

Clearing confusion about perimenopause

In an effort to improve health care for perimenopausal women, a study now under way looks at long-distance endocrine specialist consultation for symptomatic patients.

ABSTRACT: Of the 19% of women now between ages 45 and 60, 20% are experiencing perimenopausal symptoms and seeking medical help. Primary health care is under economic stress and specialists are often not available. Furthermore, confusion reigns about the major hormonal changes of perimenopause and the language used to describe them. Menopause, for example, can mean three different things—everything miserable from midlife onward, the final menstrual period, and a normal life phase beginning after 1 year without flow. The transition to menopause or perimenopause was formerly thought to involve dropping estrogen levels. Estrogen levels are now known to average 30% higher, to be chaotic, and to be associated with less progesterone. Perimenopause begins in women with regular periods and includes characteristic experiences such as heavy flow or flooding, mid-sleep disturbance, and cyclic hot

flushes. There is no consensus and little evidence-based data about treatment of symptomatic perimenopausal women. Oral contraceptives eventually improve flow but don't help with hot flushes or quality of life. In this context, a University of British Columbia research group has initiated a comprehensive long-distance endocrine specialist consultation program called the Perimenopause Experiences Project. The project aims to educate physicians about the physiology and management of symptomatic women in perimenopause and to improve medical care for perimenopausal women. A successful pilot has been completed and health care providers are now being recruited to a 1-year study that will compare consultation with usual care and the outcomes of both. The study will involve physicians' self-assessment of their clinical competence and women's self-assessment of how perimenopause interferes with their usual activity.

Currently, there is confusion about how to describe the state of midlife women who have menstruated in the last year, yet are flushing, can't sleep, and have flooding periods. Are they in menopause, perimenopause, or the menopausal transition? This is not an academic question because about 19% of all Canadian women are currently in the midst of this linguistic and conceptual midlife limbo because of the baby boom demographic. Furthermore, approximately 20% of these women will make repeated visits to primary health care providers with urgent but perplexing problems. It is not clear to these women why they are having hot flushes if vasomotor symptoms are caused by estrogen "deficiency." Don't their periods mean they have enough estrogen? Further, there is confusion about whether therapies that are suitable for women after menopause are also appropriate for menstruating midlife women.

Dr Prior is a professor of internal medicine and endocrinology at the University of British Columbia. She is affiliated with Vancouver General Hospital, the Vancouver Coastal Health Research Institute, and the Centre for Menstrual Cycle and Ovulation Research.

Confusion about perimenopause can be cleared by defining women's reproductive life phases (premenopause, perimenopause, and menopause), discussing current debates about the onset of the menopausal transition or perimenopause, and highlighting the new evidence and controversies over reproductive hormonal changes in midlife women. Understanding the ovarian hormonal changes of perimenopause leads to a physiology-based (if not yet evidence-based) approach to treatment of symptomatic midlife women.

Changing language and definitions

Does menopause mean everything that's miserable and changing in the life of women older than 40, the final menstrual period, or a life phase that starts a year after the final menstrual period? The WHO 1996 guidelines¹ and a 2001 Stages of Reproductive Aging Workshop (STRAW)² both call menopause the final menstrual period. The question is, how does a woman, or her physician, know when a particular flow *is* final? The answer comes from large prospective studies indicating that 12 months must pass for 90% of women to be confident they've had their final flow.³ For women older than 50 at the onset of amenorrhea, there's a 95% chance that the flow is final—the younger the woman who has been without a period for 12 months, the greater the likelihood of further flow. Therefore, increasingly menopause is being defined (in women over 40, without hysterectomy) as beginning after 1 year without flow. It's helpful to know that further flow is likely not caused by pathology if sore breasts, bloating, or premenstrual symptoms precede it.

For the purposes of this discussion, *menopause* is defined as 1 year without menstrual flow. The contrast-

ing life cycle phase to menopause is *premenopause*. A woman is premenopausal from her first period until she enters *perimenopause* or the *menopausal transition*. The changes that occur in perimenopause are best defined in contrast to premenopausal ovulatory menstrual cycle hormonal changes.

