The Perimenopause Transition

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Abbreviations used

- Final menstrual period (FMP)
- Menopausal transition (MT) = perimenopause
- Vasomotor symptoms (VMS)

What is the perimenopausal transition?

- Menopause = 12 months without menses
- Perimenopause = stage immediately before menopause.
  - Often begins between ages 45 and 55 years.
  - Usually lasts about 7 years but can be as long as 10 years.
  - Physical and emotional changes due to declining ovarian function.
    - Some women have few symptoms and others experience a range of symptoms.
      - Hot flashes, headaches, sleep disturbances, mood disorders, sexual dysfunction, abnormal uterine bleeding.

The menopausal transition is more than a hot flash!

Need to address the totality of the symptoms

Quality of life is an essential parameter that is often overlooked in the discussion of risks and benefits of hormone therapy

Pinkerton J et al. Menopause 2016;23(10):1053-1054

Study of Women’s Health Across the Nation (SWAN)

- Prospective, longitudinal cohort study of women ages 42-52 years at baseline recruited at 7 US sites (n=3302).
- Cohort women had an intact uterus, had at least one ovary, did not take hormone therapy, were either premenopausal or early perimenopausal.
- Self-identified as one of the study’s designated racial/ethnic groups (White, Black, Chinese, Japanese).
- Baseline interview with 6 annual follow-up visits.

Sexual function during menopause transition - SWAN

- Cohort of 1390 women ages 42-52 years, not using hormone therapy, surveyed by sexual function score.
  - No change in sexual functioning until 20 months before the FMP.
  - From 20 months before until one year after the FMP, sexual function decreased annually and continued to decline for 5 years after the FMP but at a slower rate.
- Bottom line: Pain during sexual intercourse increased and sexual desire decreased over the MT. Desire may have decreased due to dyspareunia.

Sexual function during the perimenopause

- Cross-sectional study of 518 women aged 40-55 yrs.
- Analyzed relationship between vaginal atrophy and associated symptoms and the Female Sexual Function Index (FSFI) score.
  - 19 questions about desire, arousal, orgasm, lubrication and sexual satisfaction.
- 70% of women had sexual dysfunction defined by FSFI.
  - 55% of women aged 40-45, 80% of women aged 52-55
- FSFI score decreases and sexual dysfunction increases by 30% during the perimenopause.


What was inversely related to the FSFI score?

- Age
- Menopausal status
- Weight
- Subjective vaginal dryness, dyspareunia
- Vaginal atrophy
  - Vaginal dryness was the symptom of vaginal atrophy most closely correlated to all domains of female sexuality


“Given the high prevalence of sexual dysfunction in women, identifying an eminently treatable contributing factor such as vaginal dryness may allow women to maintain their sexual function during the menopause transition”

Stephanie Faubion MD
North American Menopause Society (NAMS) Medical Director

How bothersome are vaginal dryness and sexual pain?

Vaginal atrophy testing - Need 3 confirmations

1. pH > 5. Use vaginal pH testing paper (pH 3.0-5.5) Swab vagina with cotton swab and roll on vaginal pH paper.
2. Subjective dryness related by patient.
3. One objective sign
   - mucosa pallor and dryness
   - thinning of vaginal rugae
   - mucosal fragility
   - presence of petechiae on swabbing***
Nonhormonal options for dyspareunia and vulvovaginal atrophy

**Moisturizers**
- Used on a chronic maintenance basis to replace normal vaginal secretions

**Lubricants**
- Designed to specifically reduce friction associated with sexual activity

Systemic and local estrogen for vaginal atrophy

- Effectively alleviates atrophic vaginal and vulvar symptoms (think intravaginal first!)
- All low-dose systemic and intravaginal estrogen formulations are FDA-approved for treatment of atrophic vaginitis.
- **NO** data to suggest initial benefit for use of both systemic and local vaginal estrogen for severe atrophy.


What's natural and what's not…?

All hormonal agents are derived from Mexican yams except those derived from pregnant mare urine.

- Conjugated equine estrogens (estrone, equilin + other compounds) = Premarin.

Local vaginal estradiol and conjugated equine estrogen

- Cream, ring and tablet formulations highly effective
  - Even low dose tabs (10 mcg/d) of vaginal estradiol improve symptoms.
  - Women prefer ring over cream for long term treatment
    - Comfort, ease of use, satisfaction.
  - Regimen: administered daily for 1-2 weeks as induction therapy and then used “indefinitely” at low doses for maintenance. (ACOG).


Estring (vaginal estradiol ring)

- Should be inserted in upper third of vagina. Position not critical.
- Should be comfortable and not interfere with sex.
- If expelled, wash with water and reinsert.
- Left in place for 90 days.
- May not be able to insert until vagina is estrogenized

Is progestin necessary with vaginal estrogen?

