F, V & V in ObGyn, 2011, 3 (2): 109-120



# Progesterone for Symptomatic Perimenopause Treatment – Progesterone politics, physiology and potential for peri-menopause

J. C. Prior

*Professor, Endocrinology, University of British Columbia, and Vancouver Coastal Health Research. Institute, Vancouver, Canada V5Z 1M9. Scientific Director, Centre for Menstrual Cycle and Ovulation Research (www.cemcor.ubc.ca).*

Correspondence at: Professor J. C. Prior, Suite 4111, 2775 Laurel Street, Division of Endocrinology, Department of Medicine, University of British Columbia and Vancouver Coastal Health Research Institute, Vancouver, BC V5Z 1M9. Telephone (604) 875-5927, Fax (604) 875-5915; email jerilynn.prior@vch.ca; websites: www.cemcor.ubc.ca and www.estrogenerrors.com

*Abstract*

Perimenopause, women's normal midlife reproductive transition, is highly symptomatic for about 20% of women who are currently inaccurately counseled and inappropriately treated with oral contraceptives, menopausal hormone therapy or hysterectomy. About 80% of perimenopausal women experience vasomotor symptoms (VMS), 25% have menorrhagia, and about 10% experience mastalgia. The majority of women describe varying intensities of sleep, coping or mood difficulties. Women are more symptomatic because common knowledge inaccurately says that estradiol ($E_2$) levels are dropping/deficient. Evidence shows that with disturbed brain-ovary feedbacks, $E_2$ levels average 26% higher and soar erratically – some women describe feeling pregnant! Also, ovulation and progesterone ($P_4$) levels become insufficient or absent. The most symptomatic women have higher $E_2$ and lower $P_4$ levels.
Because $P_4$ and $E_2$ complement/counterbalance each other's tissue effects, oral micronized $P_4$ ($OMP_4$ 300 mg at bedtime) is a physiological therapy for treatment-seeking, symptomatic perimenopausal women. Given cyclically (cycle d 14-27, or 14 on/off) in menstruating midlife women, $OMP_4$ decreases cyclic VMS, improves sleep and premenstrual mastalgia. Menorrhagia is treated with ibuprofen 200mg/6h plus $OMP_4$ cycle d 4-28. For insulin resistance, metformin plus cyclic or daily $OMP_4$ decreases insulin resistance and weight gain. Non-responsive migraines need daily $OMP_4$ plus usual therapies. VMS and insomnia in late perimenopause respond to daily $OMP_4$. In summary, $OMP_4$ is a physiology-based therapy that improves sleep, treats VMS, does not increase breast proliferation or cancer risk, increases bone formation and has beneficial cardiovascular effects. A controlled trial is testing $OMP_4$ for perimenopausal VMS – more evidence-based data are needed.

*Key words:* Perimenopause, vasomotor symptoms, night sweats, menorrhagia, sleep disturbance, anovulation, short luteal phase, ovulatory disturbances, oral micronized progesterone, treatment, midlife women, estradiol levels, progesterone levels, infertility, nausea, migraine headaches, mastalgia, insulin resistance, osteoporosis, rapid bone loss, cardiovascular disease, breast cancer, estradiol-progesterone tissue interactions, self-actualization, feminism, history.

*She is weeping and her normally attractive face has become twisted and swollen – almost inarticulate, she complains of extreme fatigue, flooding menstruation and night sweats robbing her of sleep.*
*You have delivered her two babies and done her yearly Pap tests, but the woman in front of you seems a stranger.* ***What has changed? Why is she so miserable?***

Your medical record shows that Emily, we'll call her, is 44 years old, apparently happily married, with a son in high school and a daughter in her early teens. She is a social worker and a community leader in your moderate-sized city. She has always been a vibrantly well woman in exceptional health who eats well, doesn't smoke and exercises regularly.

You're puzzled over Emily's current situation. You inquire about her husband, her children – she mumbles and then vehemently snorts, "***They're*** fine!"

"How are your periods besides the heavy flow?" you ask. "Spot on regular!" she retorts, "That's what's so frustrating – maybe a bit shorter, about 25 days apart."

"I don't have a clue what's happening." She goes on. "I don't *feel like myself* – ***when do I get my life back***?"

Midlife women all over the world are similarly challenging their gynaecologists. They want help to understand the changes they are experiencing, some idea of the time course of these changes and, only occasionally, do they want and need some therapeutic intervention. The purpose of this review is to first identify the current concepts, policies and politics that prevent many of us, as physicians, from understanding our midlife patients' concerns. I will define and describe the phases of the long and varying perimenopausal transition. Then I will reframe perimenopause physiology in a new and hormonally more accurate manner before embarking on my primary purpose – describing the evidence that oral micronized progesterone therapy is safe, appropriate and effective for those (relatively few) symptomatic perimenopausal women who require medical intervention.

My perspective is that of an endocrinologist who, herself, suffered a long, perplexing and highly symptomatic perimenopause. I am also a clinician-scientist, doing epidemiological, clinical observational and randomized controlled trial research on perimenopause. In the early 1990s, despite my training and roles, I like Emily, struggled to understand the changes I personally experienced – I found the hormonal changes to be the opposite of what I had been taught and always thought; instead, estradiol erratically soared and progesterone progressively decreased. Before we get to that, however, we must first review how we got to a situation where Emily is seeking yet not finding help.

## Historical and Medico-political Context of Perimenopause

With the discovery of estradiol in the mid-1920's came the concept that it was ***the*** female hormone (Oudshoorn, 1994; Baxter and Prior, 2009) and that all symptomatic women must be "estrogen deficient." Given the model of puberty, we would expect a long biological transition between potentially reproductive, menstruating premenopausal and 'hormonally deficient' menopausal women. But for cultural and pharmaceutical reasons, perimenopause and menopause came to be seen as a single, homogenous downhill slide into waning hormones, loss of health and decreased attractiveness.

Emily's symptoms don't make sense within this current view of midlife's decreasing hormone levels – with her shorter cycles and heavy flow she is highly unlikely to have deficient estradiol levels. However, if her estradiol levels are *not* low, why is she having night sweats?

Before addressing these questions about what is causing Emily's symptoms let's start with current official ideas. The North American Menopause Society (NAMS) website says, "The years between puberty (when periods start) and menopause are called premenopause." (http://www.menopause.org/expertadvice.asp). This statement totally eliminates any midlife transitional phase.

In the next sentence, however, NAMS contradicts that earlier sentence by saying: "Physical signs of menopause begin many years before the final menstrual period. This menopause transition phase is called perimenopause (literally meaning 'around menopause')."

Did you notice? In that NAMS quotation the word, "**menopause**," means *two different things* – in the phrase, "physical signs of menopause," the word means (as the average woman defines menopause) everything changing and symptomatic in midlife. However, in the phrase, "around menopause," the gynaecological definition of menopause is used, meaning the literal last menstrual period. If this is not confusing enough, there is yet a third, epidemiological, meaning of menopause (and this is how I will consistently use the word in this paper) – **menopause** is the normal woman's life phase that begins one year after the last menstruation (and is sometimes called "postmenopause"). Thus the confusing use of two key words (menopause and perimenopause) in official documents, rather than helping Emily understand what is happening to her, illustrate the unhelpfully inconsistent messages medicine and gynaecology are giving about "menopause."

