Learning Objectives:

1. Perimenopause, although characterized as a time of dropping estradiol, involves chaotic estrogen levels that average >20% higher and intermittently are extremely high and ovulatory disturbances with decreasing progesterone levels.
2. Perimenopause begins and is most symptomatic when cycles remain regular.
3. Perimenopause is highly symptomatic for more than 20% of women—symptoms typically include heavy menstrual flow, night sweats, infertility, breast tenderness and sleep disturbances.
4. Progesterone, because it normally counterbalances estradiol’s actions, is effective treatment for heavy flow, probably for night sweats, infertility and breast tenderness and definitely decreases anxiety and improves sleep.

Perspective and evidence

There are few systematic or randomized controlled trial (RCT) data on therapies for symptomatic perimenopause (as differentiated from treatments for menopausal women—those one year or more beyond their final menstruation). Therefore I will rely for treatment suggestions on first principles about perimenopausal biology and endocrinology (1), my 40-year experience in patient care, my extensive research experience and my 20-year effort to help BC’s most symptomatic perimenopausal women.

Perimenopause endocrinology and diagnosis

Ample evidence from multiple studies now shows that, despite fewer remaining ovarian follicles, estradiol (E\textsubscript{2}) levels increase (2) and become highly erratic (3) while ovulation becomes inconsistent in perimenopause (4) and progesterone levels decrease within ovulatory cycles (5). This appears to occur because of disturbed aging-related ovarian-pituitary-hypothalamic feedback relationships (1;6). From a meta-analysis, phase-specific menstruating perimenopausal E\textsubscript{2} levels are 20-30% higher than in premenopausal women (1).

There are several implications of this new knowledge about perimenopausal endocrinology—we stop using the term “menopausal symptoms” which conflates perimenopause and menopause; we avoid E\textsubscript{2} treatment until one year past flow; we consider P\textsubscript{4} to be potentially effective therapy.

Making the diagnosis of perimenopause is currently problematic despite consensus guidelines (7) because symptomatic women are often regularly menstruating and have normal FSH levels (2). Like in rheumatology, making a diagnosis with a constellation of
typical experience changes allows perimenopause to be diagnosed in regularly menstruating midlife women whose hormones and experiences have already changed (8):

**Diagnosis of the start of perimenopause in women with regular cycles**—any 3 of the following:

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

Therefore, I understand perimenopause as a life phase distinct from (post)menopause, and one that lasts over a decade for a portion of women, beginning with increases in E$_2$ and decreases in P$_4$ levels in regularly menstruating women (4).

Current definitions of perimenopause are in flux—from the Stages of Reproductive Aging Workshop (STRAW) schema (7), to Phases of Perimenopause (1;4), to the current Re-Stage Collaboration refinements of the STRAW criteria (9;10). As shown in Figure 1, perimenopause begins in women with regular flow and extends for one year after the last menstrual flow when menopause (or postmenopause) is diagnosed. The onset of the Early Menopause Transition (Early MT) is with cycles that vary by plus or minus six days (9) and of the Late MT by 60 days without menstruation (or one skipped period). Given the lack of predictive accuracy of increased FSH levels for menopause (11), they should not be used, although in the future Anti-Mullerian Hormone levels may be proven predictive.
Symptomatic Perimenopause

Women differ quite dramatically in whether or not they are troubled by the changes they experience in perimenopause. It is currently unknown why some women are miserable and other women sail through. It is likely that socioeconomic status, past life experiences and polymorphisms related to steroid metabolism and excretion all play roles. For example, that Asian women experience fewer hot flushes may not be because of eating more soy, or being in a culture that values older women, but rather because Asian women metabolize cortisol and other steroids more rapidly than Caucasians (12) and thus may not be exposed to as high $E_2$ levels.

The estimate that 20% of perimenopausal women are highly symptomatic, is just an educated guess (13). This kind of information is still needed—it is best obtained from population-based samples (such as the Melbourne Midlife Women’s Health Study, MMWHS) that can also be linked with health care administrative databases. It may be that the proportion of cycles in which women experience Luteal Out of Phase Events (LOOP) (as illustrated in Figure 2) determines whether or not they are symptomatic. Hale estimates that a third of cycles, throughout the menopausal transition, have LOOP characteristics (11).

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**Figure 1**—New proposed Timelines and Definitions of Women’s Reproductive Midlife Transition (in press, J. C. Prior & C. L. Hitchcock, Jan. 2011, Frontiers in Bioscience)

**Figure 2**—Example a Luteal Out of Phase event cycle. The midcycle $E_2$ peak is followed by a second or even third peak that is yet higher. The last $E_2$ peak and
another rise in progesterone occurs after flow starts in the following cycle (shaded) (3).

