WOMEN'S HEALTH DISORDERS

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No disclosures

CASE # 1

22 y/o women, healthy, who comes today for evaluation of **lack of mentrual periods for 8 months.**

- Had **menarche at age 12** and since then with **irregular mentrual periods** happening every 2-3 months and usually lasting 5-10 days.
- Had **normal breast development.**
- Complains of acne in face, chest and back. Thick hair in upper lip and chin. Weight stable.
- Medications: None
- Family history: Mother, father and sister healthy without medical problems
- Allergies: None
- Social history: Denies smoking, alcohol intake or illicit drugs.

AMENORRHEA

Absence of menses

AMENORRHEA

PRIMARY

-Absence of menses at age 15 years in the presence of normal growth and secondary sexual characteristics (breast development).

- Absence of menses at age 13 years with a complete lack of secondary sexual characteristics such as breast development.

- In the US prevalence is less than 1% (1)

SECONDARY

Absence of menses for **more than three months** in girls or women who previously had **regular menstrual cycles** or **six months** in girls or women who had **irregular menses.**

- In the US Prevalence of 3-4%.

(1) Timmreck LS, Reindollar RH. Contemporary issues in primary amenorrhea. Obstet Gynecol Clin North Am. 2003;30:287-302.

PRIMARY AMENORRHEA

PRIMARY AMENORRHEA

- Usually, the result of a **genetic or anatomical abnormality**.

- However, all causes of secondary amenorrhea can also present as primary amenorrhea.

Abnormality	Causes
Pregnancy	
Anatomic abnormalities	
Congenital abnormality in müllerian development*	Isolated defect
	Androgen insensitivity syndrome
	5-alpha-reductase deficiency
Congenital defect of urogenital sinus development*	Agenesis of lower vagina
	Imperforate hymen
Intrauterine adhesions	Asherman syndrome
	Tuberculous endometritis
Disorders of the hypothalamic-pituitary-ovarian axis¶	
Hypothalamic dysfunction	
Pituitary dysfunction	
Ovarian dysfunction	Gonadal dysgenesis ▪ Turner syndrome△ ▪ 46,XY◇
	Other causes of primary ovarian insufficiency
Other	Polycystic ovary syndrome
	Hyperthyroidism
	Hypothyroidism
	Uncontrolled diabetes mellitus types 1 and 2
	Exogenous androgen use

