.43, 2.53**	**1.75**	**1.31, 2.34**
Unknown	**1.92**	**1.21, 3.04**	1.41	0.90, 2.22
Ethnicity				
African-American	**1.68**	**1.21, 2.35**	1.26	0.87, 1.84
Chinese	**0.65**	**0.45, 0.95**	1.04	0.71, 1.51
Japanese	**0.44**	**0.30, 0.65**	**0.59**	**0.39, 0.88**
Caucasian	-	Referent	-	Referent
High School Grad or Less	1.35	0.99, 1.84		
Very or Somewhat Hard to Pay for Basics	**1.86**	**1.41, 2.46**	**1.57**	**1.17, 2.11**
Diabetes	**1.80**	**1.23, 2.62**		
Thyroid Condition	**1.48**	**1.00, 2.19**		
Fibroids	**1.48**	**1.11, 1.99**	1.34	0.97, 1.85
Body Mass Index, kg/m^2				
Normal weight (<=24.9)	-	Referent	-	Referent
Overweight (25.0-29.9)	**1.52**	**1.12, 2.08**	**1.40**	**1.02, 1.91**
Obese (≥ 30)	**2.92**	**2.19, 3.91**	**2.24**	**1.63, 3.08**
Every 1 Hour of Moderate or Vigorous Exercise per Week	0.97	0.92, 1.02		
Current Smoker	**2.09**	**1.54, 2.84**	**1.63**	**1.16, 2.28**
Ever Hormone Use During Study	**1.64**	**1.25, 2.16**	**1.62**	**1.21, 2.16**

[1]Each univariate model contained variable listed and adjusted for repeated measures

[2]Mulitvariate model contains menopausal transition stage, race/ethnicity, hard to pay for basics, fibroids, BMI, current smoker, ever hormone use, and adjusted for repeated measures

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CHAPTER V

Summary of Findings

This dissertation adds to scientific understanding of the natural history of change in menstrual function during the menopausal transition (MT) and how patterns of change differ by ethnicity and body size, providing a basis for distinguishing normal from abnormal change during the transition from active reproductive life to the post menopause. A greater propensity for longer menstrual cycles, more variable menstrual cycles, longer-lighter menses, and episodes of heavy menstrual bleeding occur as women progress through the MT. This propensity differs by ethnicity and body size. Japanese women are more likely to report longer menstrual cycles and less likely to report heavy menstrual bleeding, while African-American women were less likely to report longer-lighter menses. Obese women were more likely to report longer menstrual cycles and heavy menstrual bleeding.

Prior menstrual calendar studies of the MT have been conducted in predominately Caucasian populations, while this dissertation focuses on a multiethnic cohort of women.[1-5] The goal was to describe the normative pattern of change for each of the specified menstrual cycle characteristics as women progress through the MT and to identify biological, demographical, and behavioral characteristics that influence these patterns. First we assessed the validity of commonly used approaches to identifying the onset of the MT by assessing the level of agreement between staging the MT by

menstrual bleeding markers identified in menstrual calendar data, the recognized gold standard, and by annual interviews or annual follicle-stimulating hormone (FSH) measures. We then examined the overall pattern of menstrual cycle length through the MT and examined how these patterns differed by ethnicity, BMI, and medical conditions. Finally, we focused on menses duration and flow, estimating the frequency of occurrence of bleeds with extreme durations or excessive flows and assessing the association between these menstrual characteristics and ethnicity, BMI, and medical conditions.

In chapter 2 we found poor agreement between MT stages as defined by the menstrual calendars compared to the MT stage as defined by the annual interviews. The annual interview question that defined the onset of the early MT stage identified when a woman first reported that her menstrual cycles had become more variable. Prior studies of midlife women have found interview questions on menstrual cycle irregularity and variability to have low sensitivity and poor agreement.[3, 6] In our study, most women did not report this change in menstrual cycles until 1 to 3 years after it was observed in the menstrual calendars, suggesting that the questions commonly used to define the onset of early MT are inadequate. Late MT stage was also detected earlier in the menstrual calendar than by annual interview, regardless of whether the late transition was defined in the calendar as a menstrual cycle of at least 60 days, as recommended by STRAW, or as a menstrual cycle of at least 90 days to be consistent with the interview question. The annual interview question asked women if they had a menstrual cycle in the last 90 days but not whether they had experienced an episode of amenorrhea of this length within the past year or since their last interview. This question failed to capture the late MT stage in a third of the woman.