## Timelines and Definitions

I will clarify how I use language describing the transition between fertile cycles and menopause by showing a diagram that incorporates the latest evidence defining the phases of this midlife transition. It uses the world-wide epidemiology/cohort-based data from the ReStage Collaboration to refine the onset of the Early Menopause Transition (Harlow *et al.*, 2008), and the onset of the Late Menopause Transition (Harlow *et al.*, 2006), of the Stages of

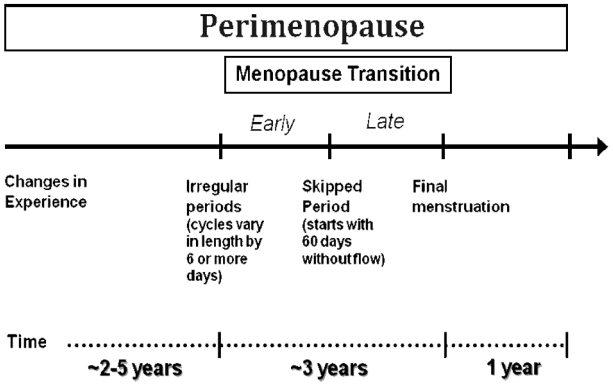


***Fig. 1.*** — The ReSTAGE Collaboration refinements of the Stages of Reproductive Aging Workshop (STRAW) definitions of the phases of midlife. The estimated timelines are based on extensive clinical experience (Prior, 2010).

Reproductive Aging Workshop (STRAW) definitions (Soules *et al.*, 2001) of the menopausal transition and perimenopause.

Early perimenopause, before the irregular or skipped cycles of the menopause transition begin, is characterized by a several-year stretch of changes in experience without any cycle interval changes (Prior, 2005a). In my view, this is the most frustrating and symptomatic time for many women. Evidence shows that hormone levels have already changed although regular cycling hasn't. For these reasons, a series of experience-changes, any three of which a woman notices, can be used to make a "diagnosis" of the onset of early perimenopause (Table 1) (Prior, 2005a).

Emily, the highly distraught woman whose story began this paper, is clearly in early perimenopause because she is miserable with heavy flow (#1 in Table 1), has regular but shorter cycles (#2) and is suffering with night sweats (#6). Evidence suggests that the shorter cycle lengths documented with reproductive aging (Vollman, 1977) are associated with, and are likely *caused by*, higher cycle estradiol production within a shorter follicular phase (Landgren *et al.*, 1980).

The early menopause transition as shown in Figure 1 requires cycle variability of +/- 6 days (Harlow *et al.*, 2008). Women often describe this variation as "irregular" cycles but they also may not notice this degree of variability (given that 29% of a population-based sample of women experience at least one cycle-to-cycle length variability of 14-days a year (Munster *et al.*, 1992) and some women may never have established, nor learned to recognize, regular cycles.

Women begin the late menopause transition with 60 days between flow episodes or what women commonly call a "skipped period" (Harlow *et al.*, 2006). Note that, in neither the early nor late menopause transition did the ReStage investigators find that the elevated FSH levels required by STRAW (Soules *et al.*, 2001) contributed to the menstrual cycle-based classification (Harlow *et al.*, 2006; Harlow *et al.*, 2008) and thus routine cycle day 3 FSH testing to determine perimenopausal status is not cost-effective. The late perimenopause, meaning the time from the final menstruation until menopause, is a year during which women's breast, heavy flow and premenstrual symptoms have improved but hot flushes and sleep problems are commonly worsening, but alternatively may be decreasing (Dennerstein *et al.*, 2000).

**Table 1.** — A 'diagnosis' of early perimenopause can be made in midlife women who continue to have regular flow if they are experiencing – *any 3* of these nine experience changes.

1. New onset heavy and/or longer flow
2. Shorter menstrual cycles (≤ 25 days)
3. New sore, swollen or lumpy breasts
4. New mid-sleep wakening
5. Increased cramps
6. Onset of night sweats, in particular premenstrually
7. New or markedly increased migraine headaches
8. New / increased premenstrual mood swings
9. Weight gain without changes in exercise or eating

## Current Evidence for the Hormonal Changes of Perimenopause

Symptomatic parous women often describe feeling pregnant during perimenopause. I had such a vivid dream in early perimenopause – when I described it to an audience of midlife women someone at the back hollered, "That's not a dream, it's a nightmare!" Likewise, a hunter-gatherer !Kung woman of the Kalahari desert told her anthropologist interviewer: "Not long ago I had a dream that I was pregnant... . I thought, 'What? Haven't I stopped menstruating?'" (Shostak, 1981). At the time Nisa was thought to be in her early 50s and from her description, was in late perimenopause (Fig. 1). Likewise, in the introduction to her book, ***"Understanding Menopause"*** activist Canadian sociologist also reported feeling pregnant during perimenopause (O'Leary Cobb, 2005). Why did all of us, culturally, ethnically and economically very different midlife women, report feeling pregnant? I believe it is because we all were experiencing the sore breasts, weight gain, bloating and other high estrogen symptoms that are common in perimenopause and in pregnancy. Our subconscious minds told us what our physicians didn't.