The time of change in midlife women has been called everything from "climacteric,"⁴ "change of life,"⁵ and "decline of life"⁶ to "perimenopause,"⁷ "menopausal transition,"⁸ and "menopause."⁹ STRAW prefers the term menopausal transition, which defines as beginning when cycles vary in length by ± 7 days in a woman with a cycle Day 3 follicle-stimulating hormone (FSH) level that is elevated.² The menopausal transition officially ends with the final menstrual flow. But problems arise with such a definition because (1) clinicians and women have a hard time documenting cycle variability with adequate specificity, (2) it is not clear what level of FSH should be considered "elevated," and (3) variability occurs in some premenopausal women. This last is confirmed by a recent retrospective analysis in 100 women who had prospectively collected cycle-length data and been without flow for 1 year. The data indicated a high degree of variability, with irregular or even regular cycles occurring after varying times without flow. Although the most common pattern was from regular to irregular to skipping cycles to amenorrhea, a high proportion of women didn't fulfill expectations.¹⁰

Perimenopause, in contrast to the menopausal transition, ends after a woman goes 1 year without flow¹² and begins when she is still having regular periods.¹¹ Often these periods are becoming shorter¹² or flow is heavy or flooding,¹³ and commonly the flow is preceded by breast tenderness and

Table. Experience changes characteristic of perimenopause onset in regularly cycling women.

Any three of the following can be used to define perimenopause onset:

- New heavy and/or longer menstrual flow
- Shorter menstrual cycle lengths (≤ 25 days)
- New sore, swollen, and/or lumpy breasts
- New or increased menstrual cramps
- New mid-sleep waking
- Onset of night sweats, especially around flow
- New or markedly increased migraine headaches
- New or increased premenstrual mood swings
- Notable weight gain without changes in exercise or food intake

night sweats,¹⁴ mood swings, and increased bloating.¹⁵

These and other symptoms such as intractable migraines, nausea, and mid-sleep waking in regularly cycling midlife women often don't make sense to us. If menopause means *low* estrogen levels and premenopause means *high* levels, then estrogen levels should be dropping in perimenopause. We were taught that hot flushes result from lower estrogen levels. However, we also know that shorter cycles, sore breasts, and heavier flow can result from *higher* estrogen levels.^{16,17} It's also confusing because menopause and perimenopause often share two common symptoms—hot flushes/night sweats and decreased sexual interest.

The paradox of perimenopause is that estrogen levels soar and become erratic before they eventually settle into the low, stable levels of menopause.^{2,7,11} Therefore, a practical definition of perimenopause onset must be based on characteristic changes in experience that likely result from

these hormonal changes and occur in women with regular flow. What are these characteristic experience changes? They include shorter cycles, the onset of cyclic night sweats, new mid-sleep wakening, and several other experiences listed in the **Table**. Women with any three of these experience changes can be diagnosed as perimenopausal.

Confusing endocrine changes of perimenopause

There are at least three hormonal changes in perimenopause. The first and most important is higher estrogen levels.^{7,11} The second major change is lower progesterone levels⁷ and luteal phase lengths that are shorter with more common anovulation.¹⁸ The final change involves disruption of the hypothalamic-pituitary-ovarian feedback system. There is less reliable suppression of FSH by higher estradiol levels and less likelihood that a luteinizing hormone (LH) mid-cycle peak will follow high estrogen levels. The practical results of these changes are higher estradiol and lower progesterone levels, but also exogenous estrogen that doesn't reliably suppress endogenous estrogen levels.