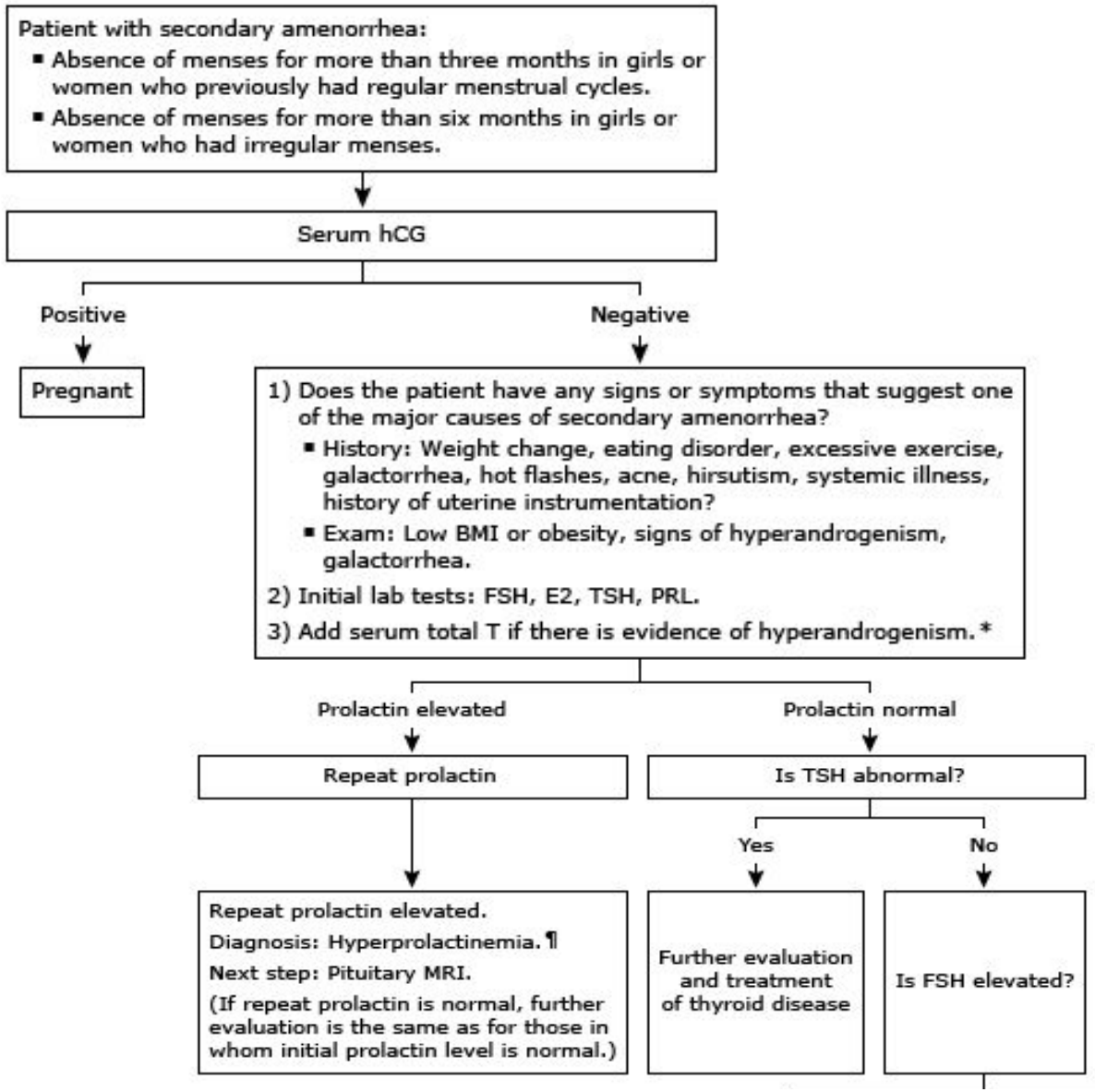
SECONDARY AMENORRHEA

Major causes of amenorrhea

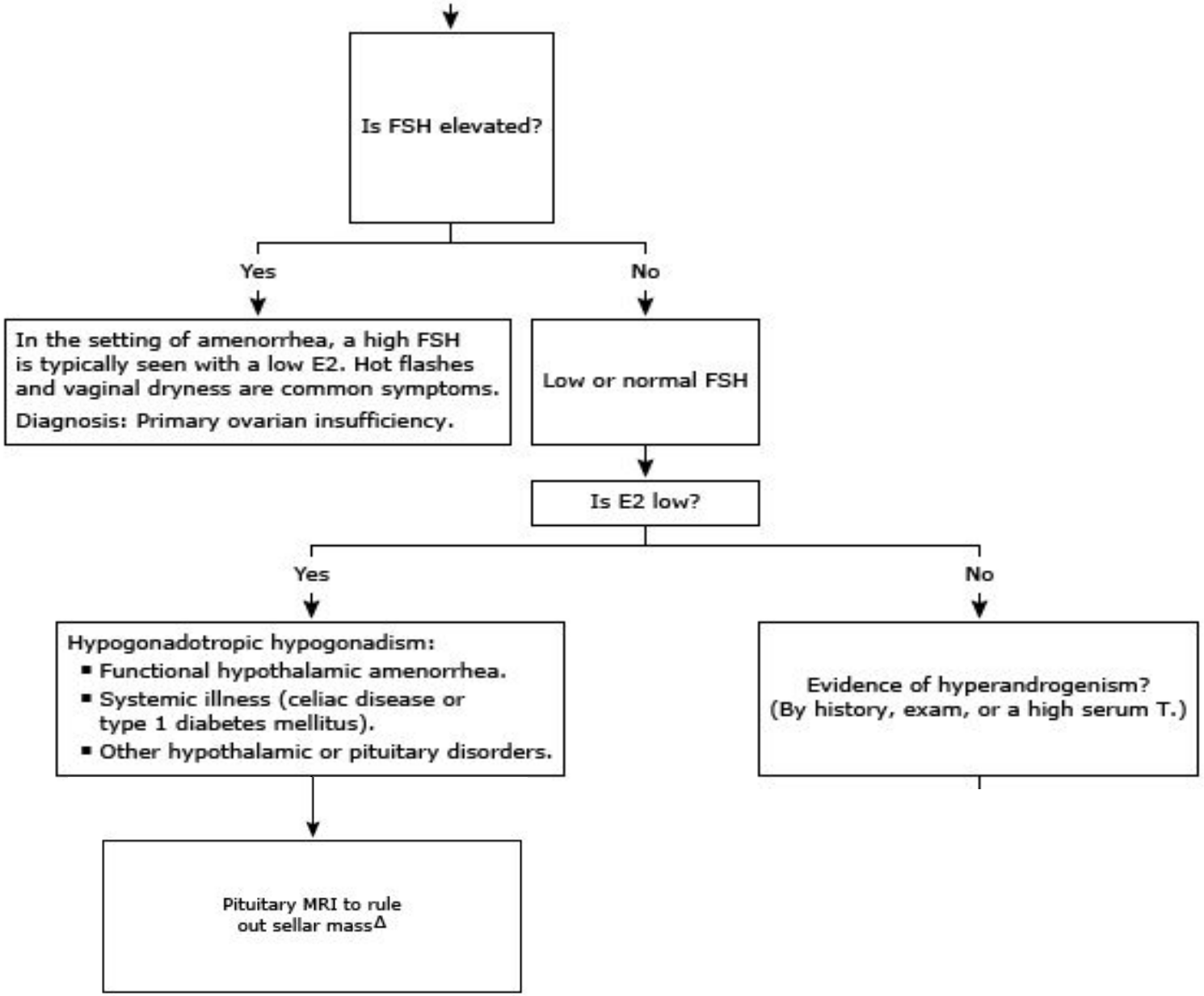
Hypothalamic-Pituitary-Ovarian axis

Abnormality	Causes
Hypothalamic dysfunction	Isolated GnRH deficiency
	Functional hypothalamic amenorrhea
	▪ Weight loss, eating disorders (eg, anorexia nervosa)
	▪ Excessive exercise (including but not exclusively: running, ballet dancing, figure skating, gymnastics)
	▪ Stress
	▪ Severe or prolonged illness
	Inflammatory or infiltrative diseases
	Brain tumors – eg, craniopharyngioma
	Cranial irradiation
	Traumatic brain injury
	Other syndromes – Prader-Willi, Laurence-Moon-Biedl, leptin mutations
Pituitary dysfunction	Hyperprolactinemia, including lactotroph adenomas
	Other pituitary tumors – acromegaly, corticotroph adenomas (Cushing's disease)
	Other tumors – meningioma, germinoma, glioma
	Genetic causes of hypopituitarism
	Empty sella syndrome
	Pituitary infarct or apoplexy
Ovarian dysfunction	Primary ovarian insufficiency (premature ovarian failure)
	▪ Turner syndrome, fragile X permutation, chemotherapy and radiotherapy, somatic chromosomal defects, autoimmune, idiopathic
Other	Polycystic ovary syndrome
	Hyperthyroidism
	Hypothyroidism
	Uncontrolled diabetes mellitus types 1 and 2
	Exogenous androgen use

