Perimenopause — Definition and Treatment

See online here

The perimenopause is a transition period that all women must go through and it marks the final years of the woman's reproductive years. There are several definitions related to this period that we need to establish before we discuss the pathophysiology behind the different symptoms of perimenopause and the treatment options. The perimenopausal period starts from the first onset of menstrual irregularity and ends after 1 year of amenorrhea. This one year of amenorrhea is preceded by what is known as the final menstrual period; therefore, the final menstrual period is defined retrospectively after the woman develops amenorrhea for one year.

Introduction to Perimenopause

The perimenopausal period **can be subdivided into early transition and late transition menopause**. The early transition stage is characterized by a regular menstrual cycle with frequent interruptions. The late transition stage is characterized by longer periods of amenorrhea that lasts for 60 days or more. The late transition stage ends with the final menstrual period.

Endogenous Hormonal Changes During the

Perimenopause

Anovulatory cycles

During the late reproductive years and before the onset of the perimenopausal period, women tend to have regular menstrual cycles with slight and infrequent irregularities. **The follicle-stimulating hormone levels are normal, but the ovarian reserve is low;** therefore, anovulatory cycles become frequent during this stage.

Early transition stage

The first stage of perimenopause, also known as the early transition stage, is characterized by **regular cycles that are commonly interrupted by periods of amenorrhea that are less than 60 days**. The average menstrual cycle duration increases by around 7 days or more. During this stage, the follicle-stimulating hormone levels can be normal or high. The ovarian reserve is low but still detectable and anovulatory cycles are more frequent.

Late perimenopausal stage

The late perimenopausal stage is characterized by prolonged cycles with **periods of amenorrhea that are 60 days or longer**. Follicle-stimulating hormone levels are universally elevated in this stage. Ovarian reserve is very low, but few ovulatory cycles can still happen.
The menopause starts when the final menstrual period happens and is followed by one year of amenorrhea. The follicle-stimulating hormone levels are high and ovarian reserve is undetectable.

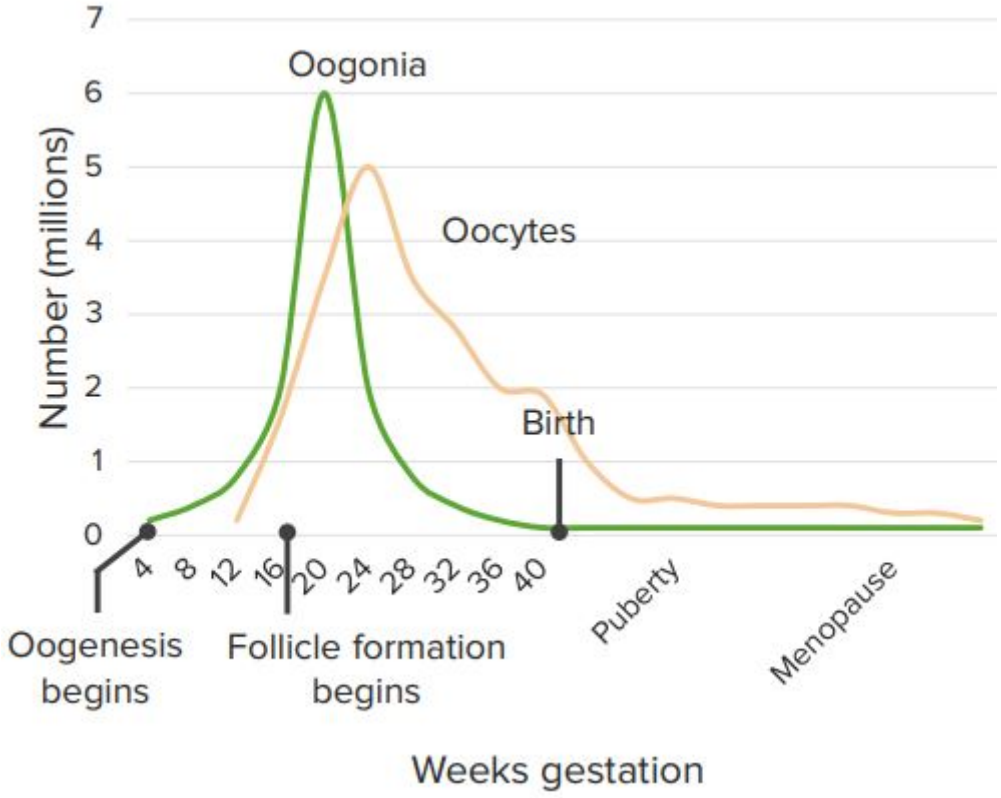
The early transition stage typically starts by the age of 47 years, whereas the late transition stage is reached in women who are 49 years or older.