The idea that estrogen levels are dropping or low in perimenopause was so common in the past that from the 1950s to the 1990s many studies didn't comment on the high estrogens they found in some perimenopausal women.⁸ The same was true in seven studies comparing hormone levels early in the cycle and premenstrually in premenopausal versus perimenopausal women.¹¹ A meta-analysis of these comparative studies, which included 292 control premenopausal women and 415 perimenopausal women, showed that follicular phase estradiol levels were 175 ± 57 pmol/L compared with 225 ± 98 pmol/L in perimenopausal women. Perimenopausal

estradiol levels were about 30% higher ($F = 16.12$, $P = 0.041$).¹¹ Higher estradiol and lower progesterone levels help explain many of women's perimenopausal experiences.¹¹ For example, in a recent case-control study high estradiol levels and endometrial hyperplasia were associated with heavy flow.¹⁷

Hot flushes and night sweats in *menopausal* women are understood to mean estrogen "deficiency." However, women with Turner syndrome who have early menopause and have never been treated with estrogen don't have hot flushes. Also, menopausal women being treated with estradiol implants every 6 months had severe hot flushes, irritability, and sleep disturbances at a time when their estradiol levels were higher than mid-cycle estrogen peak levels.¹⁹ All of this evidence suggests that vasomotor symptoms arise because the hypothalamus has become used to higher estrogen levels—hot flushes develop just as readily when estrogen levels decrease from high to normal as from normal to low. Estrogen withdrawal from previously higher levels likely explains why night sweats and hot flushes occur in 37% of perimenopausal women.²⁰ Mood swings likely result because estradiol amplifies the stress hormone responses to life stresses.²¹ Other symptoms such as waking after a few hours of deep sleep as yet have no hormonal explanation.

A therapeutic approach to symptomatic perimenopause

Treatment of symptoms in perimenopause is problematic because few randomized controlled trials have been conducted or published. One randomized controlled trial of 20 µg ethinyl estradiol-containing oral contraceptive in perimenopausal women with heavy flow showed some benefit for

menorrhagia, but no significant improvement in hot flushes or quality of life.²² Likewise, a couple of poor-quality studies suggest oral contraceptives can prevent perimenopausal bone loss.^{23,24} Acting on the assumption that menopause and perimenopause involve similarly low estrogen levels, and that hot flushes are effectively treated with estrogens,²⁵ it is common practice to treat perimenopause with estrogens or oral contraceptives. This treatment comes from the recommendation to "consider extrapolating data from postmenopausal women" and from "clinical experience when considering management recommendations" for perimenopause.²⁶

The suggestion to treat perimenopausal symptoms like those of menopause, however, ignores the differing hormonal dynamics of the two, especially the higher estrogen levels and disturbed hypothalamic-pituitary-ovarian feedback in perimenopause.^{11,27} Treatment with estrogen could cause heavier flow, worsening mood swings, and more breast tenderness. Instead, simple measures are often quite effective. These include explaining about perimenopausal hormone changes and the characteristic experiences accompanying them, giving some idea of the perimenopause timeline,¹⁸ and providing patients with a self-report form such as the Daily Perimenopause Diary¹⁴ in which they can track their experiences. In addition, maintaining or increasing exercise, increasing calcium and vitamin D intake, paying more attention to healthy eating guidelines, and taking relaxation training can all be beneficial.

These simple and practical suggestions can allow the majority of perimenopausal women to cope. However, the 20% who are highly symptomatic will likely need additional therapy. At present, no perimenopause therapies have been adequately vali-

dated in randomized controlled trials. However, based on the endocrine changes of perimenopause, cyclic or daily oral micronized progesterone in doses of 300 to 400 mg at bedtime appears to help with heavy flow, hot flushes, breast tenderness, and sleep (J.C.P., unpublished data, 2001).

In an effort to understand the concerns of primary health care providers, to provide patient-specific education and consultation, and to determine whether suggested therapies such as progesterone are acceptable and effective, the Centre for Menstrual Cycle and Ovulation Research at the University of British Columbia began a unique long-distance consultation project.