We also found poor agreement between MT staging by menstrual calendars and MT staging by annual FSH levels. Annual FSH measures frequently failed to detect the rise in FSH levels during the early MT, as almost a third of woman did not have their early MT stage identified by FSH levels. In order to capture the initial rise in FSH, more frequent testing is warranted. The late MT stage by annual FSH levels identified women earlier than the late MT stage (90 days) by menstrual calendar. However, the late MT stage by annual FSH levels did not identify women earlier than the late MT stage (60 days) by menstrual calendar.

Quantile regression was utilized in Chapter 3 to facilitate our understanding of the changes that occur in menstrual cycle length during the MT. Quantile regression allows us to examine how different portions of the menstrual cycle length distribution are influenced by women's body size, health and lifestyle characteristics. We found that, as time in the MT progresses, the largest increases in menstrual cycle length occurred in the right tail of the distribution. The initial increase in menstrual cycle length began 2 years after the start of the MT or 7 years prior to the FMP. During the 2 years prior to FMP, menstrual cycle length becomes highly variable as shown by the wider 95% confidence bands.

Factors that were associated with increased menstrual cycle length included ethnicity, BMI, and physical activity. Chinese and Japanese women were found to have menstrual cycle lengths that were longer than Caucasian women throughout the menstrual cycle distribution. Along with evidence presented in previous studies on mid-reproductive aged women [7, 8], this suggests these women have longer menstrual cycle lengths throughout the reproductive lifespan. Overweight women had menstrual cycle

lengths that were longer than normal weight women at the lower and middle part of the distribution, but not at the upper end of the distribution. In contrast, obese women had menstrual cycle lengths that were longer than normal weight women throughout the distribution. Several studies conducted on early and mid-reproductive aged women have demonstrated longer menstrual cycle lengths in heavier women [8-12], thus heavier women appear to have longer menstrual cycle lengths throughout their reproductive life. Increased moderate to vigorous physical activity was associated with longer menstrual cycle lengths at the right-tail of the distribution.

Chapter 4 demonstrated that menses of 10 or more days, menses with at least 6 days of spotting, and menses with at least 3 days of heavy bleeding are common events during the MT, occurring at least once in a large majority of women. Current guidelines define prolonged menstrual bleeding as menses exceeding 8 days.[13, 14] However, previous research suggested menses duration of at least 10 days should be the definition.[15] Studies which included perimenopausal women with only 1 year of follow-up have also suggested that menses of 10 or more days during this period of reproductive life was somewhat common.[1, 16] We found that menses of 15 or more days to be less common, suggesting a more appropriate definition of prolonged menses in perimenopausal women. More than half of the menstrual cycles with menses of 10 or more days also included six or more days of spotting, suggesting that one pattern of menstrual bleeding that increases during the MT is longer, lighter menses. Another pattern of menstrual bleeding that occurs with a high frequency during the MT is menses with at least 3 days of heavy bleeding.

We observed ethnic differences in menstrual bleeding patterns during the MT. Japanese women were less likely to have menses with 3 or more days of heavy bleeding. African-American women were less likely to have menses of 10 or more days or to report menses with spotting of 6 or more days. A prior study of post-menarcheal girls found the mean duration of menses was a half-day less among African-American girls as compared to Caucasian girls.[17] In contrast to findings for menstrual cycle length, BMI was not associated with menses of 10 or more days or with menses with 6 or more days of spotting. Other studies of late-reproductive or early perimenopausal women have also not found an association with menses duration and BMI.[1, 18] Studies of younger aged women have found lower BMI to be associated with longer menses and higher BMI was associated with shorter menses.[17, 19-23] Women who were overweight or obese were more likely to report menses with 3 or more heavy days; similar results have been shown in other studies of heavy menses or flooding.[1, 24] Of the three medical conditions of interest, only uterine fibroids were found to be associated with menses outcomes. Symptomatic fibroids tend to cause menses problems such as heavy menstrual bleeding and prolonged menses.[25]