Menstrual flooding or heavy or long flow
Because perimenopause and menopause were all called ‘menopause’ in the past, and menopause was understood to mean low estrogen levels, most of the available studies (especially those using the Kupperman or Green Indices for monitoring) did not consider heavy flow to be related to perimenopause. Therefore we have little data on its within-perimenopause time course. Kaufert, an anthropologist and therefore more open to recording women’s experiences, found that “flooding menstruation” was most prevalent around the time when periods first became irregular (Early MT) (14). The Study of Women Across the Nation (SWAN), the NIH-funded USA study, documented that longer episodes of bleeding were associated with anovulation (failure to release an egg and thus in cycles without progesterone). SWAN hormone data also noted that anovulation was more prevalent in cycles shorter than 21 days or longer than 36 days. However, heavy flow was most common in ovulatory cycles and was related to obesity (15).

Breast tenderness (also called mastalgia) The best prospective data on the within-woman breast sensitivity changes of perimenopause over time are from the MMWHS, although breast tenderness (like heavy flow) was not initially in the questionnaires. These data showed that breast tenderness decreased over time and certainly had become less by the time menstrual periods were being skipped (Late MT) (16). RCT data on E2 or P4 or both together topically applied to one breast that was scheduled for an open biopsy of a benign mass showed that E2 increased proliferation and P4 decreased it, whether progesterone was given alone or with estrogen (17;18). Given that proliferation is likely related to breast tenderness (also accounting for the breast tenderness teenagers and pregnant women may experience) and the histological results of those two previously mentioned RCTs, it is likely that perimenopausal higher E2 and lower P4 levels promote breast cell proliferation and tenderness. These hormonal perimenopausal changes likely also promote the breast enlargement and increased nodularity some women report, as well as potentially the documented increased diagnosis of breast cancer that occurs in midlife women.

Dysmenorrhea or Menstrual Cramps The life course of menstrual cramps is an increase during adolescence, improvement after childbirth or miscarriage or abortion, and worsening into the late 30s and the 40s. Women appear most likely to experience increased cramps early in perimenopause. Although the cause for perimenopausal cramps is not clear, they may increase, based on monkey studies, because the higher
E_2 and lower progesterone (P_4) levels cause greater production of prostaglandins in the uterine muscle and endometrium.

Mid-sleep Wakening and Sleep Disturbances  Sleep trouble begins early in perimenopause although it has not been clearly tracked in prospective studies. Typically women describe the experience of jolting awake after a few hours of deep sleep. Although trouble falling asleep may be associated with some increased anxiety in perimenopause, and early morning wakening with depression, the mid-sleep wakening is most typical. Sleep disturbances, based on the MMWHS data, tend to increase in later perimenopause and often extend into menopause (16). Although these may be related to night sweats, many women with insomnia have no day of nighttime vasomotor symptoms.

Hot Flashes and Night Sweats (Vasomotor symptoms, VMS)  Note that, although VMS are reported to have a prevalence of about 11% in “premenopausal” women, it is likely that these are women with regular cycles whom I would designate as being in early perimenopause (19)(Figure 1). The peculiar thing about the onset of VMS is that they usually start as night sweats that commonly occur around or just preceding menstrual flow (19). They typically then progress to occur during both day and night before becoming most intense in the Late MT and the last year of perimenopause.

According to the MMWHS, night sweats/hot flushes increased the closer to menopause a woman became (16). Interestingly, an earlier report of increased premenstrual symptoms predicted those women who were most likely to experience subsequent night sweats (20). Also, in our study of women with regular cycles and night sweats, typically they also had marked increases in premenstrual breast tenderness (19) (possibly due to LOOP events). VMS are increased by economic, social and other stressors as well as by cigarette smoking and obesity (21). VMS are decreased by various strategies that decrease the stress response (such as the regular practice of paced yoga-type breathing, mindfulness meditation, the relaxation response or meditation), by stopping smoking, and decreasing weight (if appropriate, respectively) and by regular exercise. CeMCOR is currently performing an observational prospective pilot study on cyclic night sweats in early perimenopause to determine their patterns, hormonal associations and whether or not they relate to other experiences. CeMCOR also just received Canadian Institutes for Health Research funding to do a randomized double-blind trial of oral micronized progesterone (OMP, Prometrium) for perimenopausal VMS.

