

Low libido

Minding menopause

Ease hot flashes, depression

Hot flashes

Depression

while limiting estrogen use

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Antidepressants can improve hormone-related hot flashes and mood problems, with or without supplemental estrogen

Many women and their physicians who prefer to limit estrogen use^{1,2} are turning to antidepressants to treat moderate to severe vasomotor symptoms as well as depression. And for older women with complaints of hormone-related low libido, new evidence and tests are defining the role of testosterone replacement therapies.

This article describes effective, up-to-date psychotropic and hormonal treatments for menopause-related mood and sexual problems. A companion piece ("Physiology 101," page 19) reviews how endocrine changes during menopause affect women's mood and libido.

Case report: Irritable, no interest in sex Anne, age 51, complains of depression and low libido. She says she is irritable and snaps easily at her children and husband. She has no interest in sex and has had no sexual intercourse for 6 months.

She complains of fatigue, dry hair and skin, warm flushes, and painful joints. She has no personal or family history of depression. She is not suicidal but states she doesn't want to live if "this is it."

continued



Table 1

Why mood problems may occur during menopause

| Hypothesis | Explanation |
|---------------|--|
| Psychodynamic | Onset of menopause is a critical life event and a readjustment of self-concept |
| Sociologic | Mood changes are caused by changing life circumstances at menopause ('empty nest,' aging parents, health changes) |
| Domino | Depressed mood is caused by hot flashes due to declining estrogen levels, which cause chronic sleep deprivation with subsequent irritability and memory and mood changes |
| Biochemical | Decreasing estrogen leads to neurochemical changes in the brain (serotonin, dopamine, acetylcholine, GABA, norepinephrine) |

HOT FLASHES: A SPARK FOR DEPRESSION

Women who experience their first depression after age 50 do not fit the usual DSM-IV diagnostic criteria for depression. The Massachusetts Women's Health Study³ found that 52% of women who experience depressed mood in the perimenopause have never had a depression before. This study also found a correlation between a longer perimenopause (> 27 months) and increased risk of depressed mood. At the same time, women who have had a prior depression are 4 to 9 times more likely to experience depressive symptoms during perimenopause than those who have never had a depression before.⁴

Increased mood symptoms may be related to psychodynamic, sociologic, or biochemical factors, or they may result from a domino effect triggered by declining estrogen levels (Table 1). Women who experience vasomotor symptoms such as hot flashes are at 4.6 times greater risk for depression than those who are hot flash-free.⁵

Hot flashes begin on average at age 51, which is also the average age when natural menopause begins. During menopause, most women (82%) experience

hot flashes (suddenly feeling hot and sweating during the day), warm flushes (a sensation of warmth or heat spreading over the skin), and night sweats (Table 2). All women who undergo surgical menopause experience hot flashes.

Hot flashes are moderate to severe for 40% of women who experience them and persist for 5 to 15 years. By definition, moderate to severe hot flashes occur 4 to 10 or more times daily, last 6 to 10 minutes each, and are

often preceded by anxiety, palpitations, irritability, nervousness, or panic.

A marriage under stress Anne says her husband is angry about the lack of sex. She also is worrying about her children leaving for college and about her mother's ill health.

She scores 20 on the Beck Depression Inventory,⁶ indicating mild to moderate depression. Her menstrual periods are regular, but her cycle has shortened from 29 to 24 days. She reports that hot flashes wake her at night, and she hasn't had a good night's sleep in months.

Lab tests show FSH of 25 mIU/mL and inhibin B <45 pg/mL (see Physiology 101, figure 2, page 20). Estradiol is 80 pg/mL, which is not yet in the menopausal range of 10 to 20 pg/mL. Thyroid stimulating hormone (TSH) is normal. The endocrinologic and reproductive diagnosis is perimenopause.