Strength and Limitations

The SWAN study is the only multiethnic cohort study with menstrual calendar data permitting examination of menstrual characteristics during the MT. Prior cohorts who utilized menstrual calendars have had predominately Caucasian populations. [1-5] The Penn Ovarian Study of Women and Aging [26], included both African-American and Caucasian participants but did not use menstrual calendar diaries. Our study had a larger sample participating in the menstrual calendar substudy than any of the other recent cohort studies of midlife women. This larger sample size allowed us to examine adjusted

associations. The follow-up time for our menstrual diaries was up to 10.5 years thus allowing us to observe the full MT in many women and to characterize change in menstrual cycle characteristics during the MT. Other cohorts have only reported data from a few years of observation. We also conducted annual measurements of BMI and FSH levels.

There are some limitations to SWAN that need to be addressed. One major limitation is that of left-censoring. We did not observe the start of the MT in some women. The mean age of women eligible for these analyses was 45.7 years. In an analysis using data from women 35 years and older participating in the TREMIN study, the median age of onset of the early MT was 41.0 years.[27] Women who did not have a menstrual cycle in the last 3 months were ineligible to enroll into the cohort study, therefore women who were near the end of the MT, who experienced surgical amenorrhea, or who already experienced their FMP were excluded from enrollment. In the cross-sectional survey, the average age at menopause was 51 years.[28] Since women were enrolled from age 42-52 years, the likelihood of exclusion increases with increasing age. Women at older ages who experienced the MT transition at an earlier age may have had menstrual cycle patterns that differ from the patterns we observed. Important racial differences with respect to participation were seen. In the population from which our cohort study was enrolled, African-American women were more likely to have had a hysterectomy.[28] African-American women were also less likely to have the start of the MT observed or their FMP observed in this study, while Chinese and Japanese women were more likely. Since each site recruited one specific ethnic group, we are unable to fully account for site differences.

Another limitation of this research is the use of self-report for the medical conditions. Therefore, we may have underreporting of diseases. The problem of self-report is greatest for uterine fibroids. Women are usually diagnosed with fibroids by ultrasound, and are not diagnosed unless they have a specific complaint. It is estimated that 50% of women with fibroids are asymptomatic.[29] African-American women are also more likely to be diagnosed with fibroids than Caucasian women.[30] In our study, women with diabetes, thyroid condition, or uterine fibroids were less likely to have their FMP identified. Furthermore, our power to detect associations with diabetes and thyroid conditions was limited.

Nonetheless, our study strengths outweigh our potential limitations. Although left-censoring may be a problem, most of our multiethnic participants were followed throughout the whole MT. Our large sample size has allowed us to identify important demographic, biological, and lifestyle characteristics that influence menstrual characteristics during the MT, which has never been done before. This research is the first to describe the normative patterns of menstrual cycle length, menstrual cycle variability, menses duration, and heaviness of flow as women progress through the MT.

Future Research

This dissertation provided important insights into the natural histories of change in the pattern of menstrual cycle characteristics during the MT. While this work has started to fill the gap in our knowledge about menstrual function during the MT, important questions remain. We presented data on the average population change in menstrual cycle length that occurs during the MT. There may be several specific patterns that make up this overall pattern of change, with different patterns most relevant to specific population subgroups. A recent article by Gorrindo et al, used menstrual histories

of women from the TREMIN Trust to show that five distinct patterns of menstrual cycle lengths occur throughout the reproductive lifespan.[31] Another recent article using TREMIN demonstrated six different patterns of menstrual cycle characteristics during the MT.[32] It would be of interest to see if these patterns occur within the SWAN population, and if these patterns are associated with certain demographic, behavioral, or biological characteristic.

