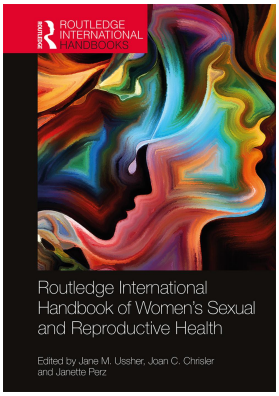

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Jane M. Ussher, Joan C. Chrisler, Janette Perz

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Jerilynn C. Prior
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THE MENSTRUAL CYCLE

Its biology in the context of silent ovulatory disturbances

Jerilynn C. Prior

The menstrual cycle is a unique expression of an individual woman's integrated genetic, metabolic, physiological, and sociocultural life history (Mishra, Cooper, Tom, & Kuh, 2009). Further, an individual woman's experience of her menstrual cycles shapes her perceptions and ways of being in the world while also profoundly, often imperceptibly, altering her biology/physiology. Normal menstrual cycles are essential for women's holistic health as defined by the World Health Organization (2006) charter: "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." In this chapter I provide an integrated physiological framework for the biology of the menstrual cycle and discuss its importance to women's sexual and reproductive health.

Biological understanding of menstrual cycles has undergone a revolution in the last 25 years (Prior, Vigna, Schechter, & Burgess, 1990). We now know that predictable, average-length menstrual cycles (defined as 21–35 days long; Abraham, 1978) may or may not involve release of an egg (the latter is known as *anovulation*). Or a cycle may be regular and ovulatory, but with a time of progesterone production from ovulation until the next flow that is too short for normal physiology and fertility (*short luteal phase*). The cycles that are clinically normal but with either anovulation or short luteal phases are described as *subclinical ovulatory disturbances*. This means that, rather than having a normal balance of progesterone and estrogen, the cycle is wholly or partially dominated by estrogen (actually *estradiol*) levels.

Estrogen and progesterone together make up a woman's hormonal reproductive *system* and are key partners. In every cell and tissue of women's bodies, estrogen acts as a powerful and continuous stimulant of cell growth (Clarke & Sutherland, 1990). Progesterone, by contrast, is briefly growth-stimulating in all the same tissues as estrogen, and then develops its major action to promote cellular maturation and continuously inhibit estrogen-stimulated cellular "overgrowth" (Clarke & Sutherland, 1990).

The presence or absence of ovulation and the duration/amount of progesterone production are highly variable within and between women; progesterone levels are higher, even in conception cycles, in women from economically well-off than women from lower-income countries (Vitzthum, Spielvogel, & Thornburg, 2004). Progesterone production is normally and universally lower (in amount and duration) in the several years following menarche and prior to the final menstrual flow. That this variability of ovulation and progesterone production is subclinical and silent (not perceptible to women or to health care providers) within

"normal" cycles makes its self-knowledge and scientific documentation difficult. Furthermore the concept of subclinical ovulatory disturbances within regular cycles is highly contested by gynecologists (Malcolm & Cumming, 2003). The concept of *silent ovulatory disturbances* is revolutionary because it both changes and explains previously inexplicable data; it also integrates mind and body in ways that could lead to effective prevention of many diseases as well as to improved treatment of women's reproductive disturbances.

Ill health (in its broadest sense) predicts ovulatory disturbances, and ovulatory disturbances, in turn, are an important but clinically silent, risk factor for ill health. The good news is that these disturbances are usually totally reversible (Prior, Yeun, Clement, Bowie, & Thomas, 1982), but only if all dimensions of ill-health are healed (Michopoulos, Mancini, Loucks, & Berga, 2013; Prior, Vigna, Barr, Rexworthy, & Lentle, 1994). Furthermore, women with reversible cycle disturbances must *not* be inappropriately "treated" with the hypothalamus-suppressing high-dose estrogen in combined hormonal contraceptives (CHC) (Falsetti, Gambera, Barbetti, & Specchia, 2002; Prior, 2016). In avoiding and treating ovulatory disturbances, we could prevent the majority of pre-menopausal bone loss that leads to osteoporotic fractures (Prior, 2018), women's earlier (ages 40–60) heart attacks (Prior, 2014), most breast (Fournier, Berrino, & Clavel-Chapelon, 2008), and almost all endometrial cancers.

For the majority of women, periodic bleeding (menstruation) is normally present for 30–45 years, or for almost half of their lifespans. Because much of what we know about menstrual cycles is biased because it was derived from women seeking medical treatment (Kaufert & Syrotvik, 1981), the focus of this chapter is on population-based data. Therefore, I share how neuroendocrine variables are assessed, and interpret the social, physical, and internal nutritional environments that cause adaptations of reproduction that may lead to ovulatory disturbances. These ovulatory changes are the least disruptive of any potential reproductive adaptations for an individual woman's long-term, healthy survival and may help preserve her potential for later fertility.

