

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

Menopausal

MEDICINE

VOLUME 19, NUMBER 3 — AUGUST 2011

FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

Impact of obesity and weight loss on urinary and bowel incontinence symptoms in women

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Obesity has become a worldwide problem, recognized as a “global epidemic” by the World Health Organization (WHO) in

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Acknowledgement

Dr Richter's work was partially funded by 2K24-DK068389 from the National Institute of Diabetes and Digestive and Kidney Diseases.

Disclosures

Dr Ballard reports no commercial or financial relationships relevant to this article. Dr Richter reports that she has served as a consultant to GlaxoSmithKline, IDEO, Pfizer, Uromedica, and Xanodyne and on the speakers bureau of Pfizer, and has received research grants from Astellas Pharma.

1997.¹ In 1990, among US states participating in the Behavioral Risk Factor Surveillance System, none had obesity rates $\geq 15\%$. In contrast, 2009 data demonstrated that only one state had obesity rates less than 20%.² Currently, the combined age-adjusted prevalence estimates for US adults classified as overweight or obese (body mass index [BMI] ≥ 25 kg/m²) is 67.1%,³ and for women is 64.1%.⁴ Of women 60 years of age and older, 68.6% (95% confidence interval [CI], 64.4-72.7) are overweight or obese. Obesity, one of the leading health issues in the United States, results in approximately 300,000 deaths per year,⁵ and it cost the nation about \$147 billion in medical care costs in 2008.⁶

Obesity is associated with higher rates of hypertension, diabetes mellitus, hypercholesterolemia, osteoarthritis, coronary artery disease, and other chronic medical conditions.⁴ In recent years, studies have identified obesity as an independent risk factor for pelvic floor disorders, including urinary incontinence (UI) and fecal incontinence (FI), which are complex and underdiagnosed problems with

physiologically and socially devastating consequences.⁷ Additionally, evidence demonstrates that weight loss and lifestyle changes help to control UI⁷⁻⁹ and, possibly, improve FI symptoms.¹⁰

This article summarizes the current literature describing the effects of obesity and weight loss as they relate to urinary and fecal incontinence in women.

Pathophysiology of pelvic floor disorders

Although the exact etiology of pelvic floor disorders is unknown, investigators have demonstrated that individuals with excess body weight have increased intra-abdominal pressure.¹¹ This, in association with upright posture, increases the pressure on the pelvic floor, including increased bladder and bowel pressure. This sequence of events is believed to potentially lead to stress UI (SUI, leakage associated with activities such as coughing, running, and laughing) and may aggravate symptoms of detrusor instability and urgency urinary incontinence (UUI, leakage associated with a strong urge that is difficult to defer). Obesity may

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The ASRM is pleased to acknowledge the generous contribution of Pfizer toward the publication of this newsletter.



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Improving quality of life for menopausal women

"Getting older is not for sissies," my mother says, "but it beats the alternative."

In this issue of *Menopausal Medicine*, we explore 2 quality-of-life issues that affect millions of older women: incontinence and depression. It may be hard to believe, but urinary incontinence alone may affect 50% of middle-aged women and can cost up to \$30 billion per year in medical charges. Depression is similarly a common problem for women transitioning into menopause, with up to 20% of women affected during their lifetime, according to some estimates.

Both urinary and fecal incontinence are embarrassing problems for postmenopausal women. These disorders seem to be even more prevalent now, with the growing obesity epidemic in America. In this issue, Alicia C. Ballard, MD, and Holly E. Richter, PhD, MD, explore the relationship between obesity and pelvic floor disorders. They present hopeful information about how weight loss can help improve incontinence symptoms.

Surprisingly, women who never had a history of depression previously may develop mood changes during the menopause transition. Hot flashes and sleep disturbances occurring during this time may muddy the water and contribute to mood disorders. Kimberly Albert, Christina Broadwell, MD, and Paul Newhouse, MD, explain how the perimenopausal period—a time when hormones may be rapidly fluctuating—is a particularly dangerous period with regard to mood disturbances. They discuss estrogen's regulatory effects on mood, ovarian hormone variability during the menopausal transition, and treatment options for menopausal women with mood dysregulation.

Getting older need not mean a diminished quality of life.