SECONDARY AMENORRHEA

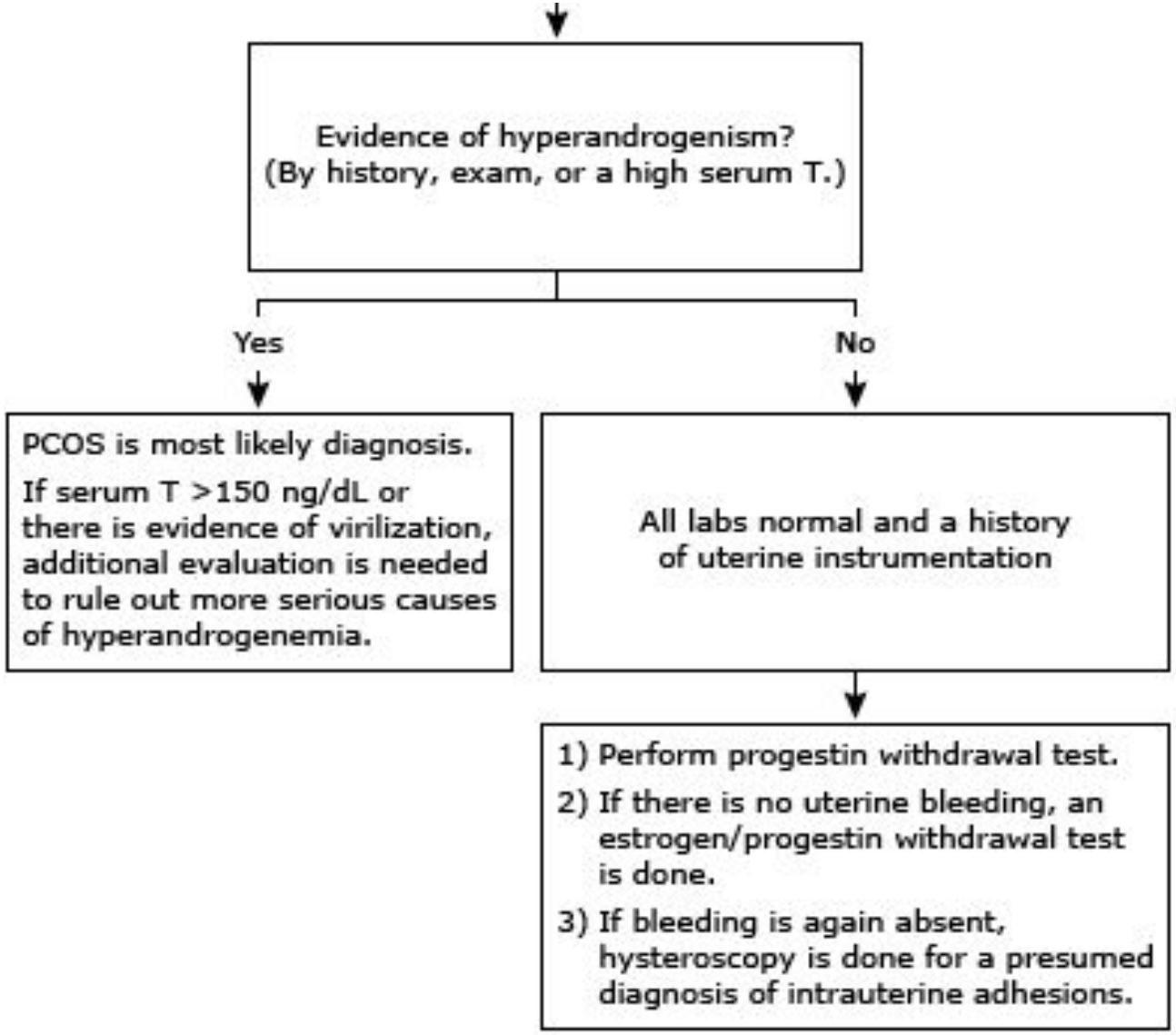


SECONDARY AMENORRHEA



SECONDARY

AMENORRHEA



SECONDARY AMENORRHEA

GOALS OF TREATMENT

- Correcting the underlying pathology, if possible.
- Helping the woman to achieve fertility, if desired.
- Preventing complications of the disease process.
  - Estrogen replacement to prevent osteoporosis.
  - Management of obesity, hirsutism and metabolic disorders.

SECONDARY AMENORRHEA

APPROACH TO TREATMENT

- **Hyperprolactinemia** — The management depends upon the cause of the hyperprolactinemia and the patient's goals (eg, pursuing fertility or not).
- **Primary ovarian insufficiency (premature ovarian failure)** — Women with primary ovarian insufficiency (POI) should receive hormonal therapy for prevention of bone loss. This can be either an oral contraceptive or replacement doses of estrogen and progestin.
- **Functional hypothalamic amenorrhea** — Can usually be reversed by weight gain, reduction in the intensity of exercise, and/or resolution of illness or emotional stress.

SECONDARY AMENORRHEA

APPROACH TO TREATMENT

- **Thyroid disorders** — Correct underlying problem.

- **Polycystic ovary syndrome (PCOS)** — treatment is directed toward achieving the patient's goals (eg, relief of hirsutism, resumption of menses, fertility) and preventing the long-term consequences of PCOS (eg, endometrial hyperplasia/cancer, obesity, and metabolic disorders).

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- Had normal **breast development.**
- **Complains of acne in face, chest and back. Increase hair in upper lip and chin area.**
- Medications: none
- Family history: mother, father and sister healthy without medical problems
- Allergies: none
- Social history: denies smoking, alcohol intake or illicit drugs.

Diagnosis: Secondary Amenorrhea

CASE # 1

Physical exam

- General: Comfortable, NAD
- Thyroid: normal size, no palpable nodules on exam
- Breast: adult configuration, no palpable masses, no discharge seen.
- Cardiac: Regular heart sounds, no murmurs or gallops
- Skin: acne face, chest, back. Acanthosis nigricans neck area.
- Neuro: alert, oriented x 3, no deficits

Labs:

HCG: Negative
Prolactin: 10 ug/L (<20 ug/L)
TSH: 2.0 mU/L (0.4 – 4.5 mU/L)
FSH: normal
Estradiol: 250 ug/dl
Testosterone: 50 ng/dl (4-45 ng/dl)
Free testosterone: 5.6 ng/dl
DHEA-s: 250 mcg/dl (71-375 mcg/dl)

Diagnosis: Secondary amenorrhea related to PCO's

PCO’S
“Polycystic Ovarian Syndrome”

Polycystic Ovarian Syndrome

- Most common endocrinopathy affecting reproductive-aged women, with impacts across the lifespan from adolescence to post-menopause.
- Has a prevalence between 10% - 13%.
- Frequent presence of associated risk factors for cardiovascular disease, including obesity, glucose intolerance, dyslipidemia, fatty liver, and obstructive sleep apnea.