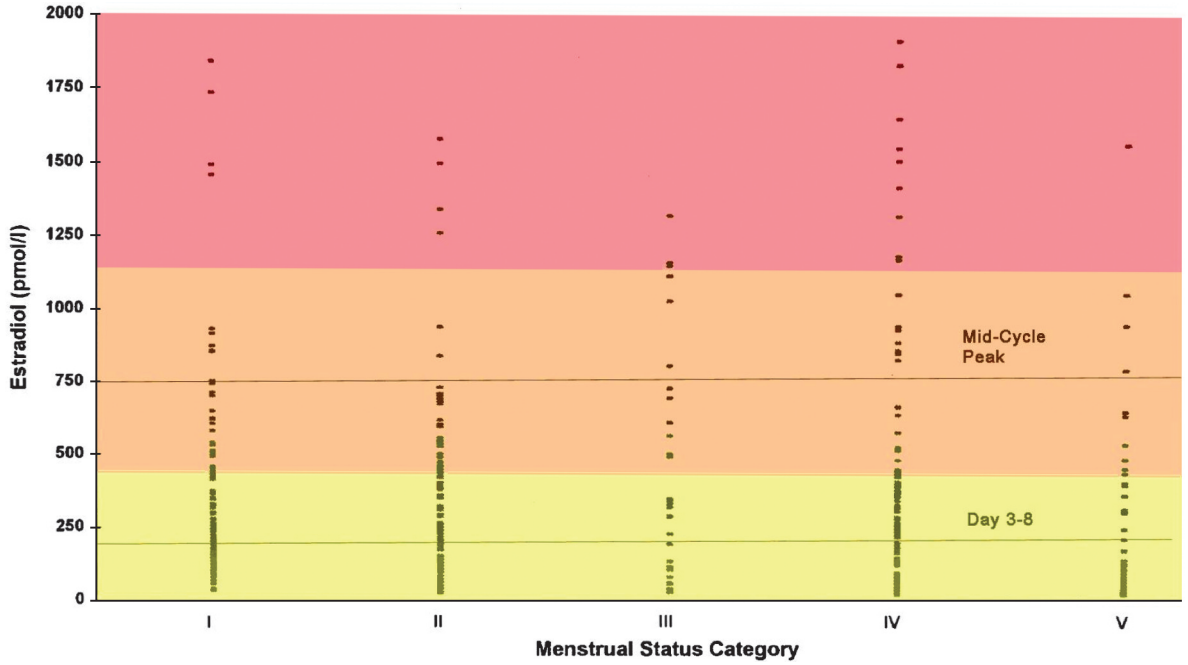


***Fig. 2.*** — The cross-sectional mid-follicular phase estradiol levels by menstrual cycle characteristics in menstruating women ages 45-55 randomly selected and enrolled in the Melbourne Midlife Women's Health Project baseline data – annotated by including the mean $E_2$ level for premenopausal follicular phase women from the Burger lab as the lower horizontal line (surrounded +/- one SD by yellow colour), and the second horizontal line as the mean $E_2$ peak level (orange). Above that are very high $E_2$ levels importantly higher than ever seen during normal premenopausal menstrual cycles (red). Reprinted from Burger *et al.* (1995) with adaptations by the author.

Reliable evidence about the hormonal changes of perimenopause was absent from the medical literature until the mid-1990s, not only because perimenopause and menopause were subsumed into the same process, but perhaps also because no questionnaires about "menopause" included questions about either flow or breast tenderness which are clinically important and distinctive for perimenopause. The first, population-based data of follicular phase estradiol ($E_2$) levels in menstruating Melbourne Australia women ages 45-55 were cross-sectional with data segregated by menstrual cycle characteristics (I = regular cycles, interpreted as "premenopausal"; II = changes in flow; III changes in cycle interval; IV changes in both flow and cycle interval; IV no flow for 3-11.9 months) (Burger *et al.*, 1995). Figure 2 shows that early follicular phase (cycle days 3-8) fasting $E_2$ levels had a large variance but the majority fell outside of the plus/minus 1 SD of the fasting normal range (yellow). Note the number of women in all phases (I-V) whose $E_2$ levels are extremely high (red).

In reporting these results, the authors did not describe observing higher than expected estradiol levels (Burger *et al.*, 1995). Moreover, their abstract says: "We conclude that an increase in serum FSH and ***decreases in $E_2$*** and Inhibin are the major endocrine changes cross-sectionally during the menopausal transition" (author's emphasis). I immediately recognized myself in these hormonal data and was flabbergasted and angry that the authors did not see the high $E_2$ levels in their data. So, with colleagues, I challenged in a letter to the editor "that the data be allowed to speak" (Prior *et al.*, 1996). Burger and colleagues responded by admitting that perimenopausal "estradiol levels are preserved. .. ." (Burger, 1996).

These illustrative but traditionally interpreted population data, however, were quickly followed by confirmatory cross-sectional data, this time urinary hormone levels across one cycle in women younger than 37 years old with regular cycles compared with symptomatic menstruating women older than age 37 (Santoro *et al.*, 1996). These data showed that estrogen excretion products were significantly higher and pregnanediol levels were importantly lower in the perimenopausal women. These authors recognized the uniqueness of their observation and clearly reported the higher estradiol level they observed.

I subsequently performed a meta-analysis of within-centre pre- versus perimenopausal serum estradiol levels that showed, in perimenopausal women (n = 415) in the follicular phase $E_2$ levels were 225 pmol/L versus 175 pmol/L in premenopausal women (n = 276; Fisher's F = 16.12, P = 0.041) (Prior, 1998). The premenstrual or luteal phase $E_2$ levels were also significantly higher in perimenopausal and than in premenopausal women – in perimenopausal women (n = 69) mean $E_2$ levels were 374 pmol/L compared with 300 pmol/L in

premenopausal women (n = 290; Fisher's F = 15.46, P = 0.016) (Prior, 1998). Most recently two reports from a systematic 2-cycle thrice weekly serum hormone study in midlife women of every STRAW stage compared with mid-reproductive aged women confirmed the higher estradiol levels, lower progesterone levels (Hale *et al.* 2007) and showed atypical secondary estradiol peaks called "luteal out of phase" or LOOP events within the luteal phases of a third of all cycles from women in the menopausal transition (Hale *et al.*, 2009). Therefore, evidence from multiple continents and many different researchers confirms what perimenopausal women's experiences (shorter cycles, heavy flow, breast tenderness, weight gain, insulin resistance and feeling pregnant) are telling them – they are experiencing higher estradiol levels.

Why are these paradoxical increased estradiol levels occurring in women whose ovaries are running out of follicles (Richardson *et al.*, 1987)? Evidence suggests that inhibin B levels (Burger *et al.*, 1998) decrease thus allowing small increases in FSH levels which, in turn, recruit more follicles each of which can make estradiol and even stimulate non-typical additional waves of follicle maturation (as in LOOP) cycles (Hale *et al.*, 2009). Furthermore, these higher estradiol levels do not reliably suppress FSH levels, at least partly because of decreases in inhibin B (Klein *et al.*, 1996; Prior, 1998).

The decreasing progesterone production across the menopausal transition (Santoro *et al.*, 2008) (Prior, 2002b) is also related to disturbed hypothalamic-pituitary-ovarian feedback loops so that estradiol peaks can occur and not be followed by LH peak levels; both estradiol and LH peak levels can also occur and not be followed by ovulation (Weiss *et al.*, 2004) although the complete physiological reasons for these observations are not yet clear. In an earlier as well as a recent study of daily urinary hormone levels, perimenopause is a time of unopposed and higher estrogen production often without counterbalancing ovulatory progesterone production (Metcalf and MacKenzie, 1985; O'Connor *et al.*, 2009).

These multiple physiological ovarian hormonal (higher estradiol and FSH levels, lower inhibin B and progesterone levels) and hypothalamic-pituitary-ovarian feedback disturbances to me represent a planned way of ending the potential for menstruation and pregnancy as women become menopausal.