TREATING HOT FLASHES IMPROVES MOOD

Until 2002, estrogen was standard treatment for hot flashes in patients such as Anne. Then the Women's Health Initiative trial^{1,2} reported that estrogen's health risks—heart attack, stroke,

breast cancer, and blood clots—exceeded potential benefits during 5 years of therapy. As a result, fewer women want to take estrogen,⁷ and many doctors are advising patients to get through menopause without hormones if they can.

For mild hot flashes—one to three daily—patients may only need vitamin E, 800 mg/d, and deep relaxation breathing to “rev down” the sympathetic nervous system when a hot flash occurs.

For moderate to severe hot flashes, estrogen is the most effective therapy. Estradiol, 1 mg/d, reduces hot flashes by approximately 80 to 90%.⁸ Many small studies show that patients’ mood often improves as estrogen reduces hot flashes.⁹ The Women’s Health Initiative Quality-of-Life study,¹⁰ however, reported that estrogen plus progesterin did not improve mood in women ages 50 to 54 with moderate-to-severe vasomotor symptoms, though hot flashes were reduced and sleep may have improved.

New drugs of choice. Because of estrogen’s effectiveness in controlling hot flashes, some women and their doctors may choose to use it briefly, such as 18 to 24 months. For others, psychotropics are becoming the drugs of choice for mood disorders with moderate to severe hot flashes.

The serotonin/norepinephrine reuptake inhibitor (SNRI) venlafaxine, 37.5, 75, or 150 mg/d, has been shown to reduce hot flashes by 60% to 70%.^{11,12} A trial is investigating whether duloxetine—also an SNRI—reduces hot flashes. Other useful agents that have been shown to reduce hot flashes by 50% or more include:

- selective serotonin reuptake inhibitors (SSRIs) paroxetine CR, 12.5 mg/d to 25 mg/d,¹³ citalopram, 20 to 60 mg/d,¹⁴ and fluoxetine, 20 mg/d¹⁵
- gabapentin, titrated from 300 mg/d to 900 mg/d.¹⁶

Table 2

Symptoms of menopause related to decreased estrogen

| | |
|--------------|--|
| Brain | Irritability, mood swings, depressed mood, forgetfulness, low sex interest, sleep problems, decreased well-being |
| Body | Hot flashes, vaginal dryness, painful intercourse, fatigue, joint pain, pain with orgasm, bladder dysfunction |

For hot flashes and moderate to major depression, try an SNRI or SSRI first (see Algorithm, page 14), but consider the possible effects on sexual function. All SNRIs and SSRIs have sexual side effects, including anorgasmia and loss of libido in women and men. Among the psychotropics that have been shown to improve hot flashes, gabapentin is the only one that does not interfere with sexual function.

Mood improves, but still no libido You and Ann decide she will try venlafaxine, 75 mg/d, to treat hot flashes and depressed mood. Four weeks later, hot flashes are 50% less frequent and her mood has improved (Beck Depression Inventory score 10). She is feeling much better and wishes to continue taking the antidepressant.

She and her husband attempted intercourse once during the past month. She did not achieve orgasm, despite adequate vaginal lubrication, and did not enjoy the experience. “I still have no libido—zero, or even less,” she says.