A question yet to be addressed is whether menstrual cycle length or patterns of change in menstrual cycle length are associated with the duration of the MT. Results from TREMIN suggested that women who have longer menstrual cycle lengths throughout their reproductive lifespan have a later age at menopause.[33-36] If certain patterns of menstrual cycle length are associated with later age at menopause, physicians could use this information to help a woman predict when her final menses is likely to occur.

Gaps of knowledge still exist with respect to expected patterns of menses duration and heaviness of flow during the MT. In the Seattle Midlife Women's Health Study, the most common menstrual cycle changes first reported were changes in menstrual flow.[3] Our data suggested that two patterns increased during the early and late MT, longer lighter menses and heavier menses. Exploring whether specific changes in menstrual flow are associated with the start of each stage of the transition would add new information to the STRAW guidelines.

This dissertation did not detect an association of menstrual cycle characteristics with diabetes. We believe this was due to the limited number of women with this condition at the start of the MT. In the cross-sectional study, diabetic women were more

likely to be post-menopausal or surgically amenorrheic and were excluded from the study.[28] Women who have diabetes may have a younger age at menopause.[37] A medical condition which is related to diabetes is polycystic ovarian syndrome (PCOS). Women with PCOS frequently experience oligomenorrhea and cannot be staged by the STRAW guidelines.[38-41] There is some evidence to suggest PCOS women have an older age at menopause [42, 43] and may experience more regular menstrual cycles during the MT.[44, 45] Menstrual calendar studies need to be conducted in these populations to elucidate their patterns of menstrual cycle characteristics during the MT.

We found that the questions frequently used to assess MT status by interview do not adequately discern whether a woman is in the early MT stage or the late MT stage. Questions in current use were in fact designed to identify women who were close to their FMP, not to define the timing of onset of these reproductive life stages.[46] New questions need to be developed to accurately identify the start of the MT.

Given the continued gaps in knowledge, it is necessary to conduct additional menstrual calendar studies among midlife women. In order to capture women who start the menopause at an earlier age, we propose enrolling women who are in their late 30's. Future studies should be conducted in a multiethnic cohort, with oversampling of women with diabetes and PCOS. It is also suggested that researchers take advantage of recent developments with electronic data collection. Currently there are some free electronic applications for smart phones that keep track of menstrual cycle information. Creating a similar program for study participants that would allow them to electronically send information, which may help with study retention and missing data.

Clinical Implications

Recent results from the ReSTAGE collaboration have demonstrated the median duration of the MT after age 40 to be approximately 5 to 8 years.[47] This dissertation work demonstrated that using currently accepted annual interview questions or annual FSH levels should not be used to distinguish between early and late MT. To stage the late MT, asking a woman if she has had a menstrual cycle of at least 60 days or using a question on skipped periods, similar to the Seattle Women's Health Study, is suggested. If it is determined that a woman's menstrual cycles have increased in variability, this suggests she has on average 1-3 years before her FMP. Accurately identifying MT stage has implications for interventions and healthcare. Bone loss is accelerated in the last couple of years prior to the FMP [48] , as is adverse change in lipid profiles.[49] Treatment and lifestyle intervention should optimally begin before this time period.

Longer menstrual cycles, more variable menstrual cycles, prolonged menses, and heavier menses are conditions that define abnormal menstrual bleeding. We demonstrated that these conditions occur frequently during the MT. Current FIGO guidelines suggest menses exceeding 8 days to be considered prolonged.[13, 14] Our research found that menses of 10 or more days occurs frequently during the MT and, therefore, the current definition does not apply to perimenopausal women. Menses of 15 or more days, occurring more than once, is a better indicator of prolonged menstrual bleeding among women undergoing the MT. While less common, menses with at least 3 days of heavy bleeding occurs more often during the MT. Obese women have longer menstrual cycles, and are more likely to report heavy bleeding. Common causes for abnormal menstrual bleeding include polyps, fibroids, malignancies, coagulopathies, and ovulatory dysfunction.[14] Clinical management of abnormal menstrual bleeding includes

nonsteroidal anti-inflammatory drugs, hormone therapy, and hysterectomy.[50] If a cause for abnormal bleeding is not found, and it is determined a woman is close to her FMP, then a wait-and see approach may be warranted.