New or increased migraine headaches  These typically start in very early perimenopause and can occur either at midcycle or, more typically, right around flow. Women who experienced pubertal migraines are most likely to have them recur in Perimenopause although women without previous migraines may also begin to experience them. In women without classical migraines, likely because of the stress hormone amplifying effects of high E_2 levels (22), ordinary tension or “stress-type” headaches are also more prevalent in perimenopause.

Increased premenstrual symptoms  Classically premenstrual symptoms are understood to include breast tenderness, bloating, inappropriate (usually increased) appetite and dysphoric mood symptoms that occur during the week prior to flow. These probably
increase very early in perimenopause—the typical population in the local “PMS Clinic”
averages age 35-45. Although depression and anxiety have not been shown to be caused by perimenopause, some women will notice that these feelings have increased. Previous depression and increased current stress make premenstrual symptoms worse while regular exercise tends to decrease the risk for perimenopausal depression (23).

Weight gain without exercise or food changes Perimenopause is a time when women normally gain weight based on population-based Canadian Multicentre Osteoporosis Study (CaMOS) data. During the 45-54 year decade, the gender difference in BMI change is huge—men gain 0.5 BMI while women gain 1.4 BMI units (24). Weight gain, however, appears related to protection against excess bone loss based on the major bone loss that occurred in those randomized to a weight loss versus maintenance programme in perimenopause (25).

Although weight gain is common, there is less good evidence that perimenopause is a time during which insulin resistance increases, as most clearly documented by a gain in waist circumference in Caucasians to over 88 cm. However, clinical data suggest that the decade of the 40s is when the diagnosis of the Metabolic Syndrome (obesity, insulin resistance or diabetes, abnormal lipids and high blood pressure) is first made.

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With this background on the symptoms and experience changes of Perimenopause, we will now discuss how progesterone treatment may assist with each. If a progestin or progestogen therapy is mentioned instead of OMP, the agent will be specifically named and the appropriate dose provided.

**Progestosterone Therapy for Symptomatic Perimenopause**

In general, in Early Perimenopause and until after the first skipped period (Early MT), progesterone is used as a cyclic therapy to supplement or “replace” the luteal phase (See Figure 3). The exception to this rule is the women with heavy flow (for whom cyclic therapy is likely to be insufficient) or for those with migraine headaches (who may experience a rebound increase in headaches with OMP withdrawal). For women with heavy flow or a history of migraine headaches, daily progesterone therapy is recommended.

Also, in general, oral micronized progesterone (OMP, Prometrium® or compounded progesterone in olive oil) is used in a dose of 300 mg at bedtime. This dose keeps the P₄ level above the lower limit of the luteal phase range for 24 hours (26), since it should only be taken right before sleep because of its causes drowsiness (27). Finally, until RCT data are available, use of OMP should be undertaken in an “experiment of one” manner in which at least one cycle of baseline data are obtained using the Daily Perimenopause Diary® (19)(free under “tools” on www.cemcor.ubc.ca) and the record is kept during a several-month trial of therapy before the pre- and treatment phases are compared.

**Figure 3 shows the typical way in which cyclic progesterone therapy is given.**
For a full patient handout see “Cyclic Progesterone Therapy”
www.cemcor.ubc.ca
As described earlier, each of the common experience changes of Perimenopause is described and what is known about progesterone and other therapies are provided.

**Menstrual flooding or heavy or long flow**
Non-steroidal anti-inflammatory drugs (NSAIDs), that block prostaglandin production in the endometrium, are effective in decreasing flow by 25-50% based on RCT data (RCT) (28). Normal doses of 200 mg ibuprofen every 4-8 hours are effective. NSAID therapy should always be used for heavy menstrual flow (in a woman of any age) and be the first line of treatment. Other important measures are to ensure adequate fluid volume if a woman with heavy flow is feeling faint or has a rapid increase in heart rate with sitting or standing, and assessing for and treating the potential blood-loss (iron deficiency) anemia.

Oral contraceptives (OC) that contain the low dose of 20µ Ethinyl Estradiol have been tested in one RCT for menorrhagia in Perimenopause (29). The results showed that during the first three cycles, OC treatment caused midcycle spotting (metrorrhagia) but no improvement in heavy flow; however, heavy flow improved during cycles four through 6 of this RCT (29).