TREATING LOW INTEREST IN SEX

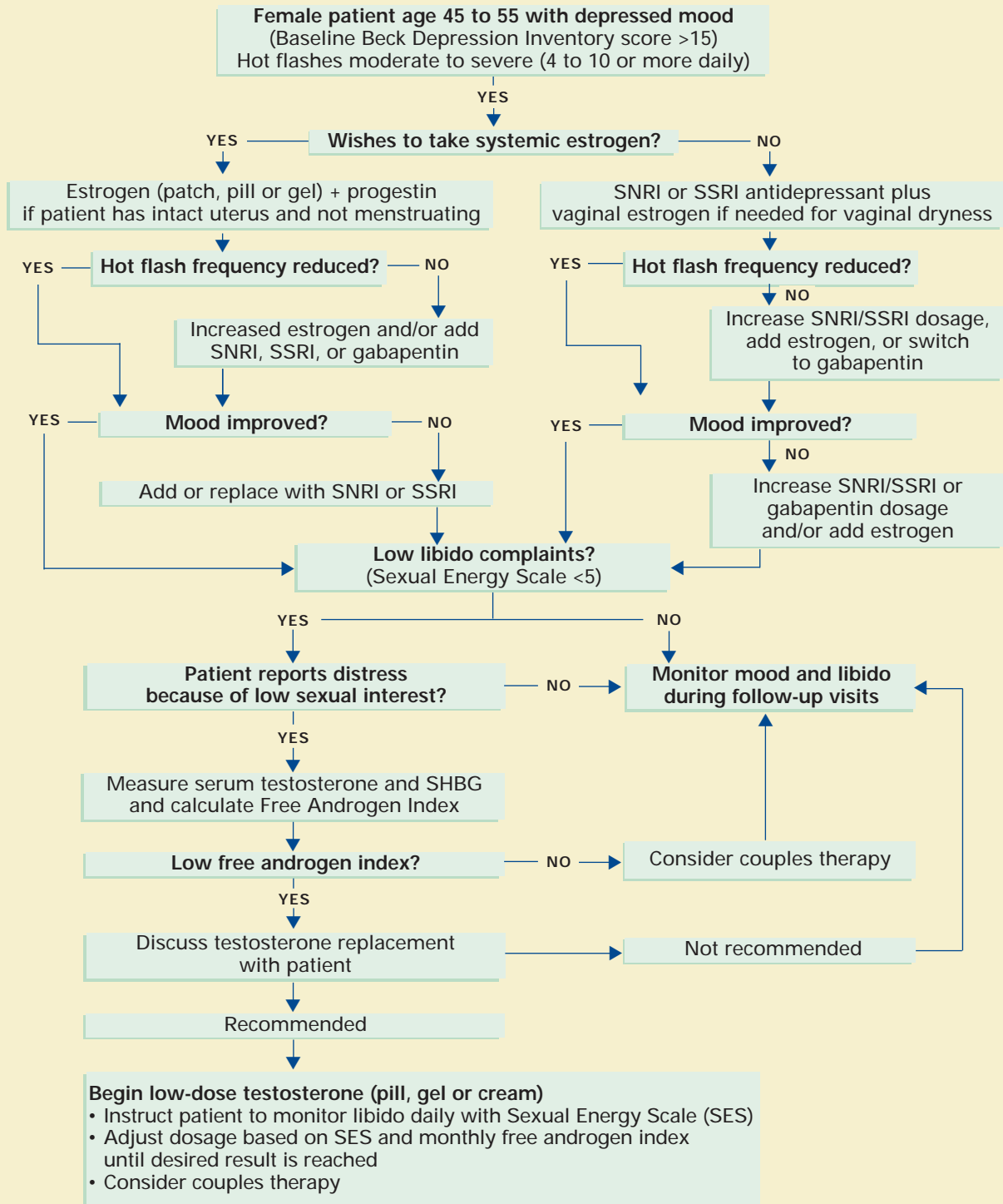
Feeling angry with one’s partner is the number-one reason for decreased sexual desire in all studies. Therefore, consider couples therapy for any partner complaining of loss of interest in sex. In addition, eliminate—if possible—any medications with known sexual side effects, such as SSRIs or beta blockers.

If a woman complains of slow or no arousal, vaginal estrogen and/or oral sildenafil, 25 to 50 mg 1 hour before intercourse, may help.¹⁷ Other



Algorithm

Managing mood and libido problems during perimenopause



agents indicated for men's erectile dysfunction—such as tadalafil and vardenafil—may also increase arousal in women.

Understanding how hormones affect female sexual desire also may help you decide what advice to give Anne.

TESTOSTERONE: NATURE'S APHRODISIAC

Testosterone is the hormone of sexual desire. Other female androgens include androstenedione, androstenediol, 5 α -dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), and its sulfate (DHEA-S). Premenopausal women produce these androgens in the ovaries (25%), adrenals (25%), and peripheral tissues (50%).