Most women do not know (other than the "typical" 28 days) how long a menstrual cycle *should* last (from Day 1—the start of flow—to the day before the next flow), or how many days of menstrual bleeding are too many. Nor do they realize that women's normal menstrual cycle subtly influences how much they eat (Barr, Janelle, & Prior, 1995), the function of the heart's electrical system (Tisdale et al., 2016), the supply of oxygen to exercising muscles (Lebrun, McKenzie, Prior, & Taunton, 1995), and whether they are losing or gaining bone (Kalyan & Prior, 2010). Such ignorance is not bliss. It results in a fundamental "mind–body" disassociation that is ultimately damaging to women's health locus of control (Wallston, Wallston, & DeVellis, 1978) and makes them vulnerable to cultural bias (Kissling, 2006) and medical misogyny (e.g., Wilson, 1966).

That normally ovulatory cycles foretell later life bone health, fewer early-in-menopause heart attacks, and likely the prevention of many breast and most endometrial cancers is actively being censored by Medicine. This includes granting agencies, editors of major medical journals, peer reviewers of unknown gender and academic status, and in multiple other ways (Inhorn & Whittle, 2001). We need to acknowledge that silent ovulatory disturbances could be prevented by a more egalitarian society, by sex and gender equality, and by universal access to basic health care services (including counselling and social support).

Menstrual cycle organization and control

Menstruation's complex neuroendocrinology means that there is still much to be understood. Although summarized elsewhere (Navarro & Kaiser, 2013; Prior, 1987; Vitzthum, 2009), it is worth re-looking at the hormonal changes across the ideal menstrual cycle (Figure 3.1).

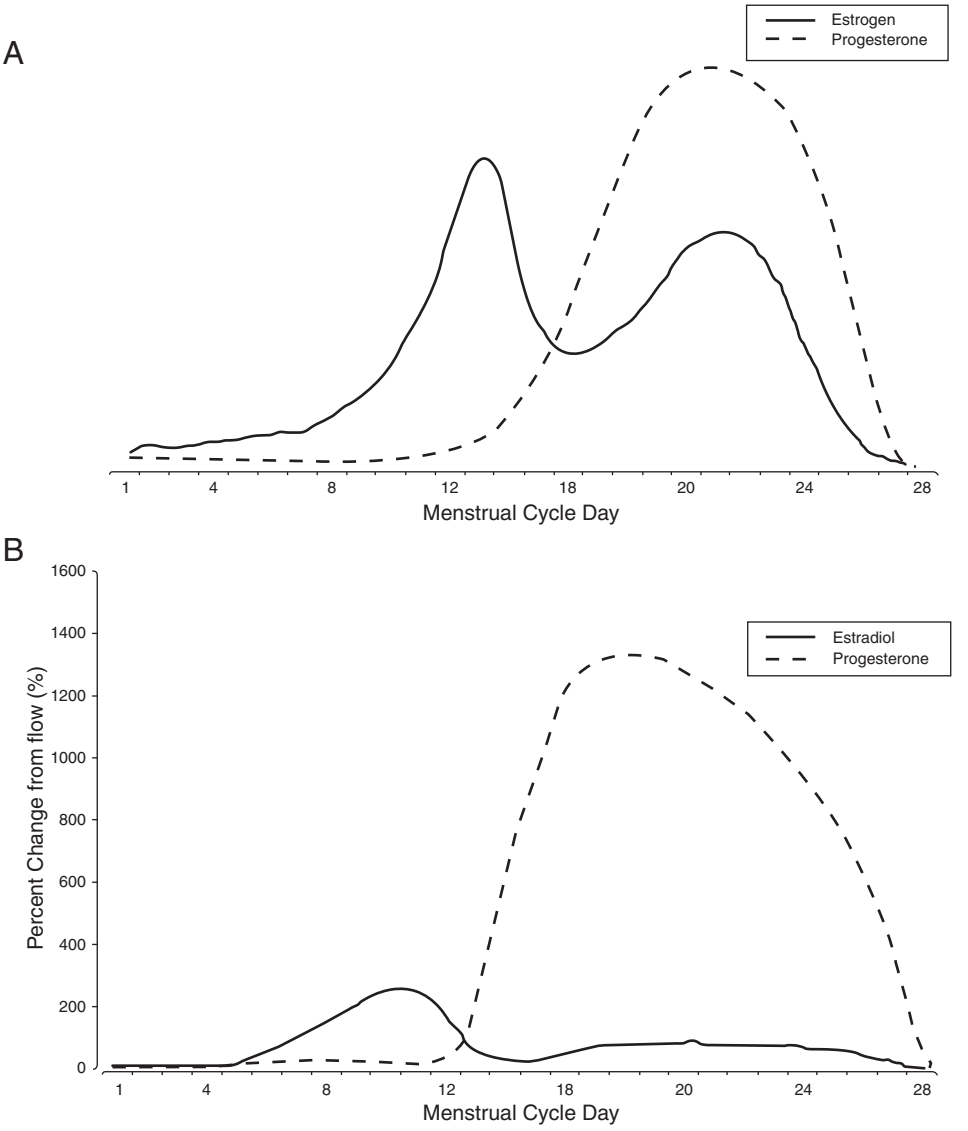

Figure 3.1 A: A typical unit-less diagram of menstrual cycle estrogen and progesterone levels readily available on the Internet. B: The percentage changes of menstrual cycle estradiol and progesterone levels related to their respective low levels during flow/early follicular phase in normal, ovulatory menstrual cycles. Redrawn from data in (Nielsen, Brixen, Bouillon, & Mosekilde, 1990).

