

## Decoding Perimenopause Part II: Strategies for Irregular Bleeding

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Perimenopause is the transition, which may last as many as 8-10 years, from regular ovulatory menstrual cycles through intermittent spurts of oligo-ovulation and ending with the final menstrual period. The hormonal fluctuations that occur during this transition will lead to irregular bleeding as well as intermittent and confusing symptoms. It is important to understand the general principles and physiology of perimenopause to be able to manage both the symptoms and the abnormal bleeding during this transition.

### General principles of perimenopausal bleeding:

1. Anovulatory Cycles:
  - Fluctuations in the ovary's response to stimulating hormones (FSH and LH) can result in anovulatory cycles, where ovulation does not occur. This can lead to changes in the menstrual cycle and generate erratic episodes of bleeding.
2. Hormonal Fluctuations:
  - Perimenopause is characterized by fluctuations in hormone levels, inconsistent ovulation, and an overall decline in estrogen, but estrogen levels may fluctuate from cycle to cycle and be high one month and low the next. These hormonal changes can lead to irregular menstrual cycles and variations in symptoms and bleeding patterns due to the imbalance between estrogen and progesterone.
3. Irregular Menstrual Cycles:
  - Women in perimenopause may experience irregular menstrual cycles, with variations in cycle length and the amount of blood flow. Some cycles may be shorter or longer than usual.
4. Heavy or Prolonged Bleeding:
  - Perimenopausal women may experience episodes of heavy or prolonged bleeding, often referred to as menorrhagia. This can be due to changes in the uterus' endometrial lining in response to prolonged and unopposed estrogen due to anovulatory cycles.
5. Light or Scanty Periods:
  - On the other hand, some women may have lighter or scant periods during perimenopause. This is also a common variation in bleeding patterns.
6. Perimenopausal Symptoms:
  - Perimenopause is associated with various symptoms, including hot flashes, mood swings, and changes in libido. Estrogen excess symptoms may exist in other cycles, including headaches, bloating, weight gain, and breast and nipple tenderness. These symptoms can coexist with changes in menstrual bleeding patterns.
7. Rule Out Other Causes:
  - While perimenopausal bleeding is often related to hormonal changes, it's essential to rule out other potential causes when the bleeding pattern does not resolve after rebalancing hormones. These may include uterine fibroids, polyps, endometrial hyperplasia, or, less commonly, gynecological cancers.
8. Monitoring and Tracking:
  - Having the patient track her menstrual cycles, the amount of bleeding, and associated symptoms can provide valuable information in assessing perimenopausal bleeding patterns.

### Abnormal Bleeding (AUB)

The perimenopausal transition is demarcated by abnormal bleeding associated with intermittent anovulation. The PALM-COEIN classification of AUB (figure 1) can be used to establish a differential diagnosis and to guide evaluation and management.<sup>1</sup>

**Figure 1**

<b>PALM: Structural Causes</b>	<b>COEIN: Nonstructural Causes</b>
Polyp	Coagulopathy
Adenomyosis	Ovulatory dysfunction
Leiomyoma	Endometrial
Submucosal myoma	Iatrogenic
Other myoma	Not yet classified
Malignancy & hyperplasia	

The PALM side of the classification refers to structural causes that may be evaluated by imaging techniques and/or histopathology. These uterine abnormalities occur independent of the perimenopausal transition, but do increase with age, so they may coexist or exacerbate abnormal bleeding resulting from perimenopausal hormone fluctuations. Perimenopausal women show a significant number of underlying organic pathologies. The key point is to assess the bleeding pattern, correct the hormonal imbalances, and proceed to histologic evaluation of the endometrium whenever the bleeding pattern does not properly respond to short-term intervention. Assessment of endometrial pathology – using endometrial biopsy, or hysteroscopy and directed biopsies is essential to rule out malignant or premalignant conditions when abnormal bleeding is persistent. Ultrasound may identify structural lesions, but they may or may not be contributing to the bleeding pattern, and transvaginal ultrasound measurement of endometrial thickness is not helpful in establishing the potential for pathology prior to menopause. In fact, the endometrial thickness cutoff of < 4mm under ultrasound does not apply to perimenopausal women, only to postmenopausal women.

