Diagnosis and Management of The Menopausal Transition

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Disclosures

- I have no financial interests to disclose

Overview

- Background
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  - Physiologic Changes
- Symptomatology
  - Vasomotor Symptoms
  - Urogenital Symptoms
- Diagnosis
- Management

Background

Definitions

- Menopausal Transition is the progressive endocrinologic loss of ovarian function that leads to the permanent cessation of menstruation
- Menopause refers to a point of time 1 year after the last menstrual period.
- Post-menopause describes the years following the cessation of menstruation
- Premature Ovarian Failure is the cessation of menses and associated elevated follicle stimulating hormone before the age of 40
- Perimenopause is a vague term referring to the late reproductive years

Background

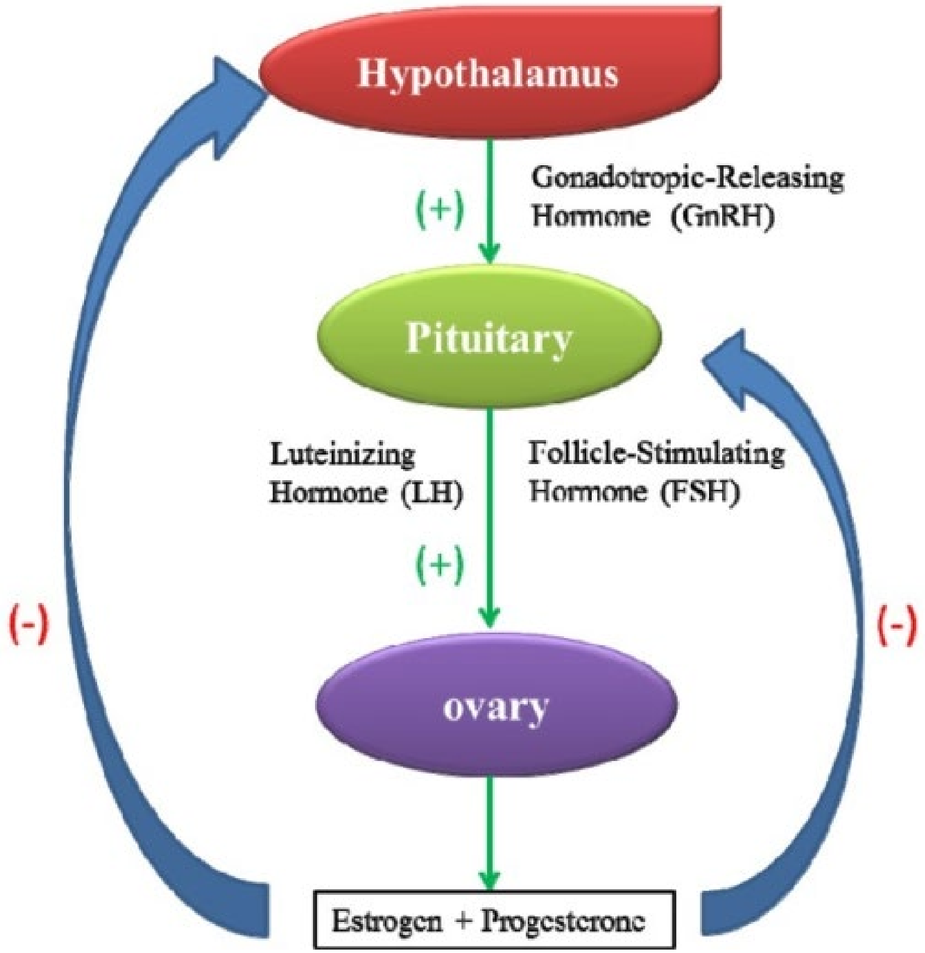
Definitions

- Median age in North America is 51.5 years old
- Average age of onset is 47 and typically spans 4 to 7 years
- Classically, menopausal transition begins with menstrual irregularity and extends until 1 year after the last period
  - Initially, interval may be altered by 7 or more days and cycle lengths are typically shorter
  - In later menopause, menses may be skipped and intermenstrual interval may extend 60 days or more
- These years are marked by fluctuations in hormone levels eventually resulting in:
  - Decrease in Estradiol and Progesterone
  - Increase in Follicle Stimulating Hormone

Background

Physiologic Changes

- In early menopause, FSH rise slightly and stimulate an increased production of estrogen
- When the supply of follicles is depleted, the ovary is unable to maintain its production of estrogen - 4-5x fold increase in FSH and significant decrease in estrogen
- Testosterone levels do not change appreciably, may decrease with decreasing SHBG