Conditions associated with an increased prevalence of PCOS

- Oligoovulatory infertility
- Obesity
- Diabetes mellitus (type 1, type 2, gestational)
- History of premature adrenarche
- First-degree relatives with PCOS
- Ethnicity (Mexican American, Australian aborigines)
- Drugs (valproate)

Polycystic Ovarian Syndrome

Main features of polycystic ovary syndrome (PCOS) include **ovulatory dysfunction, androgen excess, and/or polycystic ovaries.**

NIH consensus criteria 1990[1] (all required)	Rotterdam criteria 2003*[2] (two out of three required)	AES definition 2008[3] (all required)
Menstrual irregularity due to oligo- or anovulation	Oligo- or anovulation	Clinical and/or biochemical signs of hyperandrogenism
Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Ovarian dysfunction – oligo/anovulation and/or polycystic ovaries on ultrasound
Exclusion of other disorders: NCCAH, androgen-secreting tumors	Polycystic ovaries (by ultrasound)	Exclusion of other androgen excess or ovulatory disorders

Polycystic Ovarian Syndrome

DIAGNOSTIC ALGORYTHM IN POLYCISTIC OVARY SYNDROME
Step 1: Irregular cycles + clinical hyperandrogenism
(exclude other causes) = diagnosis
Step 2: if no clinical hyperandrogenism
Test for biochemical hyperandrogenism (exclude other causes) = diagnosis
Step 3: if ONLY irregular cycles OR hyperandrogenism
Request ultrasound for PCOM, if positive (exclude other causes) = diagnosis

Algorithm 1—diagnostic algorithm for polycystic ovary syndrome (PCOS). *Exclusion of other causes = TSH, prolactin, 17-OH progesterone, FSH or others if clinically indicated (eg, Cushing's syndrome, adrenal tumours).

Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome

Helena J Teede[1,2], Chau Thien Tay[1,2], Joop J E Laven[2,3], Anuja Dokras[4], Lisa J Moran[1,2], Terhi T Piltonen[5], Michael F Costello[2,6], Jacky Boivin[7], Leanne M Redman[8], Jacqueline A Boyle[2,9], Robert J Norman[2,10], Aya Mousa[1], Anju E Joham[1,2]; International PCOS Network

Polycystic Ovarian Syndrome

Screening, diagnostic and risk assessment

1.Ovulatory dysfunction and irregular mentrual periods

- Typically present with oligomenorrhea (fewer than 8 menstrual periods in a year) and, less often, amenorrhea (no menstrual periods for three or more consecutive months)

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Polycystic Ovarian Syndrome

2. Hyperandrogenism

Clinical hyperandrogenism

- Hirsutism, acne, male-pattern hair loss
  - Hirsutism is defined as excess terminal (thick, pigmented) body hair in a male distribution and may be noted above the upper lip, chin, peri areolar area, in the midsternum, and along the linea alba of the lower abdomen
  - For evaluation of hirsutism use the Modified Ferriman-Gallwey score (mFG)
  - Score 4-6 should be used to detect hyperandrogenism

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Polycystic Ovarian Syndrome

2. Hyperandrogenism

Biochemical hyperandrogenism

- Measure total testosterone and free testosterone.
- If total or free testosterone are NOT elevated, could consider measuring androstenedione and DHEA-s (poor specificity).
  - It is very difficult to reliably assess for biochemical hyperandrogenism in women on OCP's as they will increases SHBG and reduces gonadotrophin-dependent androgen production.
  - If already on the OCP's and assessment of biochemical androgens is imperative, these should be withdrawn for a minimum of 4-6 weeks (other groups recommend 3 months).

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Polycystic Ovarian Syndrome

2. Hyperandrogenism

Biochemical hyperandrogenism

- If androgen levels are markedly above laboratory reference ranges, causes of hyperandrogenemia other than PCOS, including ovarian and adrenal neoplastic growths, congenital adrenal hyperplasia, Cushing's syndrome, ovarian hyperthecosis (after menopause), iatrogenic causes, and syndromes of severe insulin resistance, should be considered.

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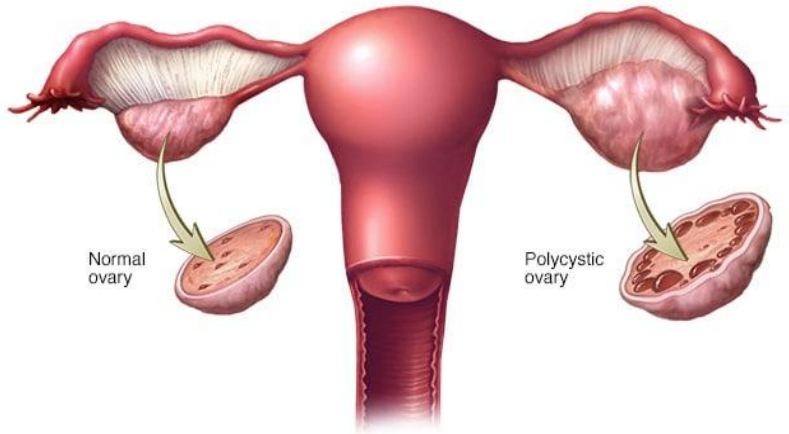
Polycystic Ovarian Syndrome

3. Ultrasound and polycystic ovarian morphology (PCOM)

- For patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is **NOT** necessary for PCOS diagnosis.
- Transvaginal approach is the most accurate for the diagnosis.
- Follicle number per ovary (FNPO) should be considered the most effective ultrasound marker to detect polycystic ovarian morphology (PCOM) in adults.
- Follicle number per ovary (FNPO) ≥ 20 in at least 1 ovary should be considered the threshold.



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Polycystic Ovarian Syndrome

Risk assessment

1. Cardiovascular disease

- Women with PCOS should be considered at increased risk of cardiovascular disease and potentially of cardiovascular mortality and should be assessed for cardiovascular disease risk factors
- All women with PCOs, regardless of age and BMI should have:
  - ✔ Blood pressure measured once a year
  - ✔ Lipid profile at time of diagnosis

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Polycystic Ovarian Syndrome

***Risk* assessment**

2. Impaired glucose and type 2 diabetes risk

- Regardless of age and BMI, women with PCOS have an increased risk of impaired fasting glucose and type 2 diabetes.
  - Glycemic status should be assessed at time of diagnosis and reassessed every 1-3 years depending on additional individual risk factors
  - An 75-gr OGGT most accurate test; if unable to be done then fasting glucose and/or HBa1c can be done.

- Women with type 1 and type 2 diabetes have an increased risk of PCOS, and screening should be considered in individuals with diabetes.

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Polycystic Ovarian Syndrome

Risk assessment

3. Obstructive sleep apnea

- Women with PCOS should be assessed for symptoms of obstructive sleep apnea (ie, snoring in combination with waking un-refreshed from sleep, daytime sleepiness, or fatigue) and if present, screen with validated tools or refer for assessment.