Average daily serum testosterone concentrations decline in women between ages 20 and 50. Lower levels are also seen with estrogen replacement therapy or oral contraceptives, lactation, anorexia nervosa, and conditions that reduce ovarian function. Total hysterectomy with bilateral oophorectomy causes a sudden 50% loss of testosterone and an 80% decline in estradiol.¹⁸

Regularly menstruating women in their 40s and early 50s can have very low testosterone levels—at least 50% lower in the first 5 to 7 days of their cycles—than women in their 30s.¹⁹ The rate of low libido increases with age until menopause—from 30% of women at age 30 to about 50% at age 50—then declines to 27% at ages 50 to 59.²⁰ After natural menopause, luteinizing hormone (LH) continues to stimulate ovarian hilar cells and interstitial cells to produce androgens, which is why many women at age 50 have adequate testosterone to sustain sexual desire.

Oral estrogen replacement therapy reduces bioavailable testosterone by 42% on average, which can induce androgen deficiency in a menopausal woman.²¹ The increased estrogen inhibits pituitary LH and decreases stimulation of the androgen-producing cells in the ovary.²²

Female androgen deficiency. A number of papers have been published on female androgen deficiency syndrome (FADS).²³ Its diagnosis requires symptoms of thinning pubic and axillary hair, decreased body odor, lethargy, low mood, diminished well-being, and declining libido and orgasm, despite adequate estrogen but low levels of testosterone and DHEA. Because FADS affects an estimated 50% of women at the menopause, your patients may ask you about this issue.

TREATING TESTOSTERONE DEFICIENCY

Benefits of replacement therapy include improved mood, well-being, motivation, cognition, sexual function related to libido, orgasm, sexual fantasies, desire to masturbate, and nipple and clitoral sensitivity.²⁴ Muscle- and bone-mass stimulation and

decreased hot flashes are also reported.²⁵ Physiologic testosterone

replacement may be indicated for women with androgen deficiency symptoms and low testosterone at menopause.²⁶

Discuss risks with the patient, too. Testosterone may lower beneficial HDL cholesterol, so consider this effect before you give testosterone to a woman with heart disease, HDL < 45 mg/dL, or other cardiac risk factors. For women

with a personal or family history of breast cancer, discuss the risk that the low-dose testosterone could be aromatized into estrogen.

A meta-analysis of eight clinical trials found no changes in liver function in menopausal women taking 1.25 to 2.5 mg/d of methyl testosterone. Liver toxicity has been reported in men using 10-fold higher testosterone dosages.²⁷

At the normal level of testosterone, darkening and thickening of facial hair are rare in light-skinned, light-haired women but can occur in dark-skinned, dark-haired women. Increased irritability, excess energy, argumentativeness, and aggressive behavior have been noted if testosterone levels exceed the physiologic range.

At age 50, one-half of women have low libido; the rate declines to 27% from ages 50-59

continued



Table 3

Free androgen index (FAI) values in women, by age

Replacing a woman's bioactive testosterone to the normal free androgen index range for her age may improve low libido.

How to calculate FAI

Total testosterone in nmol/L (total testosterone in ng/ml X 0.0347 X 100), divided by sex hormone-binding globulin (SHBG) in nmol/L.

| Age | Normal range |
|-----------|--------------|
| 20 to 29 | 3.72 to 4.96 |
| 30 to 39 | 2.04 to 2.96 |
| 40 to 49 | 1.98 to 2.94 |
| 50 to 59+ | 1.78 to 2.86 |

Source: Guay et al, reference 30.

Controlled, randomized studies are needed to assess the effects of long-term use (more than 24 months) of testosterone replacement in women.