Background

Physiologic Changes

- Ovarian senescence - rapid depletion of ovarian follicles
- Endometrium undergoes disordered proliferative changes and eventually atrophy
- Loss of bone mass
- Slowing of metabolism
- Cardiovascular changes - significant increase in SVD after menopause
- Breast changes - breast tissue replaced with adipose tissue
- Dental changes - loss of buccal epithelium and bone mass

Symptomatology

Vasomotor Symptoms

- Hot Flush / Flash - sudden sensation of extreme heat, typically in the upper body
    - Typically last 1-5 minutes
    - Characterized by perspiration, flushing, chills, clamminess, palpitations
    - Increase in heart rate and blood pressure
    - Can occur day or night
- Severity of symptoms varies greatly among women during the menopausal transition
    - Median duration of flushing has been reported anywhere from 4 to 10 years
    - Severity of symptoms and severity of lab abnormalities are not always associated
    - By cessation of menses, >50% will experience, and 1/3 can expect to have for > 10 years

Symptomatology

Vasomotor Symptoms

- Pathophysiology is not completely understood - multiple factors
  - Withdrawal of reproductive hormones - symptoms improve with estrogen replacement
    - Does not occur in chronically low estrogen
  - Thermoregulatory Zone is narrowed and becomes more sensitive to subtle changes in temperature - estrogen widens the thermoregulatory zone
  - Genetic predisposition to severity of vasomotor symptoms - sex steroid metabolism
    - African American women report most severe symptoms, Asian women the least
- Obesity predisposes women to more severe symptoms
- Environmental factors include depression and anxiety, exercise level, socioeconomic status, and smoking

Symptomatology

Genitourinary Symptoms

- Hypoestrogenic state leads to genitourinary syndrome of menopause; ie vaginal atrophy
- Vaginal symptoms include vaginal/vulvar dryness, itching, discharge, dyspareunia,
  - Changes include loss of superficial epithelial cells, loss of rugae, loss of elasticity, narrowing/shortening of the vagina, loss of fat in the labia minora, fusion of the labia, and shrinking of the clitoris
  - Elevations in vaginal pH increase risk of urogenital infections
  - Prevalence ranges from 10 - 50%
  - 25% experience dyspareunia

Symptomatology

Genitourinary Symptoms

- Urinary symptoms include dysuria, frequency, urgency, urethral eversion, prolapse, and recurrent UTIs
  - Typically result of thinning of the urethral and bladder mucosa
- Link between incontinence and menopause is controversial
  - More related to modifiable risk factors - hysterectomy, BMI, constipation, multiparity
- Rates of Pelvic Organ Prolapse increase with age
  - Multiple factors, not directly related to loss of estrogen

Symptomatology

Common Concerns

- Menstrual disturbances
- Weight gain
- Fat distribution
- Skin changes
- Sleep disturbances
- Cognitive dysfunction
- Decreased Libido

Diagnosis

- History and Physical Exam
  - Documentation of age-appropriate symptoms
- Hormone Levels
  - Exact FSH level debated, > 40 strongly associated with menopausal ovarian failure
  - Estrogen levels may be normal, elevated, or low depending on stage
- Estrogen Maturation Index
  - Rarely used clinically any longer
  - Collected as vaginal specimen at the time of speculum exam
  - Percentage of paranasal, intermediate, and superficial squamous cells on smear
    - Increase in paranasal cells indicates low estrogen exposure

Management

History and Controversy

- Early Estrogen Trials
  - Estrogen gained popularity in 60’s and 70’s - half of all menopausal women used for an average of 5 years
  - 1975 - Smith et al. revealed an increased risk of endometrial cancer with estrogen therapy
  - 1980s - progestins introduced for endometrial protection
- Women’s Health Initiative
  - Designed to obtain FDA approval for estrogen therapy as prevention for CVD
  - Launched in 1993 with a total of 16,000 participants
  - Terminated after 5 years due to an association between estrogen + progesterone therapy and diagnosis of breast cancer

Management

Hormone Replacement Therapy

- Risks
  - Thromboembolic disease
  - Coronary heart disease
  - Stroke
  - Breast Cancer
- Benefits
  - Increased bone mineral density and decreased risk of fractures
  - Decreased rates of colorectal cancer
  - Possibly cardioprotective when started < 10 years from menopause and < 60