Estradiol is produced in pmol/L amounts and is in moderate–high levels for the majority of menstrual cycle days. Progesterone, however, is secreted in nmol/L quantities (nmols are a thousand-fold larger unit than pmols) but is only at above-baseline levels for less than half of the normal cycle (Nielsen et al., 1990). Thus, although progesterone is elevated for fewer days than estradiol, in a healthy cycle the total progesterone production is greater than estradiol production. This fact is obscured by typical "Google images" (Figure 3.1) of cycle

hormones without any units that show estradiol's peak as higher than, similar to, or only slightly less than progesterone's peak. The cultural tendency to focus only on estradiol is illustrated by a recent *Nature* publication by world-recognized experts that included a menstrual cycle diagram that omitted progesterone entirely (Davis et al., 2015).

The control of this adaptive system occurs in and is integrated with nutritional, emotional/behavioral, temperature, and other neuroendocrine signals in the hypothalamus, where nerve impulses are transformed into pulsatile hormonal signals (Figure 3.2).

Gonadotrophin-releasing hormone (GnRH) pulsatile secretion can be documented in peripheral blood as rhythmic peaks of the pituitary's luteinizing hormone (LH). This integration involves insulin receptors (for adequacy of nutrition related to balance of caloric intake/expenditure), emotional signals (from the limbic system), hypothalamic temperature assessments (related to exercise, illness, and progesterone's actions to raise core body temperature), assessment of sleep, as well as feedback from levels of the ovarian hormones (estrogen and progesterone).

There is a continuum of women's potential reproductive responses to physiological and psychosocial experiences (Table 3.1). The so-called "functional" hypothalamic amenorrhea (no menstrual flow for 3–6 months) and oligomenorrhea (cycles longer than 35 days but less than 3 months) are rare in the spectrum of adaptive reproductive suppression. The most common are regular menstrual cycles with anovulation or with short luteal phases. Across a year, short luteal phases (≥2 per year) occur for 42% of women initially documented in two cycles to be normally ovulatory (Prior et al., 1990a). Anovulation is less common, and occurs for 20% of initially ovulatory women (Prior et al., 1990a). This continuum has not yet been recognized by most women's health experts (Gordon et al., 2017), who continue to discuss only low estrogen/estradiol and ignore low or absent progesterone levels.

Menstrual cycles and ovulation across the life cycle

Adolescence: maturation of menstruation and ovulation

In childhood, usually between ages 6 and 9, the neuroendocrine and hormonal changes that eventually lead to menarche and menstrual cycling are initiated. The pulses of LH that have been low and almost imperceptible become increased in size, slower, and more adult-like but only during sleep. By menarche the larger LH peaks of adulthood are also present during the day.

The age at menarche varies in different populations but it is accepted to be ages 11–13 for the majority in the advantaged world and somewhat later in other countries. First cycles are usually unpredictable, occasionally too close together, and often too far apart (longer than 45 days) with a mean of 33 days (American College of Obstetricians and Gynecologists, 2015; van Hooff et al., 1998) (Figure 3.3).

In addition, adolescents' first cycles are usually anovulatory, but by the end of the first year may develop ovulation with short luteal phases; within 5 years cycles will be intermittently normally ovulatory (Apter, Viinikka, & Vihko, 1978) (Figure 3.3). In prospective data, Vollman (1977) used a quantitative mean temperature method to document ovulation/luteal phase length (later validated by Prior, Vigna, Schulzer, Hall, & Bonen, 1990), and discovered that it took about 12 years following menarche before the most consistent, normal ovulation occurred.