Nonstructural causes should be evaluated, including coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified causes (COEIN). Of the nonstructural causes, ovulatory dysfunction is the most common in the perimenopausal phase due to the ovaries reduced responsiveness to FSH and LH stimulation. This may result in derangements of follicular maturation, ovulation or corpus luteum formation, and ultimately anovulatory cycles. Chronic anovulation, a predominant phenomenon in the perimenopausal transition, is associated with an irregular and unpredictable pattern of bleeding. Stressors and other factors that impact the hypothalamic-pituitary-ovarian (HPO) axis along with coexisting endocrinopathies may also cause anovulation. Such pathologies include polycystic ovarian syndrome (PCOS), hyperprolactinemia, hypothyroidism, as well as factors such as obesity, anorexia, weight loss, mental stress, and extreme exercise. It is important to think about these other potential causes in perimenopausal-aged patients and not just ignore them. Ultrasound, hysteroscopy and endometrial tissue sampling are used to rule out the structural causes when hormonal and nonstructural conditions have been corrected.

Iatrogenic causes of AUB include exogenous therapy that may lead to unscheduled endometrial bleeding. This is typically associated with continuous estrogen or progesterone therapy such as oral, transdermal, or intrauterine contraceptives.

Once you are reassured that there's no structural cause (rather a hormonal cause) of the bleeding, the hormonal imbalance can be treated with combined hormonal contraception, progestin IUD, or cyclic progesterone to protect the endometrium and prevent withdrawal bleeding. It is important to remember that perimenopausal patients can become pregnant even with irregular menstrual cycles. Oral contraceptives (combined or progestin only formulations) or hormonal IUDs cover both birth control and regulate bleeding. If birth control is not desired, cyclic, or intermittent progesterone therapy is helpful to mitigate the estrogen dominant symptoms.

Given the unpredictability and variable levels of estrogen in the perimenopausal period, androgens have been considered as an alternative hormone therapy to help alleviate menopausal symptoms. In 2002, Princeton organized an international consensus conference to address the underexplored role of androgens in women's health. The conference highlighted the lack of recognition and understanding regarding the impact of androgens on women's well-being. It was identified that common symptoms of androgen insufficiency include a diminished sense of well-being,<sup>1</sup> persistent, unexplained fatigue,<sup>2</sup> and changes in sexual function.<sup>4</sup> Other noted associated symptoms were vasomotor instability or decreased lubrication even though they were adequately estrogenized. Other potential signs or symptoms included bone loss, decreased muscle strength, and changes in cognition or memory.<sup>3</sup>

Dr. Susan Davis reported improvements in Hypoactive Sexual Desire Disorder (HSDD) in postmenopausal women and hinted at possible enhancements in overall symptoms and health.<sup>4</sup> Shortly afterwards, Dr.

Rebecca Glaser showed that testosterone pellet therapy could alleviate symptoms associated with menopause and the perimenopause using the validated menopause rating scale.<sup>5</sup> The 2019 International Consensus Panel highlighted improvements in HSDD and suggested exploring testosterone therapy for perimenopausal symptom relief beyond HSDD.<sup>6</sup> One concern providers may have regarding testosterone's impact on menses is the potential for aromatization leading to increased estrogen levels and an increase in bleeding. However, existing literature indicates minimal aromatase activity in the endometrium. Studies on trans women, who do not require progesterone to safeguard the endometrium, reveal that even at elevated testosterone levels, there is seldom sufficient conversion to produce estradiol levels conducive to endometrial proliferation. Furthermore, heightened androgen levels suppress estrogen production in the hypothalamic-pituitary axis, leading to cessation of menstrual bleeding.<sup>7</sup>

Based on the above research, testosterone therapy may be considered to address peri menopausal symptoms, until the patient attains true menopausal status, defined as the absence of menses for one year. In cases where symptom resolution is not achieved with testosterone monotherapy, the following options may be considered:

1. **Non-hormonal Therapy:** Non-hormonal alternatives, such as gabapentin, SSRIs, and Veozah (fezolinetant), can be considered until it is deemed safe to introduce estrogen. The North American Menopause Society's 2023 Nonhormone Therapy Position Statement provides recommendations on non-hormonal treatments.
2. **Short-Acting Estrogen Therapy:** After balancing anovulatory cycles with adequate progesterone/progestin doses, short-acting estrogen therapy may be added if vasomotor symptoms persist. It is important to choose short-acting treatments so that they may be adjusted if bleeding or estrogen excess symptoms become an issue. This may involve a .025-.05 mg estradiol patch, one pump of Estrogel, one daily spray of Evamist, compounded 1 mg estradiol cream or troche, or less preferable, oral estradiol 1 mg. It's crucial to recognize that the administration of estrogen to women with a uterus necessitates concomitant progesterone supplementation. Cycling with at least 200 mg of progesterone from days 15-25 each month is imperative. Adding progesterone is essential to prevent endometrial hyperplasia or cancer. Notably, perimenopausal patients may sporadically produce their own estrogen, resulting in excess symptoms, requiring higher progesterone doses (i.e., 400 mg at bedtime).
3. **Lowering Estradiol Dose:** Estrogen pellets are problematic during the perimenopausal transition, and in general, should be avoided. If a patient presents with abnormal bleeding having received estradiol pellets, cycle progesterone at least 200 mg from days 15-25 until bleeding ceases, then transition to nightly therapy.
4. **Referral to OB/GYN:** If necessary, refer the patient to an OB/GYN for further evaluation and treatment.

## Anovulation

Amenorrhea (the absence of menstruation) is challenging to evaluate in females in their late 30s and 40s – it may reflect PCOS, chronic anovulation, or early menopausal transition. Recall premature ovarian failure is defined as menopause prior to age 40 and early menopause is permanent cessation of menses before age 45. PCOS and/or anovulatory cycles will result in excess estrogen and irregular bleeding. One can treat this hormonal imbalance with combined hormonal contraception, progestin IUDs, or cyclic progesterone to protect the endometrium and prevent withdrawal bleeding. A clinical pearl is to initiate treatment with 12-14 days of progesterone—depending on the dose-- to synchronize the endometrium and allow for a predictable withdrawal flow prior to starting hormonal suppression.<sup>8</sup> This will potentially eliminate months and months of irregular bleeding as a dyssynchronous endometrium sheds.

Women who have undergone a hysterectomy with ovarian preservation are also difficult to diagnose given the absence of menstrual cycles. Finally, those with amenorrhea secondary to hormonal contraception (levonorgestrel-LNG IUD) or endometrial ablation are also difficult to diagnose. The LNG-IUD is a practical and highly effective method for endometrial protection, so treating these patients' perimenopausal symptoms with systemic estradiol is reasonable if the IUD remains in place. Endometrial ablation does not destroy all islands of endometrial tissue, therefore patients who have undergone endometrial ablation must be treated with progesterone whenever estradiol is contemplated.

Best practice is to treat symptoms and not be concerned with a definitive diagnosis of menopause. These patients may start on low dose estradiol depending on symptoms. However, adding estradiol to patients

during the perimenopausal hormonal rollercoaster may subject them to excess estrogen symptoms such as headaches, bloating, weight gain, and breast tenderness, in addition to increasing their bleeding risk. The point being: be cautious, start low, go slow, and ideally consider short acting therapy (patches, creams, gels, rings) prior to longer acting therapy (i.e., estradiol pellets) to start.

You almost certainly will need to use regular progesterone therapy for predictable bleeding and to prevent estrogen dominant side effects. In this instance, use micronized progesterone 300-400 mg at dinner/bedtime 10-12- days of the month or cycle. The first day of bleeding or menses is considered day 1, Ideal is to “cycle” or start this regimen days 15 through 25. Understand that a perimenopausal patient may require more progesterone to prevent hyperplasia than a postmenopausal patient on estrogen.

In summary, perimenopause is a roller coaster of symptoms and bleeding considerations. Caution needs to be taken when adding estrogen to a perimenopausal patient, and in general, pelleted estrogen can be too high and worsen bleeding even at the 6 mg lowest dose. Just because the predominate symptoms in your patient suggests estrogen insufficiency, be careful and consider shorter acting estrogen that can be stopped. Patients may initially present with bleeding and this needs attention prior to starting any therapy. The bleeding may resolve with a course of progesterone, so not every patient needs a full work up or biopsy. Testosterone may help with symptoms and should not worsen bleeding. It may be the best way to start or consider referral if you are uncomfortable with bleeding management.

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