Cynthia K. Sites, MD



also contribute an element of chronic strain and stretching, thus weakening the muscles, nerves, and other pelvic floor structures involved in bladder and bowel function.¹²

Urinary incontinence

Urinary incontinence (the inability to control urinary flow) affects nearly 50% of middle-aged and older women,⁹ and treatment costs an estimated \$19.5 to \$30 billion per year.¹³ This is greater than the annual costs of treatment for breast, ovarian, cervical, and uterine cancers combined.¹³ UI affects approximately 12.7 million women and has profound consequences on quality of life, including social isolation, stigmatization, depression, and, for some older women, the end of independent living.^{14,15}

Obesity has been identified as a significant independent risk factor for UI in postmenopausal women and as the largest attributable risk factor for daily urinary incontinence.^{16,17} Specifically, obesity is an independent risk factor for SUI and mixed urinary incontinence (MUI, having both SUI and UUI).

Weight loss and urinary incontinence

Studies of surgical and behavioral weight reduction interventions have found that weight loss has a beneficial effect on UI prevalence.¹⁸ Epidemiologic studies have consistently identified obesity as an independent risk factor for both incident and prevalent urinary incontinence. A review article summarizing studies that investigated the relationship between UI and obesity demonstrated a dose-response effect of weight on UI.¹⁹ A 5-unit increase in BMI is associated with a 20% to 70% increase in the risk of UI, the maximum effect of weight

rarely exceeding an odds ratio (OR) of greater than 4 to 5 in well-controlled analyses.

Similarly, incident UI over 5 to 10 years increased by approximately 30% to 60% for each 5-unit increase in BMI.²⁰ There may also be a stronger association of increasing weight with prevalent and incident SUI, including MUI, than with UUI and overactive bladder syndrome (a bladder condition with symptoms of urgency, frequency, UUI, and nocturia). Weight loss studies have indicated that surgical and nonsurgical weight loss approaches may lead to significant improvements in UI symptoms.

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Nonsurgical weight loss treatments

Behavioral weight loss programs are effective in decreasing the frequency of UI.⁸ Several case series and prospective cohort studies have reported that nonsurgical weight loss is associated with a significant decrease in the incidence and severity of UI, while level 1 data support the finding that weight loss can be used as a first-line treatment for UI (TABLE).^{8,20,21}

Recently, a large randomized controlled trial addressed weight loss as a first-line treatment for overweight and obese women with UI.⁹ Between July 2004 and April 2006, investigators recruited 338 women with a BMI of 25 to 50 kg/m² who reported at least 10 episodes of UI in a 7-day period.

In this single-blind trial, participants were randomized 2:1 to undergo either an intensive 6-month weight loss program of diet, exercise, and behavior modification (n=226) or a structured education program (control group, n=112). Each group also received an instructional booklet describing standard behavioral therapy for UI.

After 6 months, women in the intervention group achieved a mean weight loss of 8.0% compared with a 1.6% loss in the controls ($P<.001$). The mean number of weekly incontinence episodes decreased by 47.4% in the treatment group compared with 28.1% in the control group ($P=.01$). This decrease was mainly attributed to a lower number of stress incontinence episodes (57.6% vs 32.7%; $P=.02$). Although the decrease in frequency of UUI episodes was larger in the treatment vs the control group (42.4% vs 26.0%), these results were not statistically significant ($P=.14$).⁹

Subjective data, including patient-reported symptoms and symptom-specific quality of life, were also significantly improved in the intervention group. At 6 months, compared with those in the control group, women in the treatment group perceived greater improvement in the frequency of UI, had a lower volume of urine loss, viewed UI as less of a problem, and had higher satisfaction with the change in incontinence ($P<.001$).⁹

Surgical weight loss interventions

Surgery is not usually the first-line treatment approach for weight loss, but in certain medical situations, such as BMI >40 or BMI of 35 to 39.9 kg/m² associated with diabetes, it may be indicated.²² Several observational studies have demonstrated that morbidly obese individuals (>45 kg above ideal body weight) who underwent

TABLE Randomized trials of nonsurgical weight loss as treatment for urinary incontinence