- Systematic Review 2014
  - Data insufficient to mandate endometrial surveillance or dictate frequency or means of surveillance.
  - Clinician vigilance for possible emergence of endometrial pathology.
- ACOG
  - “The addition of progestin for endometrial protection is not needed”
- Cochrane
  - “Does not require endometrial surveillance unless there is postmenopausal bleeding”
Cochrane 2006/2016: local vaginal estrogen

- 30 RCTs of 6235 women: low quality of evidence
  - Efficacy same between the various estrogen products. (Creams, tablets, vaginal ring).
  - Significant preference for ring.
  - No difference in adverse events between various estrogen products compared with each other or placebo.
  - As effective as systemic oral estrogen in relieving symptoms.
  - 80-90% satisfaction compared to 75% using oral estrogen
  - Any abnormal uterine bleeding requires investigation.
- Bottom line: significant preference for any local agent compared to placebo and non-hormonal topical agents.

Study of Women’s Health Across the Nation (SWAN)
Menstrual cycle patterns

- Cycle interval increases over the MT, particularly in cycles without luteal activity
- Almost 25% of perimenopausal women will experience an ovulatory cycle in the last year up to their FMP
- Black and Hispanic women are less likely to experience ovulatory cycles than White and Asian women.
- Bottom line: contraception should be discussed and prescribed

Study of Women’s Health Across the Nation (SWAN)
Menstrual cycle patterns

- Pooled analysis across cohorts showed:
  - early stage of the MT by a 7+ day difference in consecutive cycles
  - late stage of the MT by 60+ days of amenorrhea.
- Smokers experience earlier MT onset, shorter MT duration and earlier age at natural menopause.
- Black women experience a longer MT duration than White women.

Study of Women’s Health Across the Nation (SWAN)
Menstrual cycle patterns

- Patterns of estradiol decline and FSH rise during the MT are heterogeneous across women.
  - change dramatically over the MT.
- Estradiol decreases beginning 2 years before the FMP and continuing for 2 years after the FMP. Stabilization thereafter.
- FSH increases remarkably beginning 7 years before the FMP until 2 years after the FMP. Stabilization thereafter.
- Oprah was wrong!

Study of Women’s Health Across the Nation (SWAN)
Vasomotor Symptoms (VMS)

- 80% of women reported VMS during the MT.
  - Highest reporting occurred during the MT from early to late perimenopause into the early postmenopause.
- Black women had the highest prevalence and longest duration of VMS and were the most bothered by them.
- Asian women had the lowest prevalence of VMS.
- Women in lower socioeconomic groups were more likely to have VMS independent of race/ethnicity.
Study of Women’s Health Across the Nation (SWAN) Vasomotor Symptoms (VMS)

- Long-held belief that VMS last only a few years.
  - SWAN demonstrated VMS persisted for median of 7.4 + yrs
- Early onset group: VMS early in the MT that continued after the FMP and then declined into postmenopausal years
- Late onset group: VMS peaked at the FMP and continued (although declining) into the postmenopausal years.
- 3rd group: few or no flashes through the MT.
- 4th group (dubbed the “super flashers”) started VMS well before their FMP and continued well into the postmenopause.

Estrogen use for VMS during the MT

- Estrogen is the most effective treatment for relief of symptoms.
  - Start with lower doses (transdermal 0.025mg or oral estradiol 0.5 mg/d) and titrate up to relieve symptoms.
  - Women will usually require systemic estrogen rather than vaginal estrogen

How much does estrogen reduce VMS?

- Meta-analysis of 24 trials of estrogen therapy in 3329 women
- Frequency of VMS decreased more in women receiving estrogen therapy (18 hot flashes per week) compared with placebo = 75% reduction.
- Conjugated equine estrogen and 17-beta estradiol appeared to be equally effective.
  - Eliminated VMS in 80% of women and reduced frequency and severity in the remainder.

Use of a progestin with systemic estrogen

- All women with an intact uterus need a progestin in addition to estrogen to prevent endometrial hyperplasia.
  - Can occur after as little as 6 months of unopposed estrogen.
- Natural micronized progesterone (200 mg for 12 days each month or 100 mg daily), norethindrone acetate 0.35 mg daily, medroxyprogesterone acetate (MPA) 2.5 mg daily.
- When adequate progestin is combined with estrogen, risk of endometrial cancer is same as untreated women.
  - In WHI, continuous equine estrogen + MPA was associated with risk of endometrial cancer similar to placebo

Non-hormonal treatment for hot flashes

- Low-dose 7.5 mg daily paroxetine capsules (Brisdelle)
  - FDA-approved for treatment of moderate to severe vasomotor symptoms (2013)
  - Taken at bedtime.
  - Safety and effectiveness established in 2 RCTs, 1175 postmenopausal women, 12 and 24 week study.
  - Unknown how drug reduces hot flashes
  - Headache, fatigue, nausea/vomiting most common adverse effects
  - Possible reduction in effectiveness of tamoxifen ***
Reasons for discontinuing or not initiating estrogen therapy

Herbal and Phytoestrogen remedies for VMS

- Herbal remedies studied for relief of VMS include:
  - Chinese herbal medicine, black cohosh, ginseng, St John's wort, ginkgo biloba.
  - Insufficient evidence to support use of herbal remedies for VMS.
  - Limited data to support safety and effectiveness.