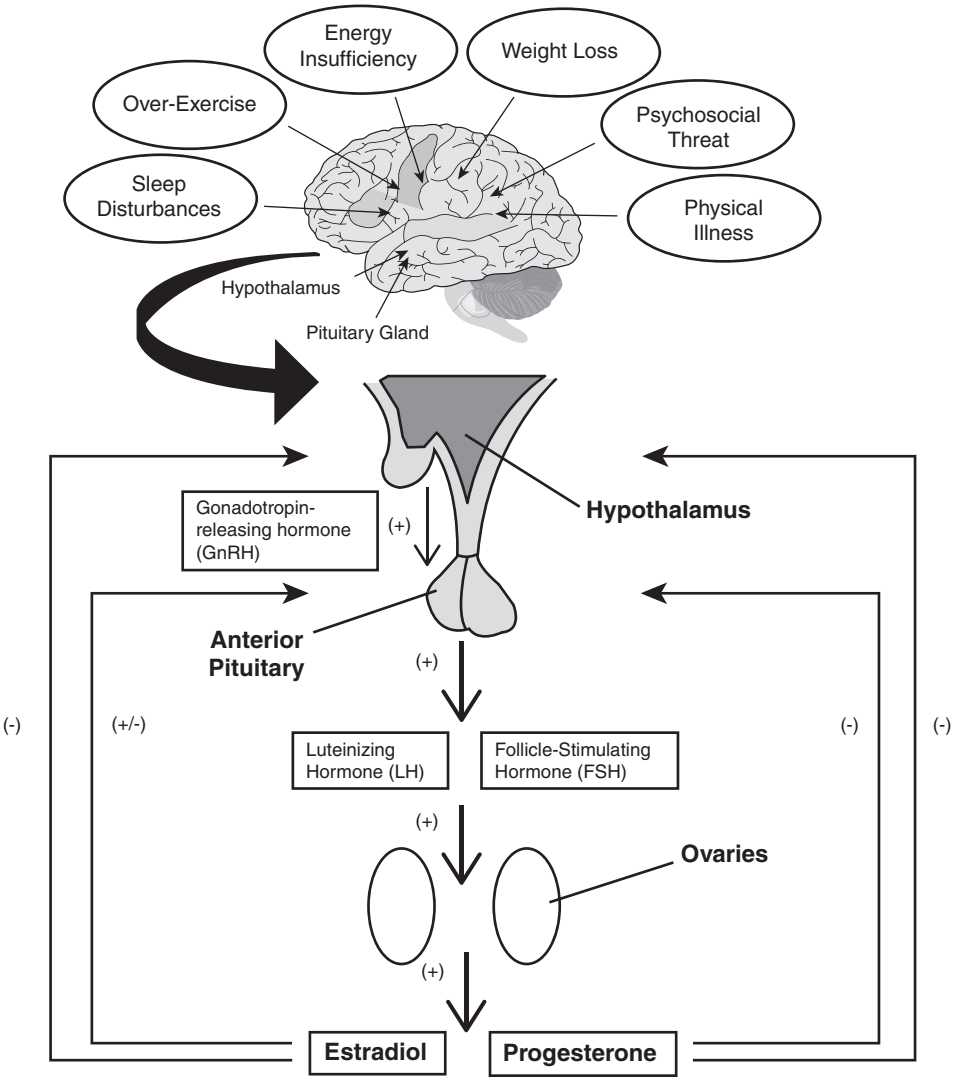

Figure 3.2 Diagram showing the inter-relationships of the internal and external environments as interpreted in the brain, pituitary, ovary and feedback of hormones and environmental variables that create an adaptable ovulatory menstrual cycle. Drawn by D. Kalidasan from a concept by Prior.

Age at menarche is associated with various health and disease characteristics. Early menarche (ages 11 or earlier, where the mean was 12.9 years), in a Canada-wide adolescent-to-adult population study with measured anthropomorphic data, was related to a significantly higher adult body mass index (BMI) with obesity in those with the earliest menarche ages (Harris, Prior, & Koehoorn, 2008). Other populations have shown the same pattern (Ahn et al., 2013), including that there is a 9% decreased risk for type 2 diabetes mellitus per year later age at menarche (Lakshman et al., 2008). Early menarche (in Great Britain characterized as <12 years, mean 13) was associated with a 20% increased risk for cardiovascular diseases and cancers plus overall mortality (Lakshman

Table 3.1 Hypothalamic Menstrual Cycle Adaptations—the spectrum of possibilities from amenorrhea to normal length, regular/predictable cycles; from regular anovulatory cycles to ovulatory but short luteal phase cycles—in addition, this outlines their hormonal changes and potential treatments.

Issue	*Manifestation*	*Hormonal situation*	*Explanation and/or treatment*
Hypothalamic Amenorrhea	No flow for 6 months (mo) (now often considered amenorrhea if flow is absent for 3 mo)	Very low estrogen and often progesterone. Moderately low estrogen and absent progesterone.	More common in the first 10 years after menarche. No flow after 14 days of cycle ⋆progesterone Flow after 14 days of ⋆progesterone.
Hypothalamic Oligomenorrhea	"Long cycles" >35 to <180 days or now 90 days	Moderately low estrogen; progesterone production usually but not always absent.	Treat with cyclic ⋆progesterone—14 days on and14 days off.
Subclinical Hypothalamic Ovulatory Disturbances—*Anovulatory Cycles*	Clinically normal cycling	Estrogen cyclic without any luteal phase progesterone levels.	Treat with cyclic ⋆progesterone—cycle days 14–27.
Subclinical Hypothalamic Ovulatory Disturbance—*Short Luteal Phase Cycles*	Clinically normal cycling	Estrogen cyclic; but progesterone high for fewer than 10 days.	Treat with cyclic ⋆progesterone—cycle days.

Note: ⋆Progesterone's physiological "luteal phase replacement" dose (given that it can be taken only at bedtime) is 300 mg per day.