In anovulatory cycles, *cyclic* oral micronized progesterone may be effective for heavy flow, but *long-cycle* (days 6-27) or *daily* OMP therapy is commonly needed for heavy flow in ovulatory cycles (30). My experience is that daily therapy with 300 mg OMP, plus NSAID, is usually needed for at least three months before flow is sufficiently controlled that the therapy can change to a cyclic OMP schedule (Figure 3). However, a few women with benign problems (a polyp, or adenomyosis) may require quite high doses of progesterone/progestin (medroxyprogesterone 20 mg twice a day). If a woman would prefer not to use the levonorgestrel impregnated IUD (Mirena), I recommend OMP 100-300 mg/vagina (or MPA 10-20 mg in the morning) plus 300-600 mg of OMP at bedtime daily for six months or longer. In my experience, heavy flow is eventually adequately controlled.

It is usually wise to do an endometrial biopsy after a 3-month trial of full dose OMP and NSAID treatment has not adequately controlled bleeding. Also, any woman with heavy flow who plans on a holiday, and especially if she plans on being out of the country, should carry with her the needed NSAID and OMP to cover her for the duration of her trip.
Breast tenderness
The first strategies to deal with breast tenderness are to decrease caffeine, begin an exercise programme and gradually (a pound a week at most) lose weight (for those who are users of caffeine or overweight). However, often in perimenopause these strategies are insufficient. Because breast tenderness tends to be cyclic and worse before flow (19), cyclic oral micronized progesterone may be effective (although unproven) therapy. In France where progesterone and progestins are commonly used for breast tenderness in perimenopause, there was no increased risk for breast cancer with their perimenopausal use, but breast cancer risk did significantly increase the longer progesterone/progestins were taken (31). This observational E3N study, however, did not differentiate between OMP and progestins. OMP, in contrast to all progestins, was not associated with postmenopausal increased breast cancer when given with exogenous estrogen (32).

Dysmenorrhea or Menstrual Cramps
If NSAID therapy taken in high doses before cramps become intense (see “Painful Periods www.cemcor.ubc.ca) is not sufficient for effective treatment, daily or cyclic OMP therapy often allows relief. Progesterone helps cramps by a mechanism that may be related to decreased endometrial or myometrial prostaglandin production. In women with severe cramps related to endometriosis, daily high dose vaginal and/or oral P₄ is often effective in my experience. It is certainly worth a try—first principles suggest that the hot flush and bone loss side effects of hypothalamic suppression with GnRH agonist/antagonist therapy will not occur with OMP therapy.

Mid-sleep Wakening and Sleep Disturbances
Oral micronized progesterone has been shown to be effective for sleep in RCTs in men and in menopausal women when given in a dose of 300 mg at bedtime (27). No matter what the hormonal or psychosocial factors are in sleep disturbance, OMP 300 mg usually assists. OMP (but not transdermal P₄) increases sleep consistency and early night rapid eye movement sleep through conversion to its metabolites that interact with the GABA system in the brain (33). It has the clinical advantage that overdose mortality is not possible because, unlike all other sleeping medications or pain/sedative medications, OMP increases rather than suppresses respiration. Furthermore, careful crossover RCT psychometric testing in the morning during the run-in and after 21 days on each of active and placebo therapies showed no within-woman differences from placebo (27). However, a clinician should warn a sleep-deprived woman to plan on sleeping in after the first few nights of OMP therapy—there is natural catch-up sleep that may otherwise be misunderstood as a daytime drowsiness side effect of OMP. Likewise, OMP should always be taken just before lying down to sleep because otherwise it will cause a strange dizzy feeling.

Hot Flashes and Night Sweats (Vasomotor symptoms, VMS)
Perimenopausal women have more prevalent and more severe VMS than do menopausal women (occurring for 79% of women with 9% being more frequent than 50/week of moderate-severe intensity) (34). Despite this fact, conventional wisdom says that “estrogen deficiency” causes hot flushes. The RCT of low dose birth control pills by Casper and colleagues did not show a significant improvement in VMS compared with placebo (29), despite the facts that OC are commonly prescribed for that purpose in Perimenopause. Also, estrogen is the gold standard therapy for VMS in menopausal women (35).
RCT evidence that OMP is effective for perimenopausal VMS is currently lacking. However, CeMCOR just completed an RCT in 127 women showing that daily OMP (300 mg at bedtime) is highly effective for VMS in treatment-seeking healthy early menopausal women (36). Also, CeMCOR has just obtained a Canadian Institutes of Health Research grant to perform an RCT of OMP for hot flushes in perimenopause. Despite lack of RCT data, there are extensive clinical data suggesting that cyclic OMP 300 mg at bedtime is effective for the cyclic night sweats in very early perimenopause and daily OMP is effective when cycles become irregular. During Early MT, VMS may consistently occur for weeks at a time (although they may also be absent again for weeks on end). However, there are abundant clinical data suggesting that OMP is effective in perimenopause—some of it is illustrated by stories in Estrogen's Storm Season (13).