Perimenopause Experiences Project

The Perimenopause Experiences Project (PEP) began as a pilot study in 2002 with 14 women and 9 health care providers from the Greater Victoria area. The purpose of the 1-year pilot study was to test the feasibility of long-distance, endocrine specialist consultation for symptomatic women in perimenopause. The two outcome variables were (1) change over the year in how much women felt perimenopausal symptoms were interfering with their daily activities, and (2) change over the year in the degree of competence physicians felt while managing highly symptomatic perimenopausal women. The pilot PEP study is currently wrapping up. Physicians have proven willing to refer their patients and have expressed appreciation for the consultation letters from specialists. The researchers have determined that the women's self-assessed mood symptoms are reproducible over time, while the physician's baseline self-assessed competence is not significantly reproducible ($r = 0.77$). The physicians' scores did positively cor-

relate with the number of symptomatic midlife women they reported seeing in a week but not with years in clinical practice. Final results for women show a significant lessening of perimenopausal mood interference with their daily activities. Although final results from physician interviews are not yet available, data collected so far shows that such a long-distance consultation is feasible, is valuable to women, and may assist family physicians.

The randomized controlled trial set to follow the pilot study will test whether active participation in PEP or usual care results in superior outcomes for health care providers and women. All women in both arms of the controlled trial will view "The Puzzle of Perimenopause," an educational video²⁸ that teaches them how to complete the Daily Perimenopause Diary.¹⁴ Data from the women's diary records for three cycles, family physician referral forms, and interviewer-administered questionnaires will then be used to write the consultation letter. A letter using the same information, but written in nontechnical language, will go to each participating woman. Communication from the specialist consultant and staff in Vancouver will go by coded computer files to the Victoria nurse-coordinator, who will print and deliver the letters to both women and their physicians. Physicians and women in the active participation arm will receive their consultation about 4 months into the study, while those in the usual care arm will not receive their consultation until the end of the year. Women from both arms will have regular support and counseling from the Victoria nurse-coordinator.

So far PEP researchers have recruited 12 family physicians and 13 women for the study. They anticipate needing a total of 30 physicians, who will each be expected to refer one to

FPs and perimenopausal women needed for study

Family doctors and primary care practitioners from the Greater Victoria region can now participate in a randomized controlled trial of specialist consultation for symptomatic perimenopausal women. If you are interested or need more information, contact Ms Marjorie Tighe, nurse practitioner, at pep@jbcpc.bc.ca or phone 250 388-7844 local 335, or 250 477-7284.

three perimenopausal women within 3 months of joining. The PEP researchers invite family physicians and nurse clinicians in the Greater Victoria region to participate. Anyone interested can send an e-mail message to pep@jbcpc.bc.ca or phone 250 388-7844 (extension 335) or 250 477-7284.

Summary

Language and definitions related to midlife women have changed. Most importantly, perimenopause is now understood to involve higher and more chaotic estrogen levels and to begin in regularly cycling women. Increasing numbers of symptomatic perimenopausal women are presenting with puzzling and intense symptoms for which there is no consensus on causes or therapy. This is happening as primary health care is under economic stress and specialist referral has become more difficult. The Perimenopause Experiences Project is performing a randomized controlled trial of long-distance specialist consultation for family physicians and their symptomatic perimenopausal patients. This study will help determine

what treatment strategies are helpful for highly symptomatic women and their health care providers.

Competing interests

None declared.