Measuring testosterone levels. Serum free testosterone is the most reliable indicator of a woman's androgen status, but accurately measuring testosterone levels is tricky:

- Only 2% of circulating testosterone is unbound and biologically active; the rest is bound to sex hormone-binding globulin (SHBG) or albumin.
- In ovulating women, serum testosterone levels are higher in the morning than later in the day and vary greatly within the menstrual cycle.
- Levels of androgens and estrogen are highest during the middle third of the cycle—on days 10 to 16, counting the first day of menstrual bleeding as day 1.²⁸
- Oral contraceptives decrease androgen production by the ovary and can result in low libido in some women.²⁹

Tests developed to measure testosterone levels in men are not sensitive enough to accurately measure women's naturally lower serum concen-

trations, let alone the even lower levels characteristic of female androgen or testosterone deficiency. New measurements and standardization of normal reference ranges have been developed for women complaining of low libido.³⁰

Tests for androgen deficiency include total testosterone, free testosterone, DHEA, and DHEA-S. Measuring SHBG will help you determine the free, biologically active testosterone level and calculate the free androgen index (FAI) for women (Table 3).³¹

A candidate for testosterone therapy? Now that Anne's mood, sleep, and hot flashes have improved with venlafaxine, she wants help with her lack of sexual interest. You measure her testosterone and SHBG levels and find that her free androgen index is very low at 0.51 (normal range, 1.78 to 2.86).

You and Anne decide to start her on testosterone replacement therapy. You prescribe Androgel, starting at 1/7th of a 2.5-mg foil packet (0.35 mg/d of testosterone), and instruct her to rate her sexual energy daily, using a Sexual Energy Scale.

TESTOSTERONE CHOICES FOR WOMEN

Replacing a woman's bioactive testosterone level to the normal free androgen index range for her age group may improve low libido. Some low-dose testosterone replacement options include:

- methyl testosterone sublingual pills, 0.5 mg/d, made by a compounding pharmacy or reduced dosages of oral pills made for men. If you prescribe methyl testosterone, routine lab tests will not accurately measure serum testosterone levels—unless you order the very expensive test that is specific for methyl testosterone.
- 2% vaginal cream, applied topically to increase clitoral and genital sensitivity. It may increase blood levels moderately through absorption
- Androgel, a topical testosterone approved for men. As in Anne's case, start with 0.35 mg/d or 1/7th of the 2.5-mg packet (ask the pharmacist to place this amount in a syringe). Instruct the

patient to apply the gel to hairless skin, such as inside the forearm. Effects last about 24 hours, and you can measure serum levels accurately after 14 days. Vaginal throbbing—a normal response—may occur within 30 minutes of testosterone application.

The FDA is considering other testosterone preparations—including a testosterone patch for women and a gel in female-sized doses.

Measuring sexual interest. To monitor therapeutic response, ask the patient to use the Sexual Energy Scale (Figure 1) daily.^{32,33} Instruct her to define her “10” as the time in life when she had the most fulfilling sexual life, was the most easily aroused, had the most sexual pleasure, and the best orgasms. Her “1” would be when she felt the worst sexually and had the least desire.

Supplemental estrogen. If you prescribe estrogen plus testosterone (Estratest), start with Estratest HS, which contains 0.625 mg esterified estrogens and 1.25 mg methyl testosterone. If the patient is postmenopausal and has not had a hysterectomy, add a progestin to prevent endometrial hyperplasia.

Women with vaginal dryness also need supplemental estrogen, which can be applied vaginally (such as Premarin cream or Estrace cream). A vaginal lubricant is not sufficient to avoid age-related vaginal atrophy, which may make intercourse difficult or impossible.

Libido improves modestly Ann returns in 4 weeks with gradually improving sex drive (Sexual Energy Score is 5). She had intercourse twice that month without “dreading it” but also did not enjoy it or reach orgasm. You have told her that venlafaxine may slow or prevent orgasm, but she wants to keep taking it. She says her marriage is improving.