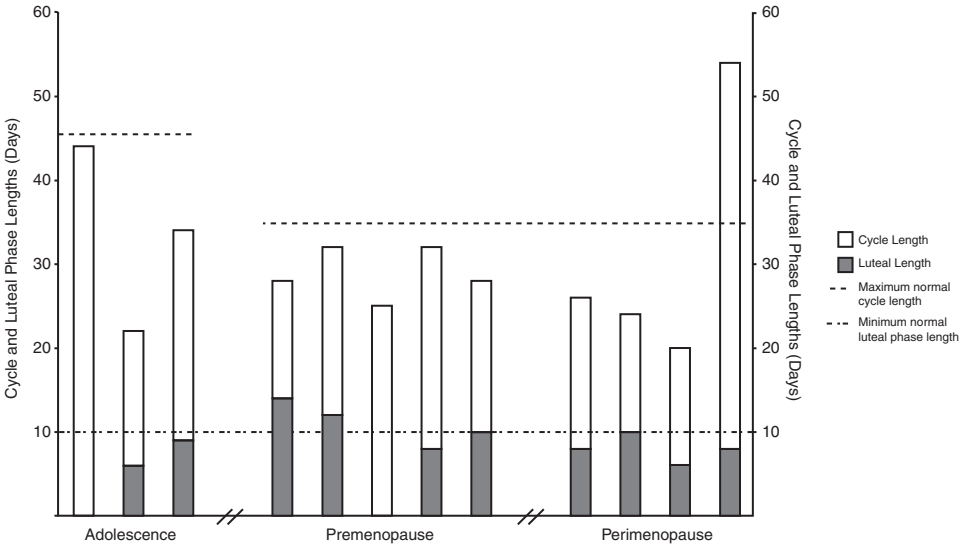

Figure 3.3 Bar graph showing cycle lengths (open) and luteal phase lengths (solid) with ovulatory changes that are typical across the menstruating lifecycle. Drawn by D. Kalidasan from a sketch by Prior.

et al., 2009); a 10% increased all-cause mortality with early menarche (ages 10–11, where the mean was 14) was confirmed by a 37-year longitudinal, whole-population Norwegian study (Jacobsen, Heuch, & Kvale, 2007). A later age at menarche (older than 15) was associated with decreased all-cause mortality in a European population-based study (Merritt et al., 2015).

The largest gain in height occurs around the time of menarche, and hip bone mineral density reaches its peak during ages 16–19 based on prospective, population data (Berger et al., 2010). There is evidence that progesterone (and thus the development of ovulation), as well as estrogen, is responsible for breast growth and transformation (Prior, Vigna, & Watson, 1989).

Premenopause: the peak of menstruating life and fertility

The normal *premenopausal* menstrual cycle length of 21–35 days (Abraham, 1978) has a population average of 27–29 days. Flow normally lasts 2–6 days. Normal ovulation is present in about two thirds of all normal-length menstrual cycles in women ages 20–49, mean age 42 (Prior, Naess, Langhammer, & Forsmo, 2015).

Normal cycle lengths between 21 and 35 days are usual from the early 20s until the mid-30s or whenever perimenopause begins (Figure 3.3). Flow of 2–6 days is associated with 30–60 milliliters (ml) of blood loss, which requires 6–12 soaked normal-sized menstrual management products (each holding ~5 ml or a teaspoon) (Hallberg, Hogdahl, Nillson, & Rybo, 1966). However, menorrhagia, which almost always causes iron deficiency anemia, is associated with blood loss of >80 ml/period (>16 soaked products; Hallberg et al., 1966). Heavy flow is characterized by needing to change (often large or "maxi" sized) sanitary products every 1–2 hours (or empty a 30 ml menstrual cup every 8–12 hours), clotting, and often increased cramping. Although premenstrual symptoms may occur during the premenopausal years and be managed by increasing exercise (Prior, Vigna, & Alojado, 1986), intense symptoms (ascertained in a population-based cohort with its purpose masked) are quite rare (Ramcharan, Love, Frick, & Goldfien, 1992).

Women's usual way of assessing whether they ovulate is to rely on "regular cycles"; some may also describe noticing "fertile mucus" at mid-cycle (i.e., several days of clear, egg-white type, stretchy secretion with a maximal thread-stretch of over 3 centimeters). This mucus is specific for cervical gland secretion in response to high mid-cycle estradiol levels (Figure 3.1). However, a mid-cycle estrogen peak (noted by the stretchy mucus) or an LH peak (documented with a urine stick) does not mean that those normal preovulatory signals have actually triggered egg release and progesterone (Brown, 2011). Nor does it mean that, if ovulation occurs, the luteal phase length is long enough for implantation and thus fertility. Quantitative basal temperature [QBT] data require 10-day luteal phases (Vollman, 1977) or 11–12 days by urine LH data (Cole, Ladner, & Byrn, 2009) to define a fertile cycle.

Can women perceive an ovulatory cycle because they *feel different* in the luteal phase? Some believe that non-troublesome premenstrual experiences (called "molimina") accurately indicate ovulation (Magyar, Boyers, Marshall, & Abraham, 1979). However, attempts to validate this have so far failed (Goshtasebi et al., 2017). As progesterone raises the core temperature by ~0.2 degrees Celsius (Landau, Bergenstal, Lugibihl, & Kascht, 1955) and this is reliably measured first thing in the morning, temperature testing seems ideal. However, basal temperature data have been shown to be inaccurate (Bauman, 1981). Quantitative basal temperature (QBT) uses a 3-day running average and assesses means during the

follicular and luteal phases. The temperature shift day correlates highly with (r = ~0.9) but lags 1–3 days behind the serum LH peak (Prior et al., 1990b). The mean temperature QBT (all of cycles' temperatures added together and divided by the number of days of data) is simpler. The luteal phase begins when the actual temperature rises above and stays above the mean temperature and lasts until the start of the next flow (CEMCOR, 2019; Prior et al., 1990b).