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Polycystic Ovarian Syndrome

Risk assessment

4. Endometrial hyperplasia and cancer

- Markedly higher risk of developing endometrial hyperplasia and endometrial cancer; although their overall risk is low and routine screening is **NOT** recommended
- Long-standing untreated amenorrhea, higher weight, type 2 diabetes, and persistent thickened endometrium are additional to PCOS as risk factors for endometrial hyperplasia and endometrial cancer
  - Women with PCOS should be informed of preventative strategies including weight management, cycle regulation

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Polycystic Ovarian Syndrome

Goals of therapy

- Amelioration of hyperandrogenic features (hirsutism, acne, scalp hair loss)
- **Management of underlying metabolic abnormalities and reduction of risk factors for type 2 diabetes and cardiovascular disease**
- Prevention of endometrial hyperplasia and carcinoma, which may occur as a result of chronic anovulation
- **Contraception for those not pursuing pregnancy, as women with oligomenorrhea ovulate intermittently and unwanted pregnancy may occur**
- Ovulation induction for those pursuing pregnancy

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Polycystic Ovarian Syndrome

Level of androgenic activity of progestins in contraceptive pills	
High	Nogestrel
	Levonorgestrel
Middle	Norethindrone
	Noretrhindrone acetate
Low	Ethynodiol
	Norgestimate
	Desogestrel
	Drospirenone
	Dienogest

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Polycystic Ovarian Syndrome

Pharmacological therapy

2. Metformin alone

- Metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m^2 for metabolic outcomes including insulin resistance, abnormal glucose, and lipid profile
- Mild adverse effects, including gastrointestinal side-effects, are generally dose dependent and self-limiting.
- Starting at a low dose, with 500 mg increments 1-2 weekly and extended-release preparations, may minimize side effects and improve adherence.

Polycystic Ovarian Syndrome

Pharmacologic therapy

3. Metformin along with oral contraceptives

- OCP could be used over metformin for management of hirsutism and irregular menstrual cycles.

- In combination with the COCP, metformin may be most beneficial in high metabolic risk groups including those with a BMI > 30 kg/m^2, diabetes risk factors, impaired glucose, or high-risk ethnic group

Polycystic Ovarian Syndrome

Pharmacologic therapy

4. Anti-androgen therapy

- In combination with effective contraception, anti-androgens could be considered to treat hirsutism in women with PCOS, if there is a suboptimal response after a minimum of 6 months of OCP and/or cosmetic therapy.
  - Spironolactone at 25-100 mg/day appears to have lower risks of adverse effects.
  - Finasteride has an increased risk of liver toxicity.

Polycystic Ovarian Syndrome

Pharmacologic therapy

5. Weight loss medications

- Anti-obesity medications could be considered, in addition to active lifestyle intervention, for the management of higher weight in adults with PCOS as per general population guidelines.
- Ensure concurrent effective contraception when pregnancy is possible for women who take GLP-1 receptor agonists, as pregnancy safety data are lacking.

CASE #2

54 y/o Women with PMH of **HTN, T2DM, CAD** who presents today with complains of hot flashes that started 2 years ago, happening multiple times a day affecting her normal activities. **LMP 18 months ago.**

- **PMH:**

- Controlled HTN, taking Lisinopril 20 mg daily.
- MI 2 years ago s/p PCI. Currently asymptomatic. Following with cardiology.
- T2DM, controlled. Hba1c 5.4%. Taking Jardiance 25 mg daily.
- Routine mamogram 1 year ago and normal.
- No history of thrombotic events.

MENOPAUSE AND HORMONAL THERAPY

MENOPAUSE

DEFINITIONS/DIAGNOSIS

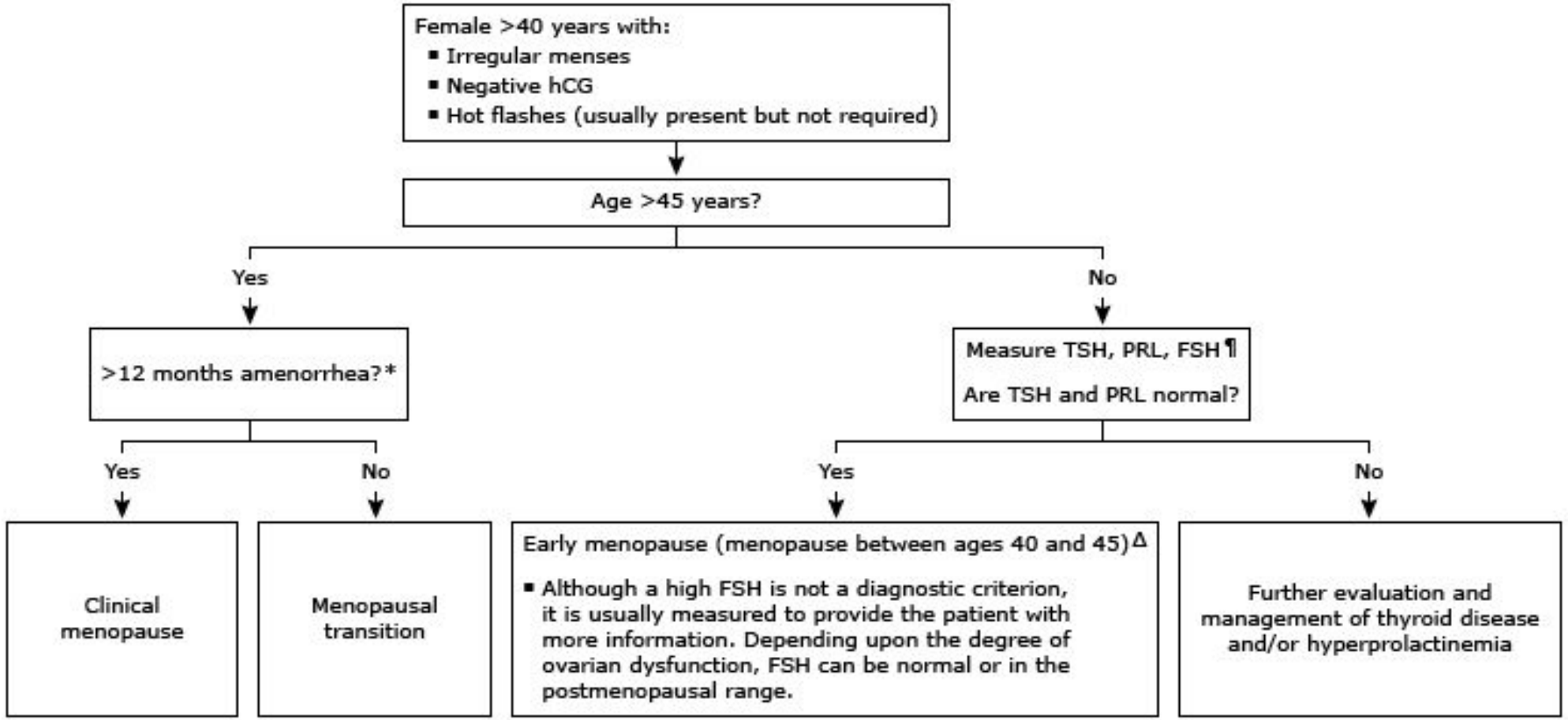
- In a woman with an intact uterus, menopause is a **clinical diagnosis** based upon **cessation of menses for at least 12 months.**