References

1. Research on the menopause in the 1990s: Report of a WHO Scientific Group. Geneva: World Health Organization; 1996. 107 pp.
2. Soules MR, Sherman S, Parrott E, et al. Executive summary: Stages of reproductive aging workshop (STRAW). *Fertil Steril* 2001;76:874-878.
3. Wallace RB, Sherman BM, Bean JA, et al. Probability of menopause with increasing duration of amenorrhea in middle-aged women. *Am J Obstet Gynecol* 1979;135:1021-1024.
4. Hagstad A, Janson PO. The epidemiology of climacteric symptoms. *Acta Obstet Gynecol Scand Suppl* 1986;134:59-65.
5. Greer G. *The Change: Women, Aging, and the Menopause*. London: Hamish Hamilton; 1991.
6. Tilt EJ. *The change of life in health and disease. A practical treatise on the nervous and other afflictions incidental to women at the decline of life*. 3rd ed. Philadelphia, PA: Lindsay and Blakiston, 1871.
7. Santoro N, Brown JR, Adel T, et al. Characterization of reproductive hormonal dynamics in the perimenopause. *J Clin Endocrinol Metab* 1996;81:4,1495-1501.
8. 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;80:3537-3545.
9. Kaufert PA. Menopause as a process or event: The creation of definitions in biomedicine. In: Lock M, Gordon D (eds). *Biomedicine Examined*. Dordrecht: Kluwer Academic Press; 1988:331-349.
10. Mansfield PK, Carey M, Anderson A, et al. Staging the menopausal transition: Data from the TREMIN Research Program on Women's Health. *Women's Health Issues* 2004;14:220-226.
11. Prior JC. Perimenopause: The complex endocrinology of the menopausal transition. *Endocr Rev* 1998;19:397-428.
12. Treloar AE, Boynton RE, Behn BG, et al. Variation of the human menstrual cycle through reproductive life. *Int J Fertil* 1967;12:77-126.
13. Kaufert PA, Gilbert P, Tate R. Defining menopausal status: The impact of longitudinal data. *Maturitas* 1987;9:217-226.
14. 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 Perimenopause Diary. *Climacteric* 2003;6:128-139.
15. Prior JC. Premenstrual symptoms and signs. In: Rakel RE, Bope ET (eds). *Conn's Current Therapy* 2002. New York: W.B. Saunders Company; 2002:1078-1080.
16. Landgren BM, Uden AL, Diczfalusy E. Hormonal profile of the cycle in 68 normally menstruating women. *Acta Endocrinol (Copenh)* 1980;94:89-98.
17. Moen MH, Kahn H, Bjerve KS, et al. Menometrorrhagia in the perimenopause is associated with increased serum estradiol. *Maturitas* 2004;47:151-155.
18. Prior JC. The ageing female reproductive axis II: Ovulatory changes with perimenopause. In: Chadwick DJ, Goode JA (eds). *Endocrine Facets of Ageing*. Chichester, UK: John Wiley and Sons; 2002:172-186.
19. Gangar KF, Cust MP, Whitehead MI. Symptoms of oestrogen deficiency associated with supraphysiological plasma oestradiol concentrations in women with oestradiol implants. *BMJ* 1989;299:601-602.
20. Guthrie JR, Dennerstein L, Hopper JL, et al. Hot flushes, menstrual status, and hormone levels in a population-based sample of midlife women. *Obstet Gynecol* 1996;88:437-442.
21. Kirschbaum C, Schommer N, Federenko I, et al. Short-term estradiol treatment enhances pituitary-adrenal axis and sympathetic responses to psychosocial stress in healthy young men. *J Clin Endocrinol Metab* 1996;81:3639-3643.
22. Casper RF, Dodin S, Reid RL, Study Investigators. The effect of 20 µg ethinyl estradiol/1 mg norethindrone acetate (Mines-trin), a low-dose oral contraceptive, on vaginal bleeding patterns, hot flashes, and quality of life in symptomatic perimenopausal women. *Menopause* 1997;4:139-147.
23. Shargil AA. Hormone replacement therapy in perimenopausal women with a triphasic contraceptive compound: A three-year prospective study. *Int J Fertil* 1985;30:15-28.
24. Gambacciani M, Spinetti A, Taponeco F, et al. Longitudinal evaluation of perimenopausal vertebral bone loss: Effects of a low-dose oral contraceptive preparation on bone mineral density and metabolism. *Obstet Gynecol* 1994;83:392-395.
25. MacLennan A, Lester S, Moore V. Oral estrogen replacement therapy versus placebo for hot flushes: A systematic review. *Climacteric* 2001;4:58-74.
26. Consensus Opinion. Clinical challenges of perimenopause: Consensus opinion of the North American Menopause Society. *Menopause* 2000;7:5-13.
27. Park SJ, Goldsmith LT, Weiss G. Age-related changes in the regulation of luteinizing hormone secretion by estrogen in women. *Exp Biol Med (Maywood)* 2002;227:455-464.
28. Prior JC. The puzzle of perimenopause—Using the Daily Perimenopause Diary [videocassette]. *JC Prior/UBC Media Services*, 1999. Distributed by BC Endocrine Research Services. 