There is a growing appreciation that the (estrogen-only) follicular and the (progesterone-estrogen) luteal phases of the menstrual cycle differ in physiological and metabolic characteristics. Healthy, weight-stable younger women eat about 300 kilo-calories more during the luteal phase (Barr et al., 1995), likely because of energy requirements of ovulation-related elevated temperatures. Insulin resistance is increased during the late follicular phase, and estrogen's influence is stronger than progesterone's and insulin resistance is highest in anovulatory cycles (Yeung et al., 2010). In a study of 60 healthy, normal-weight, non-smoking women, daily self-report of feelings of frustration, depression, and anxiety were not higher during the luteal than the follicular phase nor related to hormone levels (Harvey, Hitchcock, & Prior, 2009). Sixty-six initially ovulatory women recorded QBT, exercise, and menstrual cycles and reported fluid retention as greatest on the first day of flow (White, Hitchcock, Vigna, & Prior, 2011). Oxidative stress marker levels have been shown to be higher during follicular than luteal phases and most strongly related to higher estrogen (Schisterman et al., 2010).

Perimenopause: the unpredictable and chaotic end of menstrual cycles

An estrogen/progesterone imbalance with estrogen dominance characterizes perimenopause (Santoro, Rosenberg, Adel, & Skurnick, 1996) with loss of the usual feedback suppression of estrogen by higher endogenous/exogenous estrogen levels (Weiss, Skurnick, Goldsmith, Santoro, & Park, 2004). Beyond the mid-30s and usually in the mid-40s cycles stay "regular" but gradually become shorter until they often average ≤25 days in very early perimenopause (Prior, Seifert-Klauss, & Hale, 2012) (Figure 3.3). Cycles then become slightly or definitely irregular and unpredictable (early menopause transition) before the first skipped menstruation that signals the late menopause transition. Perimenopause is the normal mid-life transition from premenopausal menstrual cycles to menopause; it may be perceived only for a short time if mild, but women who are highly symptomatic often experience perimenopausal changes/symptoms for over 10 years (Freeman, Sammel, Lin, Liu, & Gracia, 2011; Prior et al., 2012). A comprehensive older survey of the experiences of women in different reproductive life phases showed that adolescent and perimenopausal women shared many physiological and psychosocial experiences (Neugarten & Kraines, 1965), perhaps because both were experiencing major social status as well as physiological transitions.

The usual age at onset of unpredictable or irregular cycles (early menopause transition) (Harlow et al., 2012) (Figure 3.4) is 46–48 years in population data from the USA (McKinlay, Brambilla, & Posner, 1992).

Defining the onset of perimenopause by menstrual cycle changes, however, does women a disservice because the hormonal changes of perimenopause (higher estradiol and lower progesterone levels) have *already begun despite maintaining regular menstruation* (Moen, Kahn, Bjerve, & Halvorsen, 2004; Prior, 1998, 2006; Santoro et al., 1996).

Normal perimenopause may begin as early as age 35 and still end with a normal menopause (defined as 1 year beyond the last flow) at 40–45 years. Although about 80% of women have few symptoms in perimenopause, approximately one third of women seeking

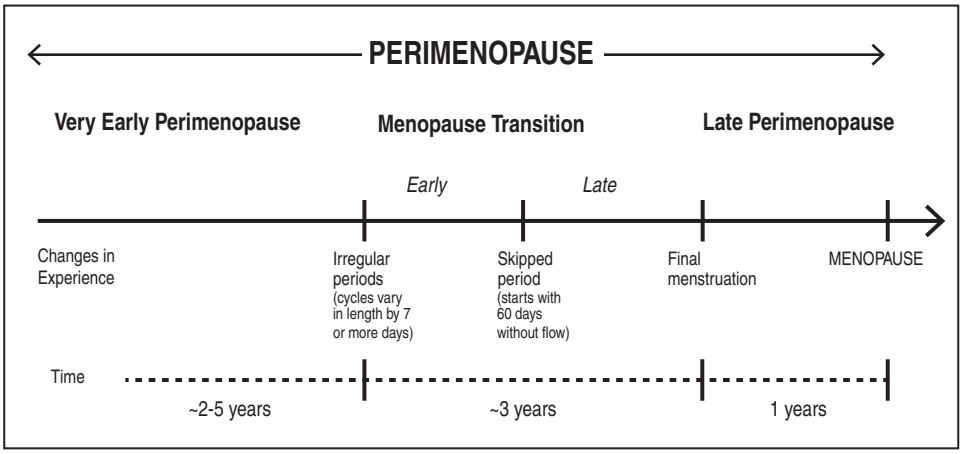

Figure 3.4 The four phases of perimenopause including very early perimenopause when women's experiences and hormones have changed but before the consensus (Harlow et al., 2012) says that the "menopause transition" has begun. Reprinted with permission from Prior et al., 2012.

medical help report very heavy flow (Kaufert, 1986). Other women become troubled by mid-sleep awakening and night sweats that tend to occur cyclically around flow (Hale, Hitchcock, Williams, Vigna, & Prior, 2003). As midlife women are often most symptomatic before their menstrual periods become irregular, it is useful to recognize those with night sweats, sleep disturbances, and shorter cycles as entering perimenopause (Prior, 2005). Other experience changes that may also indicate perimenopause onset while flow is regular are worsening cramps, heavy flow, new/worsening migraines, breast tenderness/lumpiness, premenstrual symptoms, and weight gain despite little change in diet/exercise (Prior, 2005). Any three of the nine above-listed experience changes can be used to make a diagnosis of very early perimenopause (Figure 3.4) (Prior, 2005).