- In women having undergone a hysterectomy but not bilateral oophorectomy, **elevated FSH levels and estradiol concentrations <20 pg/mL** on several occasions support but do not confirm the diagnosis

- With radiotherapy- or chemotherapy-induced menopause, it is important to recognize that ovarian function may resume after 12 months of amenorrhea, depending on the age of the woman and the dose and duration of treatment.

Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015; 100:3975

Evaluation of suspected menopause in females >40 years



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MENOPAUSE

Health Considerations

When women present during the menopausal transition, it is recommended to use this opportunity to address **bone health, smoking cessation, alcohol use, cardiovascular risk assessment and management, and cancer screening and prevention.**

- Decrease morbidity and mortality from CVD optimizing diet and exercise and management of HTN, diabetes, hyperlipidemia.
- Adequate intake of calcium and vitamin D will minimize bone loss and reduce the risk of falls and fractures.
- For postmenopausal women 65 years of age and at high risk of osteoporosis, dual-energy x-ray absorptiometry assessment of bone mineral density contributes to risk assessment.

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MENOPAUSE

Therapy

MHT

- For menopausal women **< 60 years** of age or **less than 10 years since menopause** with bothersome VMS who do **NOT** have contraindications or excess cardiovascular or breast cancer risks, start Estrogen Therapy (ET) for those without a uterus and Estrogen Progesterone therapy (EPT) for those with a uterus.

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MENOPAUSE

Benefits of MHT

- **ET is the most effective treatment for VMS and improving QOL in symptomatic women.**
- Reduces hot flash frequency by approximately 75% and severity by 87%, compared with 50% with placebo
- **Improves symptoms of overactive bladder and recurrent urinary tract infections.**
- Fewer sleep disturbances and may improve mild to-moderate depressive symptoms during or shortly after the menopause transition.
- **Arthralgia Joint pain or stiffness and general aches or pains were improved.**

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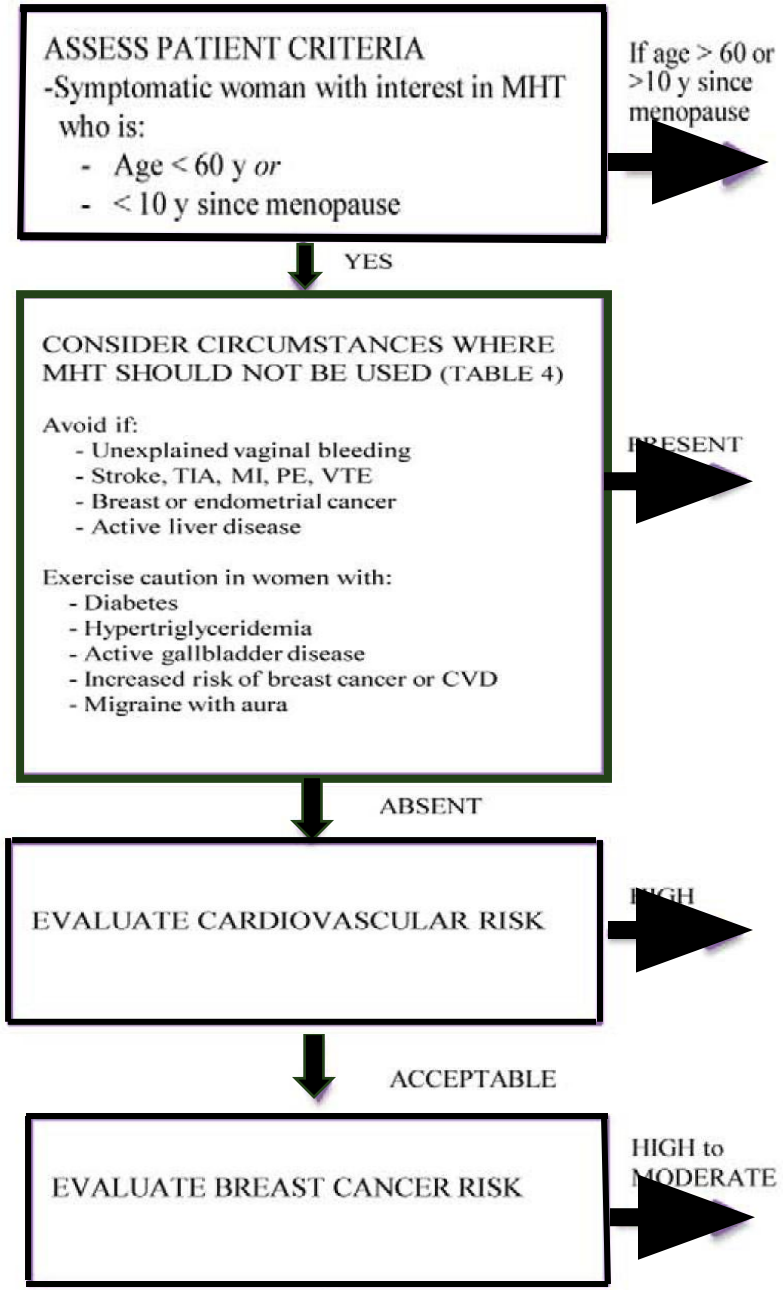
MENOPAUSE



Evaluating CVD risk in females contemplating MHT

10-year CVD risk	Years since menopause onset
	<10 years
Low (<5%)	MHT ok
Moderate (5 to 10%)	MHT ok (choose transdermal)
High (>10%)*	Avoid MHT

CVD risk calculated by ACC/AHA Cardiovascular Risk Calculator. Methods to calculate risk and risk stratification vary among countries.