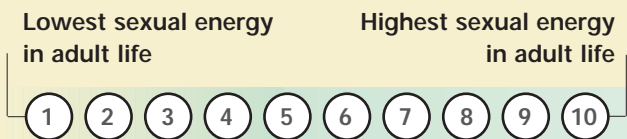
You order repeat testosterone and SHBG blood levels and find the free androgen index has

Figure 1

How to use the Sexual Energy Scale to monitor response to therapy

This scale is designed to screen patients experiencing sexual dysfunction induced by a substance or general medical condition. It can be given at every visit (including at baseline) to evaluate a patient’s sexual energy, which includes ease of arousal, sexual pleasure, orgasms, interest in sex, sexual fantasies, and sexual fulfillment.

Patient instructions: On a scale of 1 to 10, circle the number that indicates your current sexual energy.



Source: Reprinted with permission. Copyright 1997 JK Warnock, Department of Psychiatry, University of Oklahoma Health Sciences Center, Tulsa.

improved to 1.10, which is still low. You increase Androgel dosage to 1/5th of a 2.5 mg packet (0.5 mg/d) and continue to monitor Sexual Energy Scale ratings at monthly follow-up visits. Anne has set a rating of 7 to 8 as her target. She says she appreciates your help with—as she puts it—“this embarrassing problem.”

For additional information, see “Physiology 101: How endocrine changes affect mood and libido during menopause,” page 19.

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During perimenopause, 50% of women consult their physicians about mood, irritability, insomnia, and sexual symptoms. Hot flashes and depressed mood respond to estrogen but also to SSRIs or SNRIs. Testosterone replacement may help women with low libido and low serum testosterone levels.

BottomLine

Related resources

- ▶ The Women's Health Site. Duke Academic Program in Women's Health. www.thewomenshealthsite.org. Accessed March 23, 2005.
- ▶ Massachusetts General Hospital Center for Women's Mental Health. www.womensmentalhealth.org. Accessed March 23, 2005.

DRUG BRAND NAMES

Citalopram • Celexa
 Conjugated estrogens • Premarin
 Estadiol/M-testosterone • Estratest
 Fluoxetine • Prozac
 Gabapentin • Neurontin

Paroxetine • Paxil
 Sildenafil • Viagra
 Tadalafil • Cialis
 Venlafaxine • Effexor
 Vardenafil • Levitra

DISCLOSURES

Dr. Brizendine reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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PHYSIOLOGY 101 How endocrine changes affect mood and libido during menopause

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Medicine's understanding of menopause's physiologic and psychological consequences is changing, just as the "baby-boom" generation is navigating this passage called the change of life. Many midlife women are unaware that the menopause transition does not begin around age 50 but spans 30 years—from ages 35 to 65. Natural menopause begins 15 years before and ends 15 years after menstruation ceases—as the brain and tissues adjust to first fluctuating then decreased estrogen levels. It occurs in three phases—early menopause, perimenopause, and late menopause—that reflect a progression of hormone changes.

EARLY MENOPAUSE: OVULATION ACCELERATES

At approximately age 35, the ovaries start producing lower levels of inhibin—a glycoprotein that inhibits pituitary production of follicle-stimulating hormone (FSH) (Figure 2, page 20). Less inhibin means less negative feedback to the pituitary and increased pituitary FSH production. More FSH means more activin—an ovarian glycoprotein that stimulates ripening of eggs—and so ovulation begins to accelerate at approximately age 36. Activin stimulates more and more eggs in the ovary to develop faster and faster.

By age 37, the ovarian egg reserve starts to decline, and—because FSH has increased—the follicle is driven to produce greater amounts of estrogen. Estrogen serum levels in fertile women average 100 pg/mL. During perimenopause, estrogen levels sometimes soar to 300, 400, or even 500 pg/mL, then may crash down to 50 to 80 pg/mL. These wild fluctuations are thought to trigger headaches, sleep disturbance, mood swings, and sexual difficulties in some women.

Hysterectomy and mood symptoms. Women in their

early 40s are exposed to high levels of estrogen in some menstrual cycles and low levels in others. Excess estrogen thickens the endometrium—causing heavier bleeding—and stimulates fibroid growth, which is the leading reason for hysterectomies.