Following a time of irregular cycles (during which heavy flow may still occur and daytime hot flushes may begin) (Figure 3.4) women will then experience a skipped period (or cycle length >60 days) that marks the beginning of the late menopause transition (Harlow et al., 2012). This may be followed within 1–2 years by the final menstruation. The last phase of perimenopause is very late perimenopause, which characterizes the final year of menstrual life. During this year, breast tenderness and cramps have usually gone (unless they are predicting flow) and often vasomotor symptoms (VMS) reach their peak lifetime intensity (Dennerstein, Dudley, Hopper, Guthrie, & Burger, 2000).

An individual woman's path through perimenopause is marked by considerable variation rather than a predictable progression (Kaufert, Gilbert, & Tate, 1987; Mansfield, Carey, Anderson, Barsom, & Koch, 2004). The further women move from the onset of perimenopause, according to Australian population-based data, the less symptomatic they become except that some experience lower libido, more VMS (both day and night), and more frequent headaches (Dennerstein et al., 2000). Perimenopause may, and often does, last 5–10 years.

Symptomatic perimenopause is currently commonly treated with combined hormonal contraceptives (CHC) or menopausal-like ovarian hormone therapy (OHT). However, if estrogen levels are high and poorly suppressible (Prior, 1998), more estrogen is unlikely to help. One study (Casper, Dodin, Reid, & Study Investigators, 1997) showed no significant changes from placebo or CHC related to quality of life, heavy flow, or hot flushes.

Perimenopausal heavy flow, in my clinical experience, improves with ibuprofen (200–400 mg with each meal on every day of flooding menstruation) plus oral micronized progesterone in a physiological luteal phase dose of 300 mg at bedtime daily (Simon et al., 1993). In perimenopausal heavy flow, progesterone needs to be given for 3 months continuously to overcome the cumulative effects of higher estrogen levels, rather than cyclically as in premenopausal women (Prior, 1997). Another effective non-surgical option is the levonorgestrel-releasing IUD (Lethaby, Hussain, Rishworth, & Rees, 2015). Only if there is documented endometrial cancer should hysterectomy be used to "treat" perimenopausal menorrhagia. The natural history of mid-life heavy flow is that it improves the longer a woman is in perimenopause.

Cramps also tend to increase in perimenopause. Ibuprofen, or another non-steroidal anti-inflammatory agent, initially and then "on demand" also works in this situation. A recent randomized controlled trial (RCT) of oral micronized progesterone for perimenopausal VMS showed a daily diary trend to overall improvement, but women perceived significantly improved night sweats in both early and later perimenopause (Prior et al., 2018). It is well documented in RCTs that 300 mg of micronized progesterone at bedtime improves sleep (Caufriez, Leproult, L'hermite-Baleriaux, Kerkhofs, & Copinschi, 2011; Hitchcock & Prior, 2012; Schussler et al., 2008) and that this is progesterone's major "side effect."

Menopause: a new flow-less life phase

Menopause refers to the life phase that begins for a woman who has been 12 months without flow. (The term "postmenopause" should no longer be used because it refers to the now-obsolete definition of "menopause" as the literal last menstrual flow.) The normal age at menopause is officially 40–58 years, with an average age of 49–52, depending on the country. Those few who become menopausal at age 45 or younger may be at higher risk for cardiovascular diseases as well as osteoporosis. The perimenopausal woman who had a difficult time will, in general, be less symptomatic in menopause (although she may have VMS for several more years depending on how early in perimenopause they began) (Freeman et al., 2011).

The 12-month landmark is a statistical "fact": 90% of women aged 45 years or older at menopause onset will not experience a further flow (Wallace, Sherman, Bean, Treloar, & Schlabaugh, 1979). That means that 10% of women will bleed again, and as many as 20% of women younger than 45 at menopause may have flow after 12 months of amenorrhea. Asymptomatic menopausal bleeding (in women not taking OHT) is strongly associated with endometrial cancer (Kaaks, Lukanova, & Kurzer, 2002). Women experiencing flow after amenorrhea for 12 months will usually be scheduled for endometrial biopsies to exclude cancer. If women describe cramp-like pelvic pain, sore breasts, nausea, or bloating before flow, they are experiencing a *normal* flow, as all of those are signs of the higher estrogen levels that triggered the extra menstrual period. Unfortunately for them, the "12-month clock" then starts all over again. Only if they have further flow, within 3 years of the last flow, with no preceding symptoms, should they be investigated for endometrial cancer.

New understanding of symptomatic menstrual cycles

When a cycle includes only estrogen and not progesterone, there is a fundamental hormonal imbalance. Our built environment that causes stress, produces light and noise pollution, interferes with sleep, tempts with fast foods and sweet drinks related to population obesity,

includes environmental contaminants that act like estrogen, and promotes decreased physical activity also promotes excess estrogen exposure. The common menstrual cycle problems women face originate with estrogen overbalancing progesterone. I will briefly describe the most frequent disturbances. For further information see www.cemcor.ca.