STUDY	N	DESIGN	BMI OR WEIGHT CHANGE	UI PREVALENCE OR EPISODE CHANGE (P VALUE)
Subak et al ⁸	39	<p>RCT, 2 arms:</p> <p>Immediate intervention group: weight reduction intervention x 3 months (n= 20)</p> <p>Wait-list control group: delayed intervention (n=19)</p> <p>Weight reduction intervention: 3-month intensive group-based medical and behavioral weight loss program combined with low-calorie (800 kcal/day) liquid diet</p> <p>Wait-list control group: no intervention for 3 months, then entered into the weight reduction program.</p> <p>All subjects followed for 6 months after completing the weight reduction program</p>	<p>Immediate intervention group achieved a median weight loss of 16 kg (IQR, 9 to 20) compared with 0 kg (IQR, -2 to 2) in the wait-list control group ($P<.0001$)</p> <p>BMI reduction from 35 (IQR, 31 to 40) to 28 kg/m² (IQR, 26 to 34), or 16%, in the immediate intervention group; no change in the wait-list control group ($P<.0001$)</p>	<p>Number of weekly UI episodes at 3 months decreased 60% in immediate intervention vs 15% in control group ($<.0005$)</p> <p>Number of stress (0.003) and urge (0.03) UI episodes decreased in immediate vs control group</p> <p>Control group had intervention after 3 mo, with 71% weekly UI decrease after weight loss</p> <p>Incontinence Impact Questionnaire and Urogenital Distress Inventory scores significantly improved after weight loss</p>
Subak et al ²⁰	10	Low-calorie liquid diet weight loss program, 3-month follow-up	Pre BMI 38 kg/m ² ; post BMI 33 kg/m ² ; mean weight loss, 15 kg ($P<.03$)	<p>Decrease from 13 to 8 UI episodes/week after weight loss ($<.07$).</p> <p>Of 10 women, 6 with 5% or greater body weight loss had greater than 50% UI frequency decrease ($<.03$)</p>
Brown et al ²¹	1957	<p>RCT 3 arms:</p> <ol style="list-style-type: none"> 1. Lifestyle intervention (diet, exercise, and behavior modification program) (n=660) 2. Metformin (n=636) 3. Placebo (n=661) <p>Mean follow-up, 2.9 years</p>	Weight loss of 3.4 kg vs 1.5 kg vs 0.5 kg in groups 1, 2, and 3, respectively ($P<.001$)	Weekly UI prevalence after treatment 38% vs 48% vs 46% in groups 1, 2, and 3, respectively (.001)

Adapted from Subak et al.¹⁹

BMI, body mass index; IQR, interquartile range; RCT, randomized controlled trial; UI, urinary incontinence.



weight loss surgery and subsequently lost 45 to 50 kg experienced resolution of UI symptoms.^{10,11,23-26}

Bump et al reported significant improvements in UI symptoms in women (mean preoperative BMI of 49.9 kg/m²) 1 year after surgically induced weight loss.¹¹ Thirteen subjects underwent comprehensive evaluation of lower urinary tract function before and 1 year after surgically induced weight loss. Significant changes were seen in urodynamic parameters, number of incontinence episodes, and the need to use absorptive pads. Of 12 subjects who complained of UI before surgery, only 3 complained of UI after surgical weight loss ($P=.004$), and only 1 requested treatment after weight loss.

In a surgical series of 101 obese women (mean preoperative BMI of 48.8 kg/m²), Burgio et al reported a significant reduction in the prevalence and severity of UI symptoms (using validated symptom-specific quality-of-life questionnaires) 6 and 12 months after laparoscopic Roux-en-Y surgery.¹⁰ The prevalence of UI decreased from 66.7% before surgery to 41% at 6 months and 37% at 12 months, with the reduction in the prevalence of UI proportional to the magnitude of weight loss.

More recently, it has been reported that women who have undergone laparoscopic gastric banding surgery have had significant improvements in lower urinary tract symptoms. Ranasinghe et al surveyed 653 women who had undergone laparoscopic gastric banding surgery at a single center in Australia.²⁶ Significant improvements in scores were seen on the International Consultation on Incontinence Questionnaire–Urinary Incontinence Short Form (ICIQ–UI SF) with respect to urinary symptoms (female pre-ICIQ SF score, 5.24, vs post score, 3.93, $P=.0008$)

and Quality of Life ($P<.0001$) questionnaire. For each kilogram lost, there was a 0.05-unit improvement in the ICIQ SF score ($P=.03$). (The ICIQ SF is a validated questionnaire designed to assess the impact of UI on a person's life. The scoring range is 0-21; a higher score correlates to a greater impact of incontinence.) Although there were improvements in SUI, UUI symptoms worsened after adjusting for weight loss.

Population-based studies have demonstrated that up to 50% of patients with FI also have UI (double incontinence), and the risk of FI in individuals with UI may be increased by up to 6-fold.

Fecal incontinence

Fecal incontinence is defined as the involuntary loss of liquid or solid stool that causes a social or hygienic problem.²⁷ The prevalence of FI varies considerably, depending on the population studied and the definition of incontinence used. In clinic-based studies, such as in general medicine or gynecology, the reported prevalence varies from 5.6% to 28%,²⁸ and in nursing home studies, reported rates are as high as 47%.²⁹ In contrast, population-based studies of community-dwelling older adults report the prevalence of fecal incontinence ranging from 3.0% to 16.9%,³⁰ depending on the age of the population. The higher estimates in gynecology clinics and nursing homes are consistent with common assumptions regarding females, older women, and the infirm being disproportionately affected by the condition.