Conclusions

In conclusion, this research was the first to examine patterns of menstrual cycle characteristics during the MT in a multiethnic cohort using menstrual calendars. We demonstrated that current SWAN annual interviews or annual FSH levels should not be used to distinguish between the early and the late MT.

Population increases in menstrual cycle length occur at the upper tail of the distribution, reflecting a greater propensity for longer menstrual cycles. The greatest variability in menstrual cycle length is seen in the couple of years prior to FMP. Two patterns of menses characteristics are seen frequently during the MT, longer-lighter bleeding or more days of heavy bleeding, implying that the current definitions of abnormal bleeding may not be relevant to perimenopausal women. Menses of 15 or more days, occurring more than once, should be used as the definition for prolonged menstrual bleeding in perimenopausal women.

BMI is associated with menstrual cycle length and heaviness of flow but not menses duration. Taking body size into account, we found evidence to suggest that ethnic differences in menstrual cycle characteristics do exist. Chinese and Japanese women have longer menstrual cycle lengths throughout their reproductive lifespan. During the MT, Japanese women are more likely to have longer-lighter menses and less likely to experience heavy bleeding, while African-American women are less likely to report longer-lighter menses.

These results fill in some of the gaps of knowledge with regards to menstruation during the MT. Continuing research in this area will give clinicians more guidance on how to accurately stage a woman's experience of the MT, help her predict her final menses, and determine whether or not clinical intervention is needed.

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APPENDICIES

Appendix A

Table A1. **Menopausal Transition (MT) Stage by Menstrual Calendar Compared to MT Stage by Annual Interview among all eligible women**

	Early MT Stage[1] n=844		Late MT Stage ≥ 90 days n=1339		Late MT Stage ≥ 60days n=1339	
	n	%	n	%	n	%
No Interview status	78	9.2	204	15.2	376	28.1
3+ visits before Interview (-3)	67	7.9	25	1.9	88	6.6
2 visits before Interview (-2)	65	7.7	43	3.2	116	8.7
1 Visit before Interview (-1)	69	8.2	149	11.1	131	9.8
Markers at Same Time (0)	296	35.1	96	7.2	45	3.4
1 visit after Interview (+1)	54	6.4	11	0.8	4	0.3
2 visits after Interview (+2)	26	3.1	0	0.0	0	0.0
3+ visits after Interview (+3)	24	2.8	1	0.1	2	0.2
No Calendar Marker	86	10.2	99	7.4	38	2.8
Neither Marker nor Status	79	9.4	711	53.1	539	40.3
Kappa (95% Confidence Interval)	-0.18 (-0.24, -0.11)		0.06 (0.01, 0.10)		-0.01 (-0.03, 0.01)	

[1]Note for comparison of early bleeding marker to early menopause status, women who determined to be in early menopause by baseline interview were excluded.
If early transition bleeding marker occurred at same time or after the late transition bleeding marker than then early transition bleeding marker set to missing.

Table A2. Transition Bleeding Markers from Menstrual Calendars Compared to Menopausal Status by Annual Interview among Eligible Women