Menstrual cramps help shed the uterine lining during flow. They are a common experience; for 10–20%, cramps cause severe pain (dysmenorrhea) associated with missing school or work. Menstrual cramps are caused by endometrial and uterine muscle production of prostaglandins (a long fatty acid-type hormone) that increase uterine spasms. Higher prostaglandins are produced if the cervix is tight (as in a woman who has not borne a child, has had an IUD inserted, or has experienced a miscarriage/abortion). In studies with monkeys, estrogen increases and progesterone decreases uterine prostaglandin production (Eldering, Nay, Hoberg, Longcope, & McCracken, 1990). These data suggest that cramps may be worse in shorter cycles with higher estrogen levels (Landgren, Unden, & Diczfalusy, 1980) and in normal-length but *anovulatory* cycles.

Treatment of menstrual cramps involves understanding what causes them, exercise and gradual weight loss (if needed, which decreases high estrogen production), and use of one of the over-the-counter, inexpensive medications (e.g., ibuprofen) in the non-steroidal anti-inflammatory drug (NSAID) family (Marjoribanks, Ayeleke, Farquhar, & Proctor, 2015). However, most NSAIDs' and ibuprofen's inhibition of prostaglandin production appears short-lived, therefore, to control cramps effectively, a woman must take two standard-sized tablets (200 mg X 2) at the first hint and then take a further 200 mg tablet as soon as the cramps *start to come back*, even if that is only 1–2 hours after the last dose. Taking ibuprofen every 6 hours means that 46% of women may not have adequate control of their cramps (Marjoribanks et al., 2015). Combined hormonal contraceptives decrease cramps in premenopausal women, but scientific testing and evidence is lacking about whether they are effective in adolescents and perimenopausal women (Marjoribanks et al., 2015).

Menorrhagia (heavy flow) is associated with an over-thickened endometrium related to higher estrogen and lower progesterone levels. Heavy flow is associated with an imbalance of endometrial prostaglandins, and it decreases by 20–50% with NSAIDs (Lethaby, Augood, & Duckitt, 2002). One 200 mg ibuprofen tablet with each of three meals on every heavy flow day is sufficient.

Heavy flow is more common in adolescent and perimenopausal women because both have higher estrogen levels and lower progesterone levels. Although CHC are commonly recommended, cyclic oral micronized progesterone (300 mg at bedtime for 14 days on and 14 days off) provides a more physiological and usually effective heavy flow therapy for adolescent and premenopausal women (Prior, 1997). Heavy flow is associated with anemia, therefore a blood count and bone marrow iron level (ferritin) need to be assessed and low dose iron therapy taken for a full year if anemia is present. Heavy flow in perimenopause is discussed above.

Endometriosis is caused by cells of the normal uterine lining that have flowed backwards up the fallopian tubes and spilled into the abdominal cavity (most commonly in the pelvis, but they can travel anywhere, including in the lung and eye). Although no clear population data on the question are available, it is likely that endometriosis arises in a setting of chronic, silent anovulation also associated with immune changes that are poorly characterized. It is likely that cyclic progesterone would prevent endometriosis if given prophylactically to young women with a family history of endometriosis.

Fibroids are benign growths within the muscular uterine wall that estrogen stimulates and progesterone inhibits. They increase with age, the majority of women have them, and they

usually cause no clinical symptoms. Fibroids are often blamed for perimenopausal heavy flow. However, both fibroids and heavy flow are related to the higher estrogen/lower progesterone levels of perimenopause. Less than 10% of the time fibroids push into the endometrium (sub-mucus) and thus *could* cause heavy flow. In a study of women with heavy flow who had had hysterectomies (once standard heavy flow treatment), only 6 of 99 had sub-mucus fibroids at examination of pathology tissue (Seltzer, Benjamin, & Deutsch, 1990).

Infertility that is related to silent ovulatory disturbances is highly treatable, but this is usually not considered. Cyclic progesterone for ovulatory infertility needs to start after the mid-cycle LH peak or mucus has disappeared, to avoid interfering with egg release, and then continued for 14 days.

Polycystic ovary syndrome (PCOS) would be better called *anovulatory androgen excess* (AAE) (Prior, Kalyan, & Seifert-Klauss, 2014) because ovarian cysts *simply mean cycles without ovulation*. Besides cycle and ovulatory disturbances in PCOS/AAE, exposure to high levels of ovarian testosterone is essential. Given that rapid LH pulses may cause PCOS/AAE (Blank, McCartney, & Marshall, 2006) and progesterone normally slows LH pulsatility, cyclic progesterone therapy may be a therapeutic option (Prior, 1997).

Conclusion

Women's menstruation is resilient, new life-promoting, and health-producing, yet still is often viewed with negativity, squeamishness, or disgust. This chapter presents a life-affirming view of the menstrual cycle with the goal of better acquainting those who menstruate with the amazing vitality of this reproductive system. In the context of centuries-old social stigma and misogyny it is no wonder that we have not learned until recently that regular cycles may lack ovulation or have short luteal phases and thus produce infertility. Even more important is that increasing obesity in the population and the "estrogen dominance" of anovulatory cycles mean that menstrual cycle-related disturbances increase, women become symptomatic, and then begin to view their reproduction cycle as a problem. In this chapter my goal was to re-acquaint women both with the dynamic and protective responsiveness that lead to silent ovulatory disturbances and the woman-empowering ways to promote ovulatory cycle recovery and later life health.

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