Since the pathophysiologic mechanisms responsible for the development of UI and FI may overlap (nerve and sphincter damage), an association

between the two would be expected. Population-based studies have demonstrated that up to 50% of patients with FI also have UI (double incontinence), and the risk of FI in individuals with UI may be increased by up to 6-fold.^{31,32}

Less is known about the relationship between obesity and FI. In a population-based study of 2109 randomly selected middle-aged and older females (average age, 56 years), subjects reported the level of bother and impact on quality of life from FI.³³ Potential risk factors were assessed by self-report, patient interview, physical examination, and medical record review. A final multivariable model comparing any FI in women in the past year to those without FI showed that obesity was independently associated with a 20% higher prevalence of FI per 5-unit increase in BMI.

Weight loss and fecal incontinence

A 2005 study found a particularly high prevalence of anal incontinence (involuntary loss of liquid/solid stool, mucus, and gas) in a cohort of 178 morbidly obese (BMI ≥ 40 kg/m²) women undergoing consultation for bariatric surgery.³⁴ In this study, symptoms of anal incontinence were noted in one-third (32%) of the women, more than that reported in population-based studies. If flatal incontinence was excluded, that rate fell to 19.4%, which is only slightly higher than the rate for population-based studies.

In a follow-up of 101 of these 178 women (aged 20 to 55 years) who underwent laparoscopic Roux-en-Y gastric bypass,¹⁰ FI symptoms were assessed 6 and 12 months post surgery. The prevalence of FI decreased from 19.4% at baseline to 9.1% at 6 months and 8.6% at 12 months ($P=.18$). Interestingly, the prevalence of flatal incontinence increased from 12.9%

preoperatively to 20.8% at 6 months and 30.1% at 12 months ($P=.004$). In contrast, some studies have shown an increase in FI symptoms after bariatric surgery. Roberson and colleagues reported the results of a study evaluating weight loss on FI symptoms, using a detailed survey mailed to 404 adults who underwent bariatric surgery.³⁵ The survey considered the type of surgery, weight change, symptoms of bowel and bladder disorders, and perceived effects of surgery on those symptoms. Type and severity of fecal incontinence were obtained using previously validated questionnaires. Of 193 patients who responded (82% female), 51.2% who had FI prior to surgery said that their condition worsened afterward, compared with only 9.3% who reported improvement after surgery.

Fecal incontinence was common in both men and women, with 48% of the women and 42% of the men reporting liquid stool incontinence, and 21% of the women and 30% of the men reporting solid stool incontinence. Of the women with FI, 55% perceived worsening after surgery, compared with 31% of the men.³⁵

Women who had diarrhea were 4 times more likely to report FI ($P<.0001$). In addition, women who perceived worsening of diarrhea after surgery were significantly more likely to have FI ($P=.003$), suggesting that FI in this population may partially be due to an underlying weakness in continence mechanisms that is clinically unmasked after surgery because of altered diet or anatomic changes in the gastrointestinal tract.³⁵

More well-controlled studies are needed to explore the impact of obesity and weight loss on FI symptoms.

Conclusion

Pelvic floor disorders, including urinary and fecal incontinence, are

among the many medical conditions affected by obesity. Weight loss as a first-line treatment for UI and FI should be considered for all women, and concomitant behavioral treatment approaches should also be considered. These include pelvic muscle exercises, attention to types and amounts of fluid intake, and voiding habits.

Even if weight loss is unsuccessful in treating UI, subsequent continence surgery, if indicated, may be technically easier and potentially safer secondary to weight loss.

Even if weight loss is unsuccessful in treating UI, subsequent continence surgery, if indicated, may be technically easier and potentially safer secondary to weight loss. Caution should be taken, however, that although an intervention such as weight loss could be supported as first-line therapy, general practitioners should not allow this to delay referral to a specialist who can provide these women with appropriate evaluation and the full spectrum of treatment modalities for their UI and FI symptoms. ■

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Estrogen, menopause, and mood regulation

► KIMBERLY ALBERT, CHRISTINA BROADWELL, MD, AND PAUL NEWHOUSE, MD

The lifetime prevalence of major depressive disorder (MDD) in women is approximately 20%, and twice that of men,¹ with increased risk beginning at puberty and continuing until menopause.² The reasons for this difference remain to be fully understood. However, the concurrence of increased risk for MDD in women during reproductive stages characterized by fluctuating ovarian hormones suggests there is an important interaction between gonadal hormone changes and mood. Epidemiologic findings provide additional evidence

for the role of ovarian hormone fluctuations in depression: namely, women's risk for depression is increased during periods of hormone variability, and, compared with men, women have an earlier age of first depressive episode, beginning at puberty.²