- Plant-derived substances with estrogenic biologic activity.
  - Red clover, soy protein, isoflavones.
  - 2010 Cochrane review: no evidence of benefit.
  - Long-term safety data are lacking.

Bioidentical hormones

- "Bioidenitical" or "traditional hormones" carry the same risks as studied hormones.
- *** There is no scientific evidence that a different or "customized" dose of hormones would have changed results of WHI study.
- Endocrine Society supports FDA regulation.
- Caution: Have no official labeling (package insert) because are not FDA-approved.

Study of Women’s Health Across the Nation (SWAN) Sleep

- Self-reported sleep complaints increase across the MT.
  - White women have the most sleep complaints and Hispanic women the fewest.
  - Vasomotor symptoms explained part of the complaints.
  - Sleep duration and deep sleep measured objectively did not worsen and may improve.

Clinical depression and hormone therapy

- Evidence is insufficient to support use of hormone therapy in the treatment of clinical depression.
  - In small RCTs, estrogen therapy was effective in improving clinical depression in perimenopausal but not postmenopausal women.
  - Postmenopausal women with a history of perimenopausal-related depression responsive to hormone therapy may experience a recurrence of depressive symptoms after estradiol withdrawal.
  - Progestins may contribute to mood disturbance.
Use of vaginal estrogen in women with history of estrogen-dependent breast cancer

• Nonhormonal remedies are first-line choices for managing urogenital symptoms during or after treatment for breast cancer.
  – Vaginal estrogen should be reserved for women unresponsive to nonhormonal remedies.
  • Should be preceded by informed decision-making and consent process after discussion of potential risks of vaginal estrogen.
  • Decision to use vaginal estrogen should be made with the women’s oncologist.


Cancer of the endometrium is the most common type of gynecologic cancer

Premenopausal bleeding (irregular menses, intermenstrual bleeding and heavy menstrual bleeding) requires evaluation depending on risk factors.

Endometrial cancer ages 40 to menopause

• Incidence of endometrial cancer:
  – Ages 20-34: 1.6%.
  – Ages 35-44: 6.2%.
  – Ages 40-50: 14-24 cases/100,000.
  – Ages 70-74: 87 cases/100,000.
• More advanced stage disease.
• Worse prognosis.
• EMB before medical treatment.

Endometrial Biopsy (EMB)

Disposable suction piston devices have virtually replaced D&C despite little scientific validation
Both EMB and D&C are “blind” endometrial sampling procedures

Causes of AUB in women aged 40 years to menopause

• Anovulatory bleeding represented by normal physiology in response to declining ovarian function
• Endometrial hyperplasia or cancer
• Endometrial atrophy
• Leiomyomomas
• Use of hormonal contraception.

Obesity

• Take aggressive steps to educate women on diet, exercise, bariatric surgery.
• Weight loss is incredibly difficult.
  – Strongly consider hormonal protective interventions to regulate menstrual cycles and prevent cancer or hyperplasia.
  • Think OCP’s – 80% reduction endometrial cancer !!!

Perimenopausal women with abnormal uterine bleeding

- Ultrasound measurement of endometrial thickness has no diagnostic value and should not be performed (don’t request it).
- Imaging for other indications such as an enlarged uterus.
- Endometrial biopsy should be based on symptoms and clinical presentation.

ACOG Pract Bull. Obstet Gynecol 2015;125:1006-25,

Endometrial sampling in perimenopausal women with abnormal uterine bleeding (AUB)

- Endometrial tissue sampling should be performed in women with AUB who are > 45 years as a first-line test.
- Office endometrial biopsy (EMB) is first-line procedure for sampling.
- EMB has high overall accuracy for diagnosing endometrial cancer when an adequate sample is obtained and the endometrial process is global.
  - If the cancer occupies < 50% of the surface area of the endometrial cavity, the cancer can be missed by a blind EMB.


OCPs during the Perimenopause

- Low-dose OCP’s (any kind) used by non-smoking, normotensive women are not associated with stroke or MI.
  Healthy, nonsmoking women can use OCP’s until ages 50-55 after weighing risks and benefits. (ACOG Evid B)
  - Can then switch to a postmenopausal regimen.
  - Possibility of pregnancy in women 45-49 years who are not using contraception is 2-3%.
  - Controls abnormal vaginal bleeding, provides contraception and relieves MT symptoms.

Therapy for AUB in perimenopausal women

Medical first, Surgical second

- Many causes of AUB are amenable to medical management.
  - NSAIDs
  - Progestins
  - OCPs
  - Levonorgestrel IUD (Mirena)
- Surgery may be indicated
  - Uterine myomas or polyps.
- Endometrial ablation for women who have completed childbearing.
  - Minimally invasive surgery option.