Management

Hormone Replacement Therapy

- Indications
  - Estrogen replacement is only indicated for treatment of vasomotor symptoms, vaginal atrophy, and osteoporosis prevention/treatment
  - Lowest effective dose for the shortest amount of time
  - Progestin is indicated for uterine endometrial protection
- Contraindications
  - Undiagnosed abnormal uterine bleeding
  - Known, suspected, or history of breast cancer
  - Known, suspected, or history of estrogen sensitive neoplasm
  - Active or prior venous thromboembolism
  - Liver dysfunction/disease
  - Pregnancy

Management

Hormone Replacement Therapy

- Systemic hormone therapy is the most effective treatment for vasomotor symptoms
  - Estrogen can be administered via oral, parenteral, topical, or transdermal routes
    - Similar effectiveness
    - Risks of thromboembolism decreased in transdermal routes
- Progestins added to any patient with a uterus
  - Protection against estrogen-induced endometrial hyperplasia and endometrial cancer
  - May have some benefit to vasomotor symptoms
  - Offered in form of oral tablets, IUDs, combined patches, and combined tablets
  - Progestin alone is not considered a treatment for vasomotor symptoms
- Adverse effects include breast tenderness, vaginal spotting, mood changes

Management

“Bioidentical” Hormones

- Term invented by marketers to describe custom-compounded hormone products
- This term now refers to any plant-derived hormones that are chemically similar or identical to those produced in the body
- Includes FDA approved formulations such as estradiol, micronized progesterone
- Compounded hormones are not approved by FDA and are not recommended by ACOG
- These formulations are not tested for efficacy or safety

Management

Common Doses

- Transdermal Patch
  - Climera, Vivelle-Dot - 17B-Estradiol 0.025 - 0.1 mg/d - patch applied weekly or twice weekly
  - Climera Pro, Combipatch - 17B- Estradiol + levonorgestrel/norethindrone acetate
- Oral
  - Estrace - 17B Estradiol 0.5, 1.0, 2.0 mg
  - Prometrium - Micronized progesterone 200 mg nightly
  - Provera - Medroxyprogesterone acetate 2.5, 5, 10 mg
  - Prempro - Conjugated equine estrogen + medroxyprogesterone acetate - various doses
- Vaginal
  - Femring - Estradiol acetate 0.05 - 0.1 mg/d inserted vaginally x 90 days

Management

Non-hormonal options

- SSRIs/SSNRIs
  - Effective for treatment of of vasomotor symptoms of menopause
  - Only Paroxetine (Paxil) 7.5 mg is FDA approved
  - Effexor, Celexa, Lexapro, Zoloft, Prozac, and Pristiq are common off-label choices
- Clonidine
  - Alpha-2 agonist, typically used as an antihypertensive
  - Used off label in small doses for treatment of vasomotor symptoms
- Gabapentin
  - Anticonvulsant used off label to treat vasomotor symptoms
  - Typically require high doses for effectiveness, limited by side effects
- Veozah (fezolinetant)
  - First neurokinin 3 receptor antagonist FDA approved for the treatment of vasomotor symptoms

Management

Treatment of Urogenital Symptoms

- Low dose systemic estrogen therapy can be used for treatment of genitourinary syndrome of menopause
- More commonly, local vaginal estrogen therapies are used
  - Estradiol/Premarin cream - 2g/d applied vaginally
  - Vagifem/Yuvafem - 10 mcg vaginal suppository
  - Estradiol ring - 0.05 mg/d
- Typically administered daily for 2 weeks as induction, then used indefinitely 2-3 times weekly
- Progestin therapy is not typically recommended for local estrogen therapy

Management

Is Vaginal Estrogen Safe?

- Some systemic absorption of vaginal estrogen has been documented
- Risks of endometrial cancer?
  - Cochrane review found that local estrogen therapy was not associated with endometrial hyperplasia
  - Postmenopausal bleeding after initiation of therapy requires an evaluation
- History of breast cancer?
  - Non-hormonal methods have classically been considered first line
  - 2023- Argrawal et al. found no increased risk of breast caner recurrence within 5 years in women using local vaginal estrogen regardless of receptor status

Management

The Menopausal Patient

- Screening for breast cancer
- Screening and treatment of osteoporosis
- Screening for colon cancer
- Decreasing libido
- Treatment of anxiety/depression
- Weight gain
- Difficulties with exercise
- Worsening health concerns

Questions?

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