## The Physiological Rationale for Progesterone Treatment of Symptomatic Perimenopause

In order to understand why I consider progesterone an important, safe and effective therapy for symptomatic perimenopause it is necessary to see estradiol and progesterone and their interactions as I do. Estradiol has generally been considered the predominant, most important woman's reproductive hormone and 'what makes a girl, a girl' (Baxter and Prior, 2009). Progesterone – only produced after a midcycle $E_2$ peak and the LH peak it subsequently triggers – is present for fewer than half of all menstrual cycle days. However, $P_4$ is secreted in extremely high quantities (reported as nmol versus estradiol's pmol), rising 1400 percent above its low follicular phase levels; midcycle maximum $E_2$ levels, by contrast, rise only 220 percent above its low during flow (Nielsen *et al.*, 1990). Progesterone production is dependent on preceding $E_2$ production. However, nature does not spend energy making large quantities of non-essential hormones. Thus high levels of $P_4$ for at least 10 days per cycle appear necessary to counterbalance or complement estradiol's powerful and essential growth-stimulating actions (Graham and Clarke, 1997). To provide a few reproductive examples of estradiol-progesterone partnerships: $E_2$ stimulates cervical gland production of slippery, clear mucus to aid sperm transit while $P_4$ inhibits cervical mucus production; $E_2$ stimulates breast glandular development in puberty (Tanner stages I-III) while $P_4$ (plus $E_2$) is required for final breast maturation to Tanner stages IV-V as the areolar diameter expands and the ductal system and nipple mature (Prior *et al.*, 1989); both $E_2$ and $P_4$ induce intermediate cell vaginal maturation – 12-mo. following premenopausal ovariectomy during randomized double-blind treatment with conjugated equine estrogen (CEE, 0.6 mg/d) or medroxyprogesterone (MPA, 10 mg/d) the majority of cells were intermediate cells, although CEE produced significantly more superficial cells (Prior *et al.*, 1994). $E_2$ and $P_4$ work together in normal bone remodelling so that estradiol reduces bone resorption while progesterone stimulates bone formation (Prior, 1990; Seifert-Klauss and Prior, 2010). In two randomized controlled human trials with breast biopsy cellular changes as the primary objective, topical estradiol caused breast epithelial cell proliferation while progesterone decreased it (Chang *et al.*, 1995; Foidart *et al.*, 1998). In addition, the large French cohort study (E3N) shows estradiol treatment to be associated with a 29% increased risk for breast cancer compared with untreated menopausal women, estrogen plus progestin increased risk by 69%, but estrogen with progesterone had no increased breast cancer risk (HR 1.0, 95% CI 0.82, 1.22) (Fournier *et al.*, 2008). In the vascular endothelium, both $E_2$ and $P_4$ similarly increase endogenous nitric oxide activity to improve blood flow (Mather *et al.*, 2000). In the brain, estradiol is neuroexcitatory

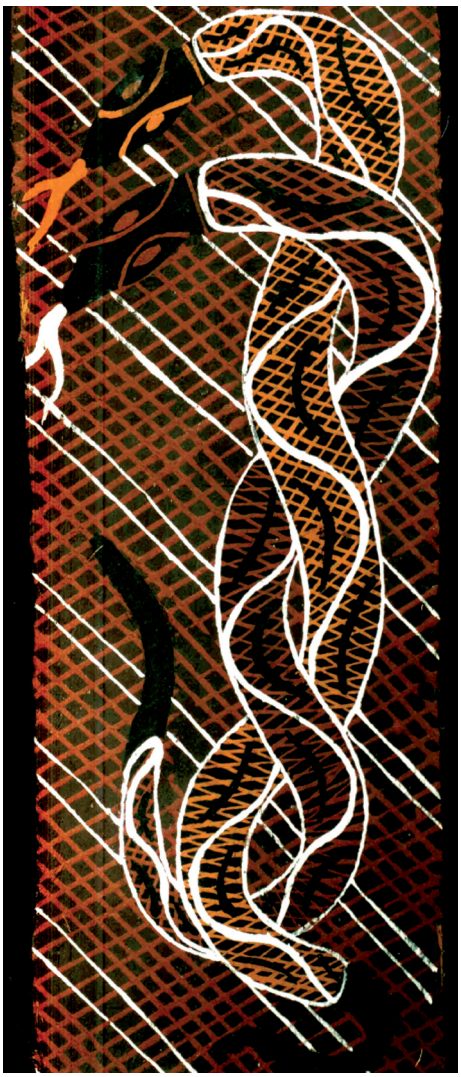

***Fig. 3.*** — Bark painting by an aboriginal man in Australia depicts two stylized snakes intimately entwined. This is a photo of art that the author purchased in Western Australia. The artist's identity is unknown.

while progesterone inhibits this action, improves sleep and decreases addictive behaviours and anxiety (Gibson *et al.*, 2009). Thus my vision is that estradiol and progesterone are both important for normal physiology; they act together in all reproductive and non-reproductive tissues (bone, blood vessels, brain) and are as closely tied together as the two snakes in this Australian aboriginal bark painting (Figure 3).

In addition, based on the above physiology, oral micronized progesterone appears safe for perimenopausal women – it should decrease their risks for endometrial cancer, does not show any indication of increasing venous thromboembolism risk, causes women to burn 300 more kilocalories/day so will help prevent rather than causing weight gain (Barr *et al.*, 1995b) and decreases anxiety and doesn't cause depression (Dennerstein *et al.*, 1985).

Having explained the changing physiology of perimenopausal hormonal levels and feedback systems, and supported the probable safety of progesterone therapy, I need to indicate why I consider the current recommendations that symptomatic perimenopausal women be treated with oral contraceptives or menopausal type hormone therapy (National Institutes of Health 2005) to be inappropriate and unsafe. Given the feedback disturbances of perimenopause, it is likely that exogenous estrogen *will not reliably suppress endogenous (often high) $E_2$ levels*. Oral contraceptives have not proven more effective than placebo for hot flushes in a controlled trial (Casper *et al.*, 1997). In addition, new retrospective clinical data suggest breast cancer in women who were treated in perimenopause with menopausal-type hormone therapy show a trend toward decreased time to breast cancer progression and decreased overall survival (P = 0.06) (Baumgartener *et al.*, 2011). Thus oral contraceptives and hormone therapy do not appear to be effective nor safe in perimenopause.

We can now begin to describe clinical data and minimal evidence-based material available suggesting that progesterone is an appropriate and effective therapy for symptomatic perimenopause. (I added the adjective, "symptomatic" because perimenopause is a normal life phase and only a small percentage of women need or want any medical treatment.)

## Oral Micronized Progesterone Treatment for Symptomatic Perimenopause

Before describing specific uses for progesterone, it is useful to provide some general clinical guidelines. I think of progesterone as counterbalancing the tissue effects of high estrogen – given the feedback disturbances, it is not realistic to expect that progesterone will suppress endogenous $E_2$ production in perimenopause. When I say "progesterone" I mean the molecularly identical hormone to that produced by the corpus luteum and not progestins. I always recommend oral micronized progesterone (OMP), rather than transdermal progesterone for perimenopausal women. The primary reason is that I have experience with it – however I think transdermal progesterone may not be "strong enough" to effectively counterbalance the tissue effects of high estrogen levels, and furthermore it has no beneficial effect on sleep disturbances that are common in perimenopause. OMP can either be prescribed as a formulary drug, or where that is not available, compounding pharmacists can make it up in olive oil (which is similarly well absorbed based on my clinical serum tests).