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	Early MT Stage[1] n=672		Late MT Stage of ≥ 90 days[2] n=1138		Late MT Stage of ≥ 60days[2] n=1138	
	n	%	n	%	n	%
No FSH Level	193	28.7	40	3.5	91	8.0
3 visits before FSH (-3)	45	6.7	9	0.8	28	2.5
2 visits before FSH (-2)	19	2.8	12	1.1	36	3.2
1 Visit before FSH (-1)	71	10.6	40	3.5	101	8.9
Markers at Same Time (0)	123	18.3	101	8.9	131	11.5
1 visit after FSH (+1)	42	6.3	84	7.4	97	8.5
2 visits after FSH (+2)	22	3.3	47	4.1	60	5.3
3 visits after FSH (+3)	23	3.4	86	7.6	67	5.9
No Calendar Marker	52	7.7	316	27.8	175	15.4
Neither Marker nor FSH Level	82	12.2	403	35.4	352	30.9
Kappa and 95%Confidence Interval	-0.29 (-0.36,-0.23)		-0.04 (-0.08, 0.01)		-0.18 (-0.23,-0.12)	

[1]For comparison of early bleeding marker to early FSH status, women who determined to have an FSH level at baseline of 15.0 IU/liter or greater were excluded.
If early transition bleeding marker occurred at same time or after the late transition bleeding marker then early transition bleeding marker set to missing.
[2] For comparisons of late bleeding markers to late FSH status, women who determined to have an FSH level at baseline of 30.0 IU/liter or greater were excluded.

Appendix B

Figure B1. Estimated Cycle Length By Time Since the Start of Transition from Univariate Quantile Regressions for Four Percentiles: 25th, 50th, 75th and 90th. Natural spline of time since the start of transition contained 5 knots at 2, 3, 4, 5, and 6 years. Figure not adjusted for any other covariates.

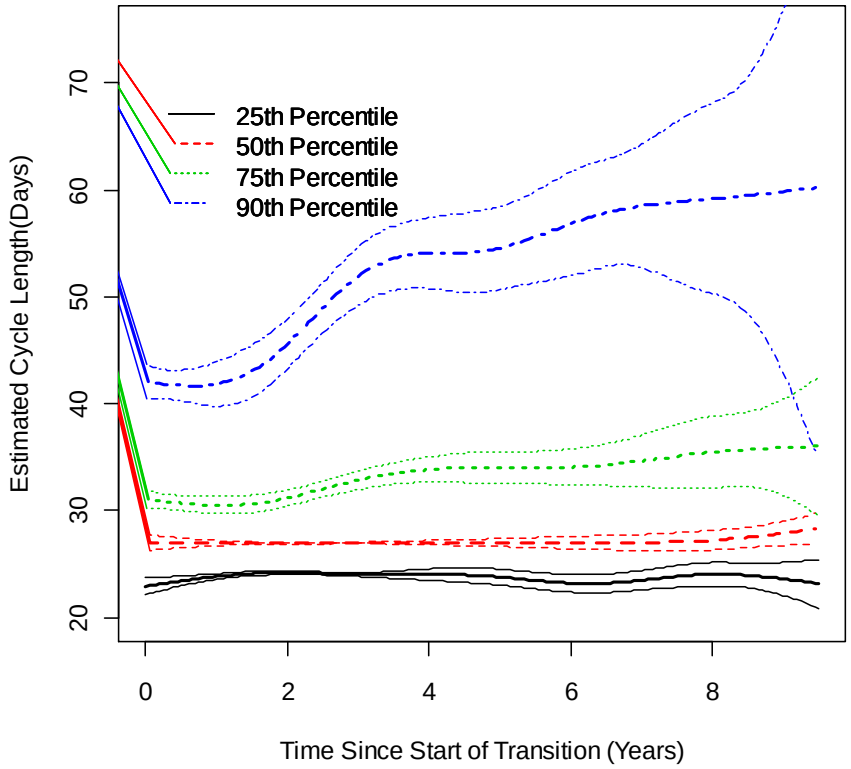

Table B1. Unadjusted Menstrual Cycle Length Differences in Days Among Women Since Start of the Menopausal Transition, by Percentile