Breast cancer cutoffs for counseling before recommending MHT

Risk category*	5-year NCI or IBIS breast cancer risk assessment (%)	Suggested approach
Low	<1.67	MHT ok
Intermediate	1.67 to 5	Caution¶
High	>5	Avoid

MHT: menopausal hormone therapy; NCI: National Cancer Institute; IBIS: International Breast Intervention Study.

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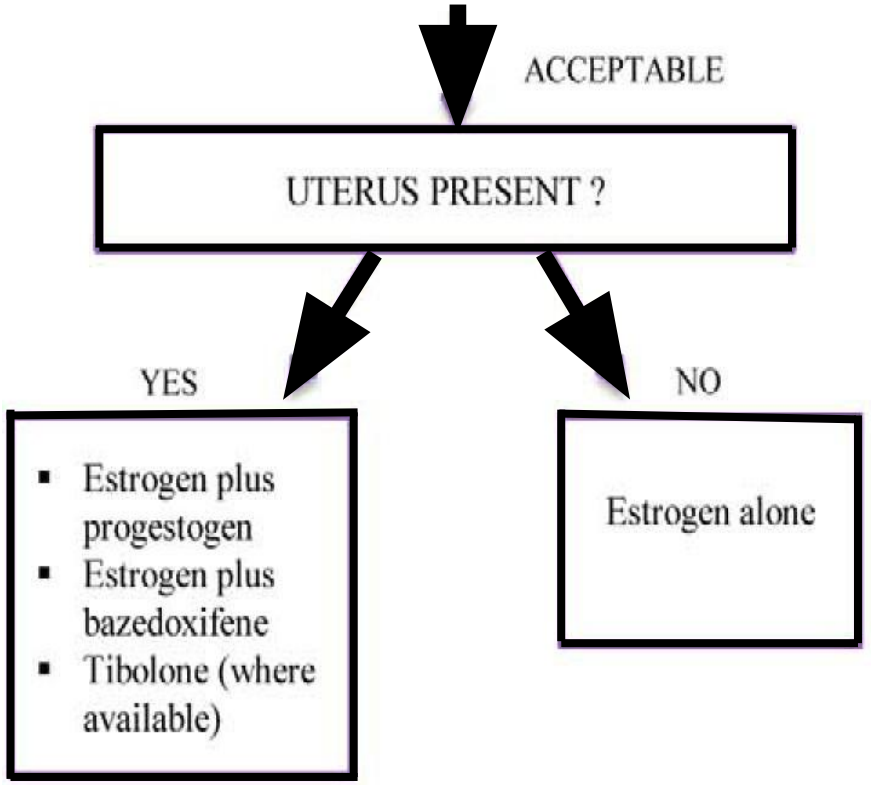
MENOPAUSE



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ESTROGEN PREPARATIONS

Drug and United States brand name	Available strengths
Estrogen preparations and doses for the management of vasomotor symptoms	
Oral estradiol*	
Estrace¶	0.5, 1, 2 mg
Oral esterified estrogen*	
Menest	0.3, 0.625, 1.25 mg
Oral CEEs*	
Premarin	0.3, 0.45, 0.625, 0.9, 1.25 mg
Oral estrogen-progesterone combination	
Bijuva	0.5 mg estradiol/100 mg progesterone, 1 mg/100 mg
Oral estrogen-progestin combinations	
Activella, Amabelz, Mimvey¶	0.5 mg estradiol/0.1 mg norethindrone acetate, 1 mg/0.5 mg
Angeliq	0.5 mg estradiol/0.25 mg drospirenone, 1 mg/0.5 mg
Prempro△	0.3 mg CEE/1.5 mg medroxyprogesterone, 0.45 mg/1.5 mg, 0.625 mg/2.5 mg, 0.625 mg/5 mg
Fyavolv, Jinteli¶	2.5 mcg ethinyl estradiol/0.5 mg norethindrone acetate, 5 mcg/1 mg
Oral CEEs and bazedoxifene	
Duavee	0.45 mg CEE/20 mg bazedoxifene
Estradiol patches*	
Alora (twice weekly)	0.025, 0.075, 0.1 mg per day
Minivelle, Lyllana¶ (twice weekly)	0.025, 0.0375, 0.05, 0.075, 0.1 mg per day
Vivelle-Dot, Dotti¶ (twice weekly)	0.025, 0.0375, 0.05, 0.075, 0.1 mg per day
Climara¶ (weekly)	0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 mg per day
Menostar (weekly)	0.014 mg per day
Estrogen-progestin patches	
Combi-Patch (twice weekly)	0.05 mg estradiol/0.14 mg norethindrone, 0.05 mg/0.25 mg per day
Climara Pro (weekly)	0.045 mg estradiol/0.015 mg levonorgestrel per day

ESTROGEN PREPARATIONS

Topical gel*	
EstroGel 0.06%	0.75 mg estradiol per pump
Elestrin 0.06%	0.52 mg estradiol per pump
Divigel 0.1%¶	0.25, 0.5, 1 mg estradiol per pouch
Topical spray*	
EvaMist	1.53 mg estradiol per spray
Intravaginal rings*	
Femring	0.05 mg estradiol per day over 3 months, 0.1 mg estradiol per day over 3 months
Depot options (oil, intramuscular)	
Estradiol cypionate	
Depo-Estradiol	5 mg/mL (5 mL)
Estradiol valerate	
Delestrogen	10, 20, or 40 mg/mL (all 5 mL)
Vaginal estrogen preparations for treatment of genitourinary atrophy (inadequate dose to relieve vasomotor symptoms)	
Vaginal ring	
Estring	7.5 mcg estradiol per day, released over 3 months
Vaginal tablet	
Vagifem, Yuvafem¶	10 mcg estradiol per vaginal tablet
Imvexxy	4 mcg or 10 mcg per vaginal softgel insert
Vaginal cream	
Estrace 0.01%¶	0.1 mg estradiol per gram cream
Premarin vaginal	0.625 mg CEE per gram cream

MENOPAUSE

Monitoring during therapy

- Regular clinical follow-up, initially, within 1 to 3 months after starting MHT, and then every 6 to 12 months, depending upon the individual (and health care system), allows for monitoring efficacy and side effects (abdominal/pelvic pain, mastalgia, metrorrhagia, weight gain, mood changes, blood pressure), and if necessary, making treatment adjustments.