A physiological luteal phase dose of OMP is 300 mg at bedtime – this keeps the $P_4$ blood level above a luteal phase threshold for 24 hours (Simon

*et al.*, 1992). OMP ***must be taken at bedtime*** because its beneficial sleep enhancing effects (Schussler *et al.*, 2008) would cause drowsiness or almost "intoxicated" feelings if taken when awake. To be cautious, especially for sleep-deprived and thin women, I recommend they begin OMP on a night following which they can sleep in. Otherwise catch-up rapid-eye-movement sleep may make them feel that OMP caused a "hang-over". These morning sleepy feelings, if present, do not persist more than a few days.

Finally, the schedule of OMP depends on women's bleeding pattern, her desires for fertility, and whether or not she gives a history of migraine headaches. (I'll discuss the use of cyclic OMP to aid perimenopausal fertility later.) For women with daily symptoms such as night sweats or hot flushes, especially if they have irregular or skipped cycles, I prescribe OMP daily. For women with regular cycles, unless they have migraines, I always start with cyclic OMP as shown in Figure 4 (http://www.cemcor.ubc.ca/help_yourself/articles/cyclic_progesterone therapy). Women with migraine headaches are sensitive to a host of changes thus, although OMP does not cause migraines, its withdrawal can trigger them. For migraneurs I always also prescribe daily OMP even if they are regularly cycling – daily OMP will make perimenopausal flow light but usually doesn't entirely prevent periods.

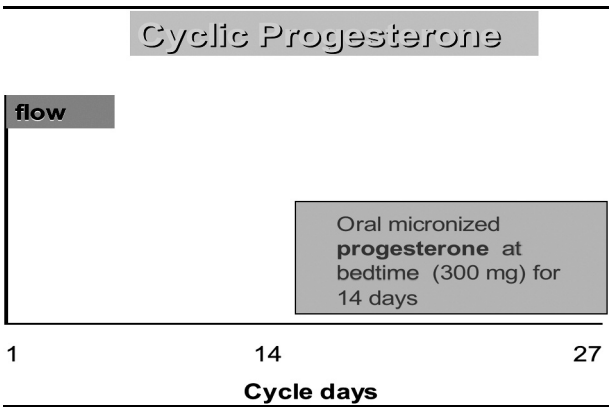


***Fig. 4.*** — Graph depicting the idealized regular 28-day menstrual cycle showing on which cycle days to prescribe 300 mg of oral micronized progesterone at bedtime to provide "luteal phase replacement" progesterone therapy for treating symptomatic perimenopausal women (http://www.cemcor.ubc.ca/help_yourself/articles/cyclic_progesterone_therapy) (Prior, 2000).

### Progesterone for heavy or prolonged flow

In my experience, heavy flow occurs in all phases of perimenopause and is experienced by about 25% of all midlife women. (Heavy flow was not included in the questions asked in the Melbourne Midlife Women's Health Study therefore we have no population-based prospective data). The usual gynaecological approach to heavy bleeding is to assume fibroids or other pathology – it is far more likely, however, that heavy flow is related to the disturbed ovarian hormonal physiology of perimenopause. Therefore, for perimenopausal women I don't recommend endometrial biopsies or ultrasounds or screening for bleeding disorders unless at least three cycles of ibuprofen plus progesterone therapy have not importantly improved the abnormal bleeding. All evidence, especially this case-control clinical study (Moen *et al.*, 2004) ] strongly suggest that the higher $E_2$ and lower $P_4$ levels typical in perimenopause cause the heavy flow. This suggests that OMP, which stabilizes the endometrium and, when given in long cycles, thins it, would be a beneficial therapy.

Once I have a clear understanding of a woman's heavy flow experience (hopefully from Daily Perimenopause Diary records (Hale *et al.*, 2003) that are downloadable from the CeMCOR website http://www.cemcor.ubc.ca/help_yourself/handouts/daily_diaries), I provide women with this practical lay language handout: (http://www.cemcor.ubc.ca/help_yourself/articles/very_heavy_menstrual_flow). I always begin therapy with an over-the-counter non-steroidal anti-inflammatory (NSAID) drug such as ibuprofen. NSAIDs restore a normal balance of endometrial prostaglandins and thus cause a 25-50% decrease in flow (Lethaby *et al.*, 2002) – *I believe NSAIDs should be taken on all heavy flow days by women of all ages.* For ibuprofen, the dose is 200 mg (with food) every 4-6 hours while awake.

In addition to ibuprofen I use cyclic OMP (Figure 4) treatment for all perimenopausal women with regular cycles and the recent onset of heavy flow. I would continue ibuprofen and cyclic OMP for at least three cycles. If, as often happens, flow starts while the 14 days of OMP therapy are still being taken, the full OMP duration should always be completed. The flow-start day is called a new Day 1 – OMP is started on the next cycle day 14, even if that gives only a few days off progesterone each cycle.

However, if I see a perimenopausal woman who has had heavy flow for months, in addition to assessing for and treating anemia, I will usually *start* long-cycle OMP – this means prescribing OMP for cycle days 4-28, along with ibuprofen as described above. In my clinical experience, even in women with documented bleeding disorders, long-cycle OMP plus ibuprofen therapies are usually effective. The natural history of heavy flow in perimenopause is that it improves over time and the closer a woman becomes to menopause. Therefore OMP and ibuprofen are temporizing measures. If these are not sufficient, my next approach is to recommend the levonorgestrel impregnated IUD (LNG-IUD) (Irvine *et al.*, 1998).

Obviously the LNG-IUD would be an earlier choice if the perimenopausal woman with heavy flow had no night sweats, breast tenderness or other experiences that may be helped by the physiological actions of OMP, and she also had practical access to it (despite its high cost in some jurisdictions).

One or all of the above mentioned measures to treat perimenopausal menorrhagia are almost always successful – in my practice, perimenopausal women with heavy menstrual flow or flooding almost never needed endometrial ablation or hysterectomy. Although Cochrane reviews and randomized controlled trials support the use of ibuprofen and cyclic or long-cycle progestins for heavy flow, there are no data of which I'm aware that have studied OMP for perimenopausal heavy flow.

### Shorter cycles

Unless cycles become consistently less than 21 days apart, these usually do not require any therapy. However, often the shorter cycles are associated with increased premenstrual symptoms, breast tenderness or heavy flow, and these need treatment. If cycles are routinely less than 21 days apart I suggest cyclic OMP as described above but beginning two days earlier and taken on cycle days 12-25.

### Breast Tenderness and/or Swelling and Nodularity

Breast tenderness is a symptom for 33% of early perimenopausal women and decreases as cycles become irregular (Dennerstein *et al.*, 2000). Clinical evidence based on daily diary records suggests that breast tenderness does not occur unless $E_2$ levels exceed the usual midcycle peak values. Some non-published data show that women with breast tenderness have increased breast cell proliferation (Anne Gompel, 2011, personal communication). Given that progesterone decreases breast cell proliferation (Chang *et al.*, 1995; Foidart *et al.*, 1998), cyclic OMP is likely to be effective therapy for breast tenderness occurring, as it commonly does, premenstrually (Hale *et al.*, 2003). Unfortunately, no controlled trial data are available to document that OMP causes significant symptomatic improvement of breast tenderness although the trend in a small cross-over trial was toward less tenderness (Dennerstein *et al.*, 1985).