One in four American women undergoes surgical menopause. The average age of the 700,000 U.S. women who undergo hysterectomy each year is 40 to 44. Women who have had a hysterectomy with oophorectomy are likely to experience menopause-related mood disorders and sexual adjustment problems earlier than women who undergo a more gradual natural menopause.

PERIMENOPAUSE: HOT FLASHES, DRY VAGINA

At ages 45 to 55, most women (90%) who have not had an oophorectomy start to cycle irregularly, tending at first toward shorter cycles and then skipping periods. Some periods are heavier and some lighter than usual. The remaining 10% of women continue to cycle regularly until their menstrual periods stop abruptly.

Many women notice temperature dysregulation during perimenopause. When they exercise, their cool-down times may double. Menopausal symptoms such as hot flashes occur when estrogen levels drop below the point that some researchers call a woman's "estrogen set point."

Screening for estrogen decline. When you see a patient in your office, you can often determine whether her affective symptoms—irritability, mood swings, depressed mood, and forgetfulness—might be related to estrogen decline by asking two screening questions:

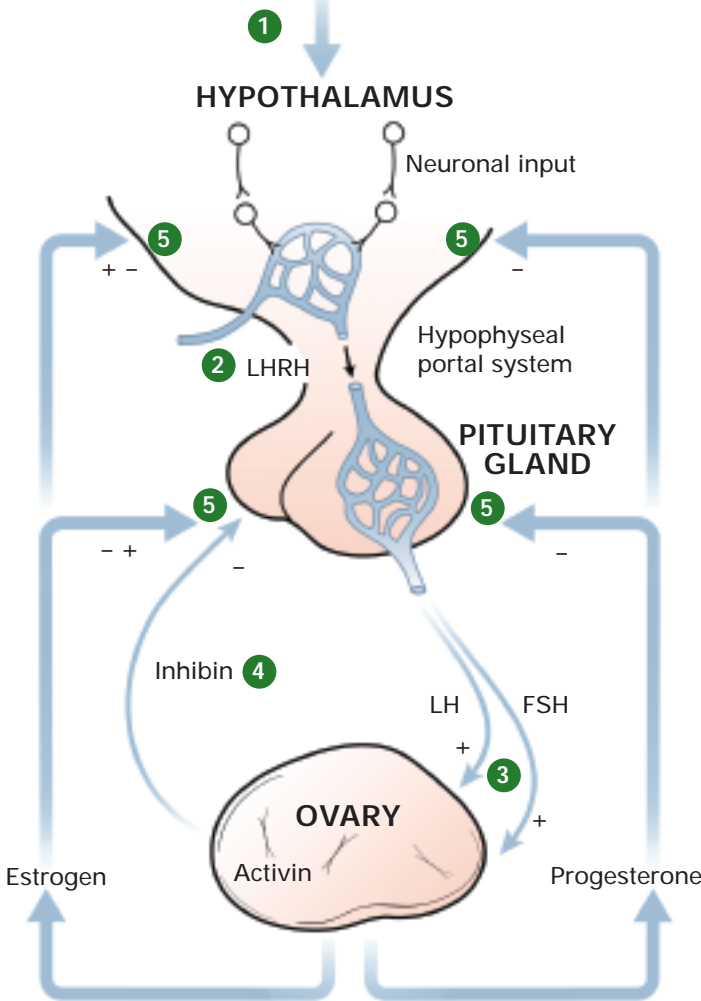
- Are you having any warm flushes or hot flashes?
- Do you have vaginal dryness?

continued

Figure 2

Normal female reproductive cycle: The rhythm of the hypothalamic-pituitary-ovarian axis