**New or increased migraine headaches**
Progestosterone therapy for migraine headaches in perimenopause is, yet again, a topic on which there are no RCT data. However, daily OMP appears to be an effective strategy for some women with migraines, especially when it is added to their usual acute treatments. OMP may act similarly to beta blockers or tricyclic antidepressants to decrease the frequency and severity of migraine attacks, perhaps through its sleep enhancing or anti-inflammatory, anti-oxidant and other positive brain effects (37).

**Increased premenstrual symptoms**
The primary approach to premenstrual fluid, breast tenderness, appetite and mood symptoms occurring and increasing before flow is to provide social and emotional support, and reassurance that perimenopause ends and she will enter a less symptomatic menopausal world. In addition, women's own record-keeping with the Daily Perimenopause Diary© may itself be therapeutic in providing insight and the ability to predict difficult times. In addition, gradually increasing exercise intensity and distance will likely help with symptoms (as they do in premenopausal women (38)) but they may not because the feedback disturbances of perimenopause prevent suppression of hypothalamic gonadal stimulation (1).

There is one early, well performed crossover trial showing that cyclic OMP (300 mg at bedtime) is effective for premenstrual symptoms (39). It should be used for women with regular cycles and in the cyclic OMP schedule in Figure 3. In addition, women need to be provided with lifestyle advice and emotional support.

**Weight gain without exercise or food changes**
Although there are no direct data that OMP therapy (either cyclically or daily) will improve the weight gain and insulin resistance of perimenopause, several lines of evidence suggest that it may. In a prospective observational study in which women collected 3-day diet diaries in the early follicular phase and premenstrually, all of the weight-stable young women who ovulated in the cycle ate about 300 calories more than in the follicular phase—those women who were anovulatory in that cycle showed no caloric intake difference from the follicular phase (40). This is because about 300 calories a day are required to raise the core temperature the mean of 0.2 degrees as progesterone and medroxyprogesterone do. Also, in a 1-year comparative RCT of medroxyprogesterone (MPA, 10 mg/d) with conjugated equine estrogen (CEE, 0.6
mg/d), those just-surgical menopausal women on MPA gained significantly less weight and BMI, and tended to gain less truncal fat than did women on CEE (41). Therefore, OMP therapy may be rationally used along with a diet rich in whole grains, vegetables and fruit and an exercise programme as a strategy to assist the perimenopausal woman in preventing excess weight gain and development of metabolic syndrome. Those whose waist circumference has become over 88 cm, especially if they have a family history of diabetes mellitus, I would also treat with metformin (500 mg with the two meals a day when they are most hungry).

Infertility related to ovulatory disturbances
Yet again there are clinical data but trial evidence that cyclic OMP will be helpful for treatment of ovulatory disturbance-related infertility. Since short luteal phase cycles become common (4) and luteal insufficiency is progressive (5) in perimenopause, for those women who have kept the Daily Perimenopause Diary© and documented ovulation by the validated quantitative basal temperature method (42;43) may be assisted to fertility by cyclic OMP therapy. There is a chapter in Estrogen’s Storm Season(13) describing its use for someone with high cycle day-3 FSH and estradiol levels who had repeated short luteal phase cycles. The important difference from the diagram in Figure 3 when OMP is used for fertility is that it should only be started when the stretchy cervical mucus has begun to wane (indicating that it is well past the midcycle estradiol peak) or after a urine LH test has become positive, in order to avoid potentially suppressing the LH peak. The other difference is that it should be continued until flow starts (which would usually indicate that she has not become pregnant). If other testing indicates that a pregnancy occurred but underwent early miscarriage, then in subsequent cycles, OMP could be continued in a dose of 300 mg at bedtime plus 200-300 mg vaginally at bedtime until the 12th week should she become pregnant. Based on clinical evidence that spontaneous fertility is possible in women in their 40s despite what are currently considered clear evidences of infertility (44), cyclic OMP is at least worth a try.

In Summary
The above information represents my personal effort to integrate biological, hormonal and clinical data intermixed with sparse RCT information all of which suggest that it is hormonally appropriate and clinically safe to use cyclic or daily oral micronized progesterone for treatment of symptomatic women in perimenopause. The evidence for OMP’s effectiveness is strongest for heavy flow, sleep disturbances and VMS—these tend to be the most troublesome problems for which perimenopausal women seek health care provider assistance.

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