### Mid-sleep Wakening or Sleep Disturbances

Sleep disturbances occur in 31% of early perimenopausal women and increase to 38% in late perimenopause (Dennerstein *et al.*, 2000). This sleep disturbance typically occurs in three different patterns: increased trouble falling asleep, early morning wakening or, as is most common, abrupt waking after a few hours of deep sleep. Perimenopausal women commonly, as did Emily, describe disturbed sleep as something that is troublesome for them and for which they seek treatment.

Oral micronized progesterone is rapidly converted in the brain into allopregnanolone which acts through the $GABA_A$ receptors to decrease anxiety and induce sleep (Friess *et al.*, 1997). Randomized double blind cross-over trials in men (Friess *et al.*, 1997) and menopausal women (Schussler *et al.*, 2008) clearly document significant increases in early rapid-eye movement sleep, decreased sleep interruption and no changes in morning neurocognitive function (Schussler *et al.*, 2008). Therefore, OMP is an effective and evidence-based treatment for sleep disturbances, although it has not yet been proven effective in perimenopause. Note that usually sleep disturbances are associated with other experience changes such as night sweats. I usually don't prescribe OMP *only* for sleep problems.

### Increased Dysmenorrhea or Cramps

In my experience perimenopausal cramps respond well to intense ibuprofen prophylaxis in women without a history of persistent severe cramps or endometriosis. This handout for women describes the early and repeated use of ibuprofen to stay ahead of the symptoms and thus prevent the pain-causing build-up of prostaglandins (http://www.cemcor.ubc.ca/help_yourself/articles/painful_periods). However, if perimenopause causes a flair of endometriosis symptoms, then I have found that daily OMP is effective along with ibuprofen therapy. As opposed to premenopausal women, daily OMP will not suppress estradiol levels and therefore inducing rapid bone loss is not a concern.

### Night Sweats and Hot Flushes

Ten percent of women ages 45-55 with regular menstruation report night sweats and ten percent hot flushes (Dennerstein *et al.*, 2000). Often these night sweats have a cyclic pattern and cluster around flow (Hale *et al.*, 2003). However, at present it is unclear how to treat vasomotor symptoms (VMS) in perimenopausal women – estrogen-based treatments are the gold standard for menopausal women (MacLennan *et al.*, 2004) but perimenopause has a different physiology. Although oral contraceptives and menopausal type ovarian hormone therapy are both currently advocated for VMS treatment (National Institutes of Health, 2005), a randomized controlled

trial of 20 mg ethinyl estradiol oral contraceptive showed no meaningful improvement versus placebo in perimenopausal women (Casper *et al.*, 1997). Although there are no such controlled trial data for the use of menopausal ovarian hormone therapy for VMS in perimenopause, epidemiological data suggest VMS don't improve during estrogen-based treatment until women become menopausal (Johannes *et al.*, 1994).

A recent randomized controlled trial showed that OMP was effective for both daytime and night VMS in healthy early menopausal women (Prior and Hitchcock, 2010). The mechanisms through which OMP helps VMS are not known, but probably involve actions in the hypothalamus, on temperature centres and by decreasing neuroexcitotoxicity and inflammation in the brain (Gibson *et al.*, 2009). The Centre for Menstrual Cycle and Ovulation Research has just secured Canadian Institutes for Health Research funding to perform a similar trial in 175 perimenopausal women. This trial will use daily OMP (to avoid the problems of heavy bleeding or need to exclude migraneurs) and stratify women into "early perimenopause" if they have not had a 60-day cycle and "late perimenopause" if they have. Results are not expected until at least 2014.

In the mean time, extensive clinical evidence says that OMP is effective for perimenopausal VMS. In addition, it improves the sleep disturbances with which night sweats are often associated. Cyclic OMP is effective for cyclic night sweats in regularly cycling early perimenopausal women. However, once VMS occur more consistently across the cycle, as often happens by the early menopause transition, daily OMP is then necessary.

### Migraine Headaches

Headaches are common in perimenopause and 32-36% of perimenopausal women across all phases report their experience in the last two weeks (Dennerstein *et al.*, 2000). Migraine headaches may occur for the first time in perimenopause. However, typically a woman will have experienced them at puberty or when first using oral contraceptives. What is unique about perimenopausal migraines is that they seem more refractory to management with acute therapies, and often occur at midcycle and peri-menstrually, thus twice a month. This can be debilitating if each migraine episode lasts for 3-5 days. To my knowledge there are no data on OMP for migraine therapy however, it has multiple anti-oxidative, anti-apoptotic effects and decreases neuroexcitotoxicity (Gibson *et al.*, 2009). Therefore it appears to be an appropriate therapy to try as a neuromodulating treatment (rather than the less specific beta blockers or tricyclic anti-depressants that are often used). In addition, most perimenopausal women with migraines are also symptomatic with other experience changes that OMP will likely help.

### Perimenopausal Premenstrual and Mood Symptoms

Premenstrual symptoms are of obscure etiology in premenopausal women (Harvey, 2009) but clearly increase in perimenopause, and typically become most evident in women with regular cycles. Approximately 30 percent of women across perimenopause reported depression and "nervous tension" experiences in the last two weeks (Dennerstein *et al.*, 2000). What is even more fascinating is that women who reported PMS when they still had regular cycles were more likely to later experience night sweats and VMS (Morse *et al.*, 1989). It makes most sense to me that women with a genetic or other predisposition to estrogen sensitivity will develop increased breast tenderness, bloating, inappropriately increased appetite and mood symptoms premenstrually in perimenopause as they experience higher $E_2$ and lower $P_4$ levels (Prior, 2002a). Calcium carbonate supplementation is the only evidence-based treatment for premenopausal premenstrual symptoms (Thys-Jacobs and Alvir, 1995; Douglas, 2002). However, women with severe depression that has a premenstrual exacerbation will be helped by serotonin reuptake inhibitors (Douglas, 2002). Cyclic OMP may be an appropriate treatment for women who have become unable to cope because of combined sleep disturbances, night sweats and breast tenderness with or without premenstrual mood swings. Again, although there are numerous negative trials of cyclic progesterone for premenstrual symptoms in premenopausal women with premenstrual symptoms (Douglas, 2002), none to my knowledge have been performed in perimenopause. However, I have never prescribed cyclic OMP *only* for premenstrual mood symptoms.