- Recommendation is that the decision to continue MHT be revisited at least annually, targeting the shortest total duration of MHT consistent with the treatment goals and evolving risk assessment of the individual woman.

Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015; 100:3975

MENOPAUSE

Symptom/Condition When MHT Started	Approach to Resolution
Persistent, intolerable VMS	Switch mode of administration or adjust dose of estrogen and/or progestogen.
Hot flashes that persist after treatment adjustment	Consider another etiology of flashes (Table 2). Ensure absorption: if transdermal, consider serum estradiol determination.
Bleeding: approach depends on time since menopause, MHT regimen, duration of therapy, duration and character of bleeding	Sequential regimen may be more appropriate for recently menopausal (<2 y), because unscheduled bleeding with continuous combined MHT can be problematic. Persistent irregular bleeding (>6 mo) should be evaluated for endometrial pathology; if obese, diabetic, or having family history for endometrial cancer, evaluate sooner. Atrophic endometrium in women more remote from menopause may respond to increased estrogen dose if otherwise appropriate.
Breast tenderness	Usually responds to a reduction in estrogen dose or change in progestogen preparation. CEE/BZA may improve symptoms. Changing to tibolone may be helpful in women who develop mastalgia on conventional MHT.
Baseline TG level >200 mg/dL	Review family history and seek contributing factors. Transdermal ET is preferred. If oral estrogen is selected, monitor serum TG levels 2 wk after starting therapy.
Hypothyroid on thyroid replacement	Monitor TSH 6 to 12 wk after starting oral MHT; T_4 dose may need to be increased (209).

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Comparison of FDA-approved MHT with custom-compounded bioidentical HT

	MHT (FDA approved)	BIH (unregulated)
Goal of intervention	Treatment: Clinicians prescribe estrogen to treat symptoms (primarily vasomotor) They add progestin only for females with a uterus to prevent endometrial hyperplasia	Replacement: Clinicians prescribe replacing multiple sex steroids with the goal of restoring levels to the premenopausal range Progesterone is often recommended for all females, even those without a uterus
Pretreatment testing	No pretreatment testing is required Baseline hormones do not predict dose requirements	Extensive salivary or blood testing is required
Biochemical testing for monitoring	This is rarely needed	Routine salivary or blood testing to monitor and adjust doses is required
FDA approval status and concerns	FDA-approved estrogens and progestins, including 17-beta estradiol and progesterone, are required to: 1. Demonstrate sufficient purity, potency, efficacy, and safety for approval 2. Have a failure rate of <2% in quality and potency tests 3. Have indications (hot flashes, vaginal atrophy, prevention of bone loss) 4. Be supported by well-conducted RCTs 5. Have package inserts that provide extensive product information, which may include black box warnings 6. Have all adverse events reported to the FDA both before approval and after marketing 7. E3 not approved	Compounded bioidenticals have: 1. No requirement to prove efficacy or safety before use 2. No requirement for routine monitoring for purity or potency (sporadic assessments indicate high failure rates) 3. Unsupported claims that the approach is safer and more effective than conventional HT 4. No requirement for package inserts or black box warnings 5. No listed concerns about possible overdosing or underdosing or the risk of higher estrogen/inadequate progesterone exposure 6. No requirement for adverse event reporting 7. E3 is a commonly included agent

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MENOPAUSE

Non-hormonal therapies for VSM

- For **mild or less bothersome hot flashes**, recommendation is to follow a series of steps that do not involve medication, such as **turning down the thermostat, dressing in layers, avoiding alcohol and spicy foods, and reducing obesity and stress**.

- For women seeking pharmacological management for **moderate to severe VMS** for whom MHT is contraindicated, or who choose not to take MHT, option is to use **selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin or pregabalin** (if there are no contraindications).

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SSRIs/SNRIs

- Clinical trials of paroxetine, venlafaxine, desvenlafaxine, citalopram, and escitalopram demonstrated statistically significant efficacy with a reduction of frequency of hot flashes ranging from 25 to 69%.
- Other agents such as sertraline and fluoxetine are associated with non-statistically significant trends toward the reduction of hot flashes.
- The only FDA-approved agent in this class is low-dose paroxetine mesylate, but others have been used off-label in the United States.

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GABAPENTIN

- Four RCTs confirmed moderate efficacy in relieving hot flashes. On the basis of clinical experience, women whose hot flashes occur primarily at night respond well to a single bedtime dose.
- Individual dose requirements vary widely, as determined by empiric dose escalation, and range from 300 to 1200 mg.
- When used during the day, gabapentin may result in a level of lethargy that is not tolerable.

PREGABALIN

- In one 6-week RCT, pregabalin (75–150 mg twice daily) decreased mean hot flash scores by 65 and 71%, compared with 50% by placebo (242), and was reasonably well tolerated.

Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015; 100:3975

MENOPAUSE

- For those women seeking relief of moderate to severe VMS who are not responding to or tolerating the nonhormonal prescription therapies, SSRIs/SNRIs or gabapentin or pregabalin, a trial of clonidine can be done.

CLONIDINE

- Several RCTs demonstrated that this α-2-adrenergic receptor agonist reduced hot flashes, but less effectively than the SSRI/SNRIs, gabapentin, and pregabalin, and with more side effects.
- Clonidine transdermal patches are preferred over tablets because of more stable blood levels.

Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015; 100:3975

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- For women seeking relief of VMS with over-the-counter (OTC) or complementary medicine therapies, there is lack of consistent evidence for benefit for botanicals, black cohosh, omega-3-fatty acids, red clover, vitamin E, and mind/body alternatives including anxiety control, acupuncture, paced breathing, and hypnosis.

Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015; 100:3975

“When you think of all that a woman's body has to do over the course of her lifetime, going from being prepared to give birth to actually giving birth and then having that whole reproductive system shut down in menopause, the changes, the highs and lows and the hormonal shifts, there is power in that.“

Michelle Obama