Percentile	25th		50th Median		75th		90th	
Effect	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Above Median Age at Transition (46.25 years)	0.00	(-0.92,0.92)	0.00	(-0.69,0.69)	**2.00**	**(0.70, 3.30)**	**10.00**	**(7.60, 12.40)**
Race/Ethnicity								
African-American	1.00	(-0.11, 2.11)	0.00	(-1.19, 1.19)	**2.00**	**(0.14, 3.86)**	2.00	(-1.02, 5.02)
Chinese	1.00	(-0.12, 2.12)	0.00	(-1.20, 1.20)	**2.00**	**(0.56, 3.44)**	**6.00**	**(3.12, 8.88)**
Japanese	**1.00**	**(0.28, 1.72)**	0.00	(-0.87, 0.87)	1.00	(-0.33, 2.33)	**4.00**	**(0.39, 7.61)**
Caucasian	Ref	-	Ref	-	Ref	-	Ref	-
Body Mass Index, kg/m^2								
Normal weight (≤24.9)	Ref	-	Ref	-	Ref	-	Ref	-
Overweight (25.0-29.9)	1.00	(-0.25, 2.25)	0.00	(-0.74, 74)	1.00	(-0.23, 2.23)	2.00	(-0.97, 4.97)
Obese (≥ 30)	1.00	(-0.27, 2.28)	1.00	(-0.22, 2.22)	**2.00**	**(0.66, 3.34)**	2.00	(-1.29, 5.29)
Current Smoker	0.00	(-1.00, 1.00)	0.00	(-0.29, 0.29)	1.00	(-1.05, 3.05)	0.00	(-3.22, 3.22)
High School Graduate or Less Education	0.00	(-0.90, 90)	0.00	(-0.59,0.59)	**3.00**	**(1.25, 4.75)**	**3.00**	**(0.22, 5.77)**
Every hour of moderate or vigorous physical activity per week	0.00	(-0.10, 0.10)	0.00	(-0.01, 0.01)	0.00	(-0.20, 0.20)	**0.67**	**(0.02, 1.31)**
Diabetes	1.00	(-0.01, 2.01)	**1.00**	**(0.24, 1.76)**	**2.00**	**(0.04, 4.00)**	3.00	(-1.27, 7.27)
Fibroids	**-1.00**	**(-1.80, -0.20)**	0.00	(-0.69,0.69)	-1.00	(-2.25, 0.26)	-1.00	(-3.83, 1.83)
Thyroid Condition	**-1.00**	**(-1.95, -0.05)**	0.00	(-0.70, 0.70)	-1.00	(-2.52, 0.52)	1.00	(-3.31, 5.31)
Past Hormone Use	-1.00	(-2.11, 0.11)	0	(-0.59, 0.59)	2.00	(-0.13, 4.13)	**8.00**	**(3.06, 12.94)**

All associations are not adjusted for any other factors listed or time since the start of the transition.

Each model contains 37,288 observations from 963 women.

Numbers in bold are significant

Figure B2. Estimated cycle length by time until FMP from univariate quantile regressions for four percentiles: 25th, 50th, 75th and 90th. Natural spline of time until FMP contained 5 knots at -5, -4,-3,-2, and -1 years. FMP is at time 0. Figure not adjusted for any other covariates.