Clinical Presentation of the Perimenopause

The most common symptom of the perimenopausal period is hot flashes. These vasomotor symptoms are experienced by all women who are going into menopause. **Hot flashes are experienced by around 30% of women in the early transition stage** and by approximately 70% of women in the late transition stage.

Etiology of perimenopause

African American and Native American women tend to have more vasomotor symptoms compared to white women. **Chinese and Japanese women are the least likely to complain of or report vasomotor symptoms during the perimenopausal period.** Additionally, obese women are more likely to have worse hot flashes during the perimenopausal period. In the past, it was believed that the withdrawal of estradiol is the main pathology behind hot flashes.



“Etiology Perimenopause” Image created by Lecturio

Hot flashes

Nowadays, it was shown that **the frequency and severity of hot flashes are more dependent on the levels of follicle stimulating hormone in the blood**. Cigarette smoking and anxiety or mood disorders are risk factors for worse vasomotor symptoms. Hot flashes are more frequent in the perimenopausal period, but they tend to persist in a significant number of women many years after menopause.

Insomnia and sleep disorders

Another important symptom during the perimenopausal period is sleep disturbance and insomnia. Insomnia has been reported to become worse in the late reproductive years and to be worse during the perimenopausal period. The exact mechanism of worsening insomnia in perimenopausal women is unknown, but **hormonal replacement therapy has been shown to improve sleeping problems**. Hot flashes contribute adversely to the picture and they might be responsible for worsening sleep habits in many women during the perimenopausal period. Obese women and those who smoke cigarettes are also more likely to experience sleep difficulties during the perimenopausal period.

Vaginal dryness

Vaginal dryness is a serious symptom that is common in perimenopausal women. **Vaginal dryness is more common during the late transition stage when estrogen levels drop significantly**. Vaginal dryness, irritation, and dysuria are collectively known as the genitourinary syndrome of menopause. White Americans are more likely to complain of vaginal dryness during the perimenopausal period compared to other ethnicities.

Depression and mood swings

Depressive symptoms are also more common in perimenopausal women but luckily, they improve over time without any specific treatment. While depressive symptoms are common in perimenopausal women, major depressive disorder is not; therefore, **it is important to exclude major depressive disorder in any woman who complains of significant depressive symptoms** before attributing her symptoms to perimenopause.

Loss of bone density and osteoporosis are more common during the menopause and are rarely reported during the perimenopausal period.

Treatment of Perimenopausal Symptoms

Hormonal replacement therapy

The four main symptoms of perimenopause, i.e. hot flashes, sleep disorders, vaginal dryness and mood swings, are attributed to endogenous hormonal abnormal changes; therefore, the presence of these symptoms in a woman who is older than 47 years of age should warrant the start of hormonal replacement therapy.

Estradiol (E_2)		**Estrone (E_1)**	
Seems to only decrease less than a year before menopause		Primary estrogen in menopausal women, termed extragonadal estrogen	
Premeno E_2: 30-200 pg/ml	Postmeno E_2: 25-30 pg/ml	Premeno E_1: 35-500 pg/ml	Postmeno E_1: 10-15 pg/ml

Low-dose continuous oral contraceptive hormone replacement therapy is preferred as it was found to have a better impact on the symptomatology of the woman. Estrogen alone, or estrogen plus progestin preparations are available for the symptomatic treatment of perimenopause. Fortunately, hormonal replacement therapy also works in preventing the most serious complication of menopause, i.e. osteoporosis.

Other specific treatments

More specific treatments are also available for women who do not wish to take hormone replacement therapy.

- **Paroxetine mesylate** is now FDA approved for the symptomatic management of hot flashes.
- **Ospemifene**, a selective estrogen receptor modulator, has been recently approved for the treatment of vaginal dryness.
- Women, who have significant depressive symptoms, might benefit from the prescription of **selective serotonin reuptake inhibitors**. Gabapentin and clonidine have also been successfully used for the treatment of hot flashes with variable success.

Note: The only single agent that clearly works against almost all the symptoms of perimenopause is hormone replacement therapy.
Women who have other comorbidities should be offered monotherapy whenever possible. For instance, a woman who has hot flashes and a history of chronic hypertension should receive clonidine. On the other hand, a woman who has hot flashes, sleep disturbances and severe depressive symptoms are better off with a selective serotonin reuptake inhibitor rather than hormone replacement therapy.

References

Santoro N. Perimenopause: From Research to Practice. Journal of Women’s Health. 2016;25(4):332-339. doi:10.1089/jwh.2015.5556

Notes