### Weight Gain Despite Appropriate Diet and Exercise

Before I experienced perimenopausal weight gain and perpetual hunger (that a patient once aptly described as, "my teeth feel hungry"), I was a skeptic that overweight could be increased by perimenopausal metabolic change and not simply by overeating and/or under-exercising. However, there are clearly changes in metabolic rate that occur in midlife women based on the 1.5 BMI unit gain in the 45-54 decade in population based data from Canadian women; men experienced a more gradual

0.5 BMI gain per decade starting in their 30s (Hopman *et al.*, 2007). Perimenopausal women with a past history of gestational diabetes, those with a Type 2 diabetes mellitus family history and those who are most generally symptomatic seem to be at increased risk for weight gain. Obviously, before doing anything else, the health care provider must review actual exercise and food records and work to ensure that both of these are optimal with at least 30 minutes of moderate exercise daily. There is some rationale for treatment with OMP given that progesterone increases core temperature and requires 300 kcal/d to do that in weight stable premenopausal women (Barr *et al.*, 1995). However, I have rarely treated women with OMP only to assist them in weight control. Instead I have found that metformin, a drug which makes insulin more effective and thus decreases insulin resistance, is a very helpful therapy for women who have an increasing waist circumference (normal for Caucasians is less than 88 cm) or a rising hemoglobin A1C level to values of 6.0 or higher (Mogul *et al.*, 2001). Obviously, if a woman with increasing weight also has night sweats or breast tenderness or sleep disturbances, cyclic or daily OMP will be a helpful therapy.

### Cyclic Progesterone Treatment for Infertility in Early Perimenopause

Because perimenopause physiology involves ovulatory disturbances with decreases in progesterone levels (Santoro *et al.*, 1996) and in luteal phase lengths even within regular, ovulatory cycles (Hale *et al.*, 2007; Prior, 2002b), it makes sense that infertility might be related to these ovulatory disturbances. The natural extension of that thought is to supplement with cyclic OMP (Figure 4). However, OMP has the potential to interfere with the LH peak and ovulation if given too early in the cycle. Therefore I recommend that women who observe increased clear cervical mucus at midcycle should wait to start their 14 days of OMP until after that mucus is decreasing or has disappeared. My clinical experience is that at a large number of fertility desiring women were able to achieve fertility only by using cyclic OMP. Again, there are no controlled or even observational studies in support of this idea. But repeated spontaneous perimenopausal conceptions and full term pregnancies have been documented despite markers suggesting *in vitro* fertility treatments are futile (Check and Giangreco, 2009).

### How to help Emily

We started this discussion with a familiar but strangely distraught patient. Emily is extremely tired yet isn't getting restful sleep and is having night sweats as well as heavy flow. "Lack of energy," although non-specific, is the most prevalent experience of perimenopausal women. It occurs for 38-43% of women and is equally likely throughout all phases of perimenopause (Dennerstein *et al.*, 2000). After assessing and treating for anemia or hypothyroidism, I would treat her sleep disturbance and night sweats with cyclic OMP. She also needs ibuprofen 200 mg every 4-6 hours on every heavy flow day. In my experience, once Emily understands the hormonal changes she is experiencing and has an idea of what's ahead for her, effective treatment of night sweats and sleep disturbances will allow her to regain her ability to cope. But, given the unpredictability of perimenopause, she needs a skilled and empathetic physician to work with her through this protracted and sometimes difficult "estrogen's storm season" of perimenopause (Prior, 2005b).

### References


National Institutes of Health State-of-the-Science Conference statement: management of menopause-related symptoms. Ann Intern Med. 2005;142:1003-13.

Barr SI, Janelle KC, Prior JC. Energy intakes are higher during the luteal phase of ovulatory menstrual cycles. Am J Clin Nutr. 1995;61:39-43.

Baumgartner AK, Hausler A, Seifert-Klauss V *et al.* Breast cancer after hormone replacement therapy – does the prognosis differ in perimenopausal and postmenopausal women? Breast J. 2011; in press.

Baxter S, Prior JC. The Estrogen Errors: Why Progesterone is Better For Women's Health. Westport: Praeger Publishers, 2009.

Burger HG. The controversial endocrinology of the menopausal transition - Author's Response. J Clin Endocrinol Metab. 1996;81:3128-9.

Burger HG, Dudley EC, Hopper JL *et al.* The endocrinology of the menopausal transition: a cross-sectional study of a population-based sample. J Clin Endocrinol Metab. 1995;80:3537-45.

Casper RF, Dodin S, Reid RL. The effect of 20 ug ethinyl estradiol/1 mg norethindrone acetate (Minestrin™), a low-dose oral contraceptive, on vaginal bleeding patterns, hot flashes, and quality of life in symptomatic perimenopausal women. Menopause. 1997;4:139-47.

Chang KJ, Lee TTY, Linares-Cruz G *et al.* Influence of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. Fertil Steril. 1995;63:785-91.

Check JH, Giangreco J. Three successful pregnancies following natural conception over an 8-year time span despite serum follicle stimulating hormone level greater than 15 mIU/ml. Clin Exp Obstet Gynecol. 2009;36:12-4.

Dennerstein L, Dudley EC, Hopper JL *et al.* A prospective population-based study of menopausal symptoms. Obstet Gynecol. 2000;96:351-8.

Dennerstein L, Spencer-Gardner C, Gotts G *et al.* Progesterone and the premenstrual syndrome: a double blind crossover trial. Br Med J. 1985;290:1617-21.

Douglas S. Premenstrual syndrome. Evidence-based treatment in family practice. Can Fam Physician. 2002;48:1789-97.

Foidart J, Collin C, Denoo X *et al.* Estradiol and progesterone regulate the proliferation of human breast epithelial cells. Fertil Steril. 1998;5:963-9.

Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. 2008;107:103-11.
Friess E, Tagaya H, Trachsel L *et al.* Progesterone-induced changes in sleep in male subjects. Am J Physiol. 1997;272: E885-E891.
Gibson CL, Coomber B, Rathbone J. Is progesterone a candidate neuroprotective factor for treatment following ischemic stroke? Neuroscientist. 2009;15:324-32.
Graham JD, Clarke CL. Physiological action of progesterone in target tissue. Endocr Rev. 1997; 18:502-19.
Hale GE, Hitchcock CL, Williams LA *et al.* Cyclicity of breast tenderness and night-time vasomotor symptoms in mid-life women: information collected using the Daily Peri-menopause Diary. Climacteric. 2003;6:128-39.
Hale GE, Hughes CL, Burger HG *et al.* Atypical estradiol secretion and ovulation patterns caused by luteal out-of-phase (LOOP) events underlying irregular ovulatory menstrual cycles in the menopausal transition. Menopause. 2009;16:50-9.
Hale GE, Zhao X, Hughes CL *et al.* Endocrine features of menstrual cycles in middle and late reproductive age and the menopausal transition classified according to the Staging of Reproductive Aging Workshop (STRAW) staging system. J Clin Endocrinol Metab. 2007;92:3060-7.
Harlow SD, Cain K, Crawford S *et al.* Evaluation of four proposed bleeding criteria for the onset of late menopausal transition. J Clin Endocrinol Metab. 2006;91:3432-8.
Harlow SD, Mitchell ES, Crawford S *et al.* The ReSTAGE Collaboration: defining optimal bleeding criteria for onset of early menopausal transition. Fertil Steril. 2008;89:129-40.
Harvey A, Hitchcock CL and Prior JC. Ovulation disturbances and mood across the menstrual cycles of healthy women. J Psychosom Obstet Gynaecol. 2009;30:207-14.
Hopman WM, Leroux C, Berger C *et al.* Changes in body mass index in Canadians over a five-year period: results of a prospective, population-based study. BMC. Public Health. 2007;7:150.
Irvine GA, Campbell-Brown MB, Lumsden MA *et al.* Randomised comparative trial of the levonorgestrel intra-uterine system and norethisterone for treatment of idiopathic menorrhagia. Br J Obstet Gynaecol. 1998;105:592-8.
Johannes CB, Crawford SL, Posner JG *et al.* Longitudinal patterns and correlates of hormone replacement therapy use in middle-aged women. Am J Epidemiol. 1994;140:439-52.
Klein NA, Illingworth PJ, Groome NP *et al.* Decreased inhibin B secretion is associated with the monotropic FSH rise in older, ovulatory women: A study of serum and follicular fluid levels of dimeric inhibin A and B in spontaneous menstrual cycles. J Clin Endocrinol Metab. 1996;81:7: 2742-5.
Landgren BH, Unden AL, Diczfalusy E. Hormonal profile of the cycle in 68 normally menstruating women. Acta Endocr Copenhagen. 1980;94:89-98.
Lethaby A, Augood C, Duckitt K. Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding. Cochrane Database Syst Rev. 2002;CD000400.
MacLennan AH, Broadbent JL, Lester S *et al.* Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst Rev. 2004; CD002978.
Mather KJ, Norman EG, Prior JC *et al.* Preserved forearm endothelial responses with acute exposure to progesterone: a randomized cross-over trial of 17-b estradiol, progesterone, and 17-b estradiol with progesterone in healthy menopausal women. J Clin Endocrinol Metab. 2000;85: 4644-9.
Metcalf MG, MacKenzie JA. Menstrual cycle and exposure to estrogens unopposed by progesterone: relevance to studies on breast cancer incidence. J Endocrinol. 1985;104:137-41.
Moen MH, Kahn H, Bjerve KS *et al.* Menometrorrhagia in the perimenopause is associated with increased serum estradiol. Maturitas. 2004;47:151-5.
Mogul HR, Peterson SJ, Weinstein BI *et al.* Metformin and carbohydrapte-modified diet: a novel obestiy treatment protocol: Preliminary findings from a case series of nondiabetic women with midlife weight gain and hyperinsulinemia. Heart Disease. 2001;13:285-92.
Morse CA, Dudley E, Guthrie J *et al.* Relationships between premenstrual complaints and perimenopausal experiences. J Psychosom Obstet Gynaecol. 1989;19:182-91.
Munster K, Schmidt L, Helm P. Length and variation in the menstrual cycle – a cross-sectional study from a Danish county. Br J Obstet Gynaecol. 1992;99:422-9.
Nielsen HK, Brixen K, Bouillon R *et al.* Changes in biochemical markers of osteoblastic activity during the menstrual cycle. J Clin Endocrinol Metab. 1990;70:1431-7.
O'Connor KA, Ferrell RJ, Brindle E *et al.* Total and Unopposed Estrogen Exposure across Stages of the Transition to Menopause. Cancer Epidemiol Biomarkers Prev. 2009; 18:828-36.
O'Leary Cobb J. Understanding Menopause. Toronto: Key Porter Books, 2005.
Oudshoorn N. Beyond the Natural Body: an archeology of sex hormones. London: Routledge, 1994.
Prior JC. Progesterone as a bone-trophic hormone. Endocr Rev. 1990;11:386-98.
Prior JC. Perimenopause: The complex endocrinology of the menopausal transition. Endocr Rev. 1998;19:397-428.
Prior JC. Premenstrual symptoms and signs. In: Rabel RE, Bope ET, editors. Conn's Current Therapy 2002. New York: W.B. Saunders Company, 2002a:1078-80.
Prior JC. The ageing female reproductive axis II: ovulatory changes with perimenopause. In: Chadwick DJ, Goode JA, editors. Endocrine Facets of Ageing. Chichester, UK: John Wiley and Sons Ltd, 2002b:172-86.
Prior JC. Clearing confusion about perimenopause. BC Med J. 2005a;47:534-8.
Prior JC. Estrogen's Storm Season- Stories of Perimenopause. Vancouver, BC: CeMCOR, 2005b.
Prior JC, Alojado N, Vigna YM *et al.* Estrogen and progestin are equally effective in symptom control post-ovariectomy – a one-year, double-blind, randomized trial in premenopausal women. Program of the 76th Annual Meeting of the Endocrine Society, Anaheim, Ca. Abstract 12H, 411. 1994.
Prior JC, Barr SI, Vigna YM. The controversial endocrinology of the menopausal transition (letter). J Clin Endocrinol Metab. 1996;81:3127-8.
Prior JC, Hitchcock CL. Progesterone for vasomotor symptoms: A 12-week randomized, masked placebo-controlled trial in healthy, normal-weight women 1-10 years since final menstrual flow. Endocr Rev. 2010;31:S51.
Prior JC, Vigna YM, Watson D. Spironolactone with physiological female gonadal steroids in the presurgical therapy of male to female transexuals: a new observation. Arch Sex Beh. 1989; 18:49-57.
Richardson SJ, Senikas V, Nelson JF. Follicular depletion during the menopausal transition: evidence for accelerated loss and ultimate exhaustion. J Clin Endocrinol Metab. 1987;65:1231.
Santoro N, Crawford SL, Lasley WL *et al.* Factors related to declining luteal function in women during the menopausal transition. J Clin Endocrinol Metab. 2008;93:1711-21.
Santoro N, Rosenberg J, Adel T *et al.* Characterization of reproductive hormonal dynamics in the perimenopause. J Clin Endocrinol Metab. 1996;81:1495-1501.
Schussler P, Kluge M, Yassouridis A *et al.* Progesterone reduces wakefulness in sleep EEG and has no effect on cognition in healthy postmenopausal women. Psychoneuroendocr. 2008; 33:1124-31.
Seifert-Klauss V, Prior JC. Progesterone and bone: Actions promoting bone health in women. J Osteop. 2010; 845180.
Shostak M Nisa: the life and words of a !Kung woman. New York: Vintage Books, 1981.
Simon JA, Shangold MM, Andrews MC *et al.* Micronized progesterone therapy: the importance of route of administration

and pharmacokinetics on clinical outcome. J Contracept Fertil Sex. 1992;20:13-8.
Soules MR, Sherman S, Parrott E *et al.* Executive summary: stages of reproductive aging workshop (STRAW). Fertil Steril. 2001;76:874-8.
Thys-Jacobs S, Alvir MJ. Calcium-regulating hormones across the menstrual cycle: evidence of a secondary hyerparathyroidism in women with PMS. J Clin Endocrinol Metab. 1995;80:2227-32.
Vollman RF. The menstrual cycle. In: Friedman EA, editor. Major Problems in Obstetrics and Gynecology, Vol 7. Toronto: W.B. Saunders Company, 1977:11-193.
Weiss G, Skurnick JH, Goldsmith LT *et al.* Menopause and hypothalamic-pituitary sensitivity to estrogen. JAMA. 2004;292:2991-6.