INTERNAL & ENVIRONMENTAL STIMULI



- 1 Hypothalamic neurons produce pulses of luteinizing hormone releasing hormone (LHRH)—formerly called gonadotropin-releasing hormone (GnRH)—under the influence of internal and environmental stimuli and circulating levels of estrogen and progesterone.
- 2 LHRH passes through the hypophyseal portal system and stimulates the pituitary gland to secrete follicle stimulating hormone (FSH) and luteinizing hormone (LH).
- 3 Circulating levels of FSH and LH stimulate (+) the ovary to produce activin, a glycoprotein that activates eggs in the follicle and promotes ovulation. FSH and LH also stimulate the secretion of estrogen (estradiol), progesterone, and testosterone.
- 4 At the same time, inhibin—another glycoprotein produced by the ovary—inhibits (-) the production of FSH by the pituitary gland.
- 5 Through a feedback loop, circulating estrogen and progesterone act on LHRH in the hypothalamus to increase (+) or decrease (-) the pulsatility (rhythm) of the hormones controlling the menstrual cycle. They also modulate the production of FSH and LH by the pituitary gland.

Illustration for CURRENT PSYCHIATRY by Jennifer Fairman

LATE MENOPAUSE: ESTROGEN LOW, MOOD UP

During late menopause, approximately age 55 and older, women commonly complain of vaginal dryness, hot flashes, night sweats, sleep problems, and fatigue. Sexual interest may decrease, and a decline in sexual activity can become a problem for some couples. Asking “How is your sex life?”

often will open a discussion of the couple’s sexual and emotional relationship.

Other physiologic changes caused by estrogen and androgen deficiency include thinning body hair—including pubic, axillary, and leg hair—decreased body odor, thinning skin, wrinkling skin, and decreasing bone density.

Table 4

Three phases of menopause: A 30-year process

| Early Ages 35 to 45 | Middle (perimenopause) Ages 46 to 55 | Late Ages 56 to 65+ |
|--|--|---|
| <p>Physiologic changes</p> <p>Ovary starts producing less inhibin 15 years before menses stop</p> <p>Decreased inhibin increases FSH and stimulates follicle to produce more estrogen</p> <p>Increased estrogen thickens endometrium and leads to heavier menstrual bleeding and increased risk of fibroids</p> <p>Increased FSH produces more activin, which makes eggs develop faster and accelerates egg depletion</p> | <p>Irregular menstrual cycles, with shorter cycles, skipping periods for 90% of women</p> <p>Some periods heavier, some lighter than usual</p> | <p>Depletion of eggs and follicle</p> |
| <p>Lab values</p> <p>Menses: Normal</p> <p>FSH day 3: 10-25 mIU/mL</p> <p>Estradiol day 3: 40-200 pg/mL</p> <p>Inhibin B day 3: Varies</p> | <p>Cycle shorter (24-26 days)</p> <p>20-30 mIU/mL</p> <p>40-200 pg/mL</p> <p><45 pg/mL</p> | <p>None for >12 months</p> <p>50-90 mIU/mL</p> <p>10-20 pg/mL</p> <p>0</p> |
| <p>Symptoms</p> <p>Headaches, sleep disturbances, mood swings, urinary problems, sexual complaints</p> | <p>Warm flushes, hot flashes, night sweats in 82% of women (moderate to severe in 40%)</p> | <p>Vaginal dryness, hot flashes, night sweats, sleep problems, fatigue, sexual interest changes, thinning body hair (pubic, legs, axillary), decreased body odor, thinning skin, wrinkling skin, decreasing bone density, BUT mood starts to stabilize</p> |

FSH: follicle-stimulating hormone

Urinary symptoms. Bladder problems and urinary symptoms are persistent menopause symptoms for 75% of women. Review the urinary system, and remember that women often do not volunteer that they are having incontinence problems. Embarrassment because of involuntary urine loss during sex may be the cause of a woman's "loss of interest" in sexual intercourse.

Despite sometimes-difficult physiologic changes, the good news for many women is that mood symptoms start to stabilize after perimenopause (Table 4). Women whose moods are very responsive to hormonal fluctuations—such as those with severe premenstrual syndrome or premenstrual dysphoric disorder—sometimes get much better after menopause.