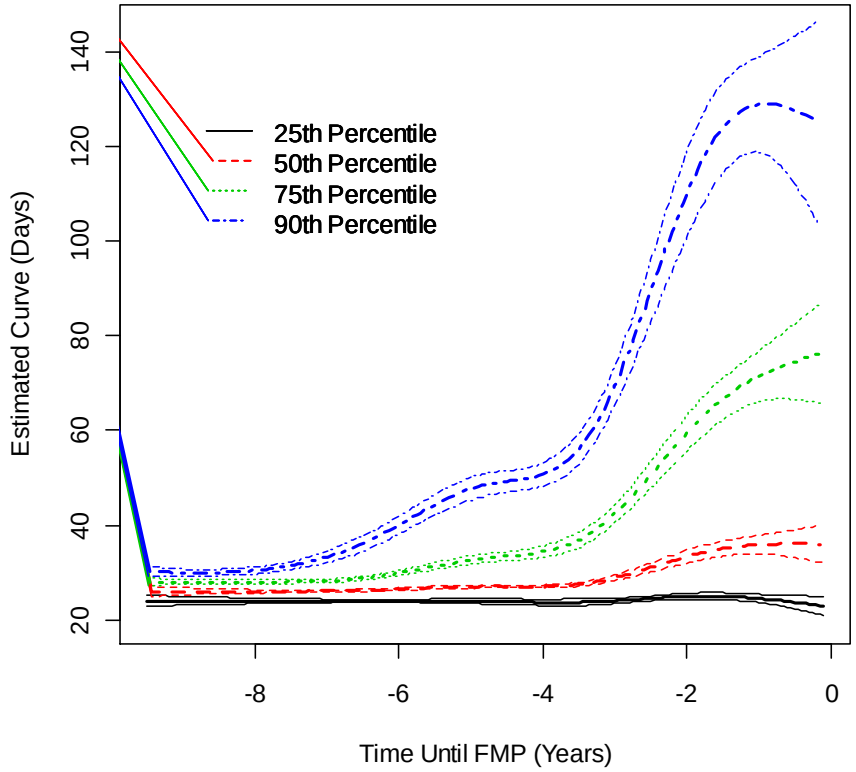

Table B2. Unadjusted Menstrual Cycle Length Differences in Days Among Women until the FMP, by Percentile

Percentile	**25th**		**50th Median**		**75th**		**90th**	
Effect	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Above Median Age at FMP (46.25 years)								
Race/Ethnicity								
African-American	0.00	(-1.76, 1.76)	**3.00**	**(1.19, 4.81)**	**5.00**	**(2.54, 7.46)**	5.00	(-1.27, 22.27)
Chinese	1.00	(-0.27, 2.27)	1.00	(-0.04, 2.04)	2.00	(-0.77, 4.77)	**7.00**	**(1.34, 12.66)**
Japanese	0.00	(-1.76, 1.76)	1.00	(-0.02, 2.02)	2.00	(-0.02, 4.02)	**6.00**	**(0.15, 11.85)**
Caucasian	Ref	-	Ref	-	Ref	-	Ref	-
Body Mass Index, kg/m^2								
Normal weight (≤24.9)	Ref	-	Ref	-	Ref	-	Ref	-
Overweight (25.0-29.9)	0.00	(-1.00, 1.00)	0.00	(-1.02, 1.02)	2.00	(-0.41, 4.41)	5.00	(-0.60, 10.60)
Obese (≥ 30)	0.00	(-1.03, 1.03)	0.00	(-1.20, 1.20)	2.00	(-0.22, 4.22)	3.00	(-2.75, 8.75)
Current Smoker	0.00	(-0.99, 0.99)	0.00	(-0.64, 0.64)	0.00	(-2.59, 2.59)	-3.00	(-9.70, 3.70)
High School Graduate or Less Education	0.00	(-0.95,0. 95)	0.00	(-0.23, 0.23)	0.00	(-2.00, 2.00)	0.00	(-5.54, 5.54)
Every hour of moderate or vigorous physical activity per week	0.00	(-0.04, 0.04)	0.00	(-0.01, 0.01)	**0.86**	**(0.42, 1.29)**	**3.33**	**(1.96, 4.71)**
Diabetes	1.00	(-0.23, 2.23)	1.00	(-0.14, 2.14)	4.00	(-1.34, 9.34)	9.00	(-4.89, 22.89)
Fibroids	0.00	(-1.04, 1.04)	0.00	(-0.46, 0.46)	1.00	(-1.32, 3.32)	3.00	(-2.82, 8.83)
Thyroid Condition	0.00	(-0.88, 0.88)	0.00	(-0.74, 0.74)	0.00	(-2.38, 2.38)	5.00	(-2.65, 12.65)
Past Hormone Use	-1.00	(-2.55, 0.55)	0.00	(-1.15, 1.15)	**4.00**	**(0.71, 7.29)**	**8.00**	**(1.97, 14.03)**

All associations are not adjusted for any other factors listed or time until the FMP.

Each model contains 18,305 observations from 431 women.

Numbers in bold are significant