The perimenopause, characterized by large fluctuations in ovarian hormone levels, also represents a period of increased risk for MDD episodes, even in women with no prior history of depression.³ Although the putative role of ovarian hormones in depression has been investigated, estrogen's lack of a strong antidepressant effect⁴ and recent neuroimaging⁵⁻⁷ and behavior⁸⁻¹¹ findings indicate that the interaction between ovarian hormones and negative mood is complex and likely related to hormone variability rather than simple circulating levels.

This article reviews recent findings on estradiol (E2) in mood regulation and depression and the relevance for perimenopausal and postmenopausal hormone treatment.

Ovarian hormone effects on emotion and mood regulation

The role of ovarian hormones in emotion systems and mood regulation has been an area of research interest, in part, because of the sex difference in depression risk^{1,2} and reproductive event-related mood disorders (such as premenstrual dysphoric disorder, postpartum depression, and perimenopausal depression) in women.¹² The effects of estrogen on brain systems are complex; however, evidence supports a mood regulatory

role of estradiol in premenopausal women.^{5,9,13-15} During the reproductive years, a woman's brain is exposed to cyclic fluctuations of ovarian hormones that exert effects on brain circuits. For the majority of women, this variability in hormone levels does not result in pathology, suggesting that the brain's mood systems are able to adapt to the normal cyclic changes in the hormonal milieu. In a subgroup of women, however, the plasticity of the brain's response appears to be impaired, resulting in a vulnerability to mood dysregulation that is revealed during times of ovarian hormone variability.

One of the proposed mechanisms for the increased risk of depression in women is that estrogen may influence depression risk through its interaction with neurotransmitter systems that are relevant to mood regulation.^{16,17} Abnormal functioning of brain systems that are involved in mood regulation, and that are sensitive to monoamines, may contribute to depression. Although some evidence suggests that estrogen may interact with monoamine neurotransmitter systems, more recent investigations indicate that the effects of estrogen in the brain are more widespread and nuanced than a simple enhancement of monoamine transmission.^{5,8,13,14} Behavioral⁸⁻¹¹ and neuroimaging⁵⁻⁷ findings support a role for estradiol's effects in brain regions important for mood regulation. In animal models, anxiety and depressive behaviors are influenced by the estrus cycle phase and by estrogen administration.^{18,19}

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Acknowledgements

Preparation of this work was supported in part by NIA R01 AG021476 and NCR-00109.

Disclosures

The authors report no commercial or financial relationships relevant to this article. Dr Newhouse reports that he has received grant/research support from AstraZeneca, Targacept, and Lilly and has served as a consultant to AstraZeneca.



Estrogen may be an important modulator of affect in humans, according to studies examining the effects of estradiol administration in women who have reproductive event-related mood disorders, as well as behavior and imaging studies in healthy women. Few studies have reported on the effects of estradiol on emotion perception and reactivity. In healthy premenopausal women, however, high endogenous estrogen and exogenous estrogen administration have been associated with reduced activity in brain areas involved in emotional processing of negative stimuli.

Pearson and Lewis demonstrated that recognition of emotional facial expressions is reliably altered across the menstrual cycle, with the recognition of fear improving when estradiol levels were high.²⁰ Goldstein et al¹³ and Protopopescu and colleagues¹⁴ showed that brain areas associated with negative emotional responses (the amygdala, anterior cingulate gyrus, and orbital frontal cortex) exhibited altered activity during menstrual cycle phases when estradiol levels are high compared with low-estradiol phases (FIGURE).

Although there have been consistent findings of normal ovarian hormone levels in women with mood disorders, studies that have used hormone manipulations indicate that estradiol modulates depressive symptoms as well as functional activity in brain regions involved in mood regulation.^{8,21} In healthy women, the mood regulatory effects of estradiol may be subtle and work in concert with the brain's adaptive response to the menstrual cycle. Thus, high or stable circulating estrogen may enhance cognitive regulation of emotional and sensory processing and provide protection against the neuroendocrine and emotional consequences of negative life

events. In the menopausal transition, however, the beneficial mood effects of estradiol's actions in the brain may be reduced because of fluctuating or lowered circulating ovarian hormone levels or through changes in the brain's response to ovarian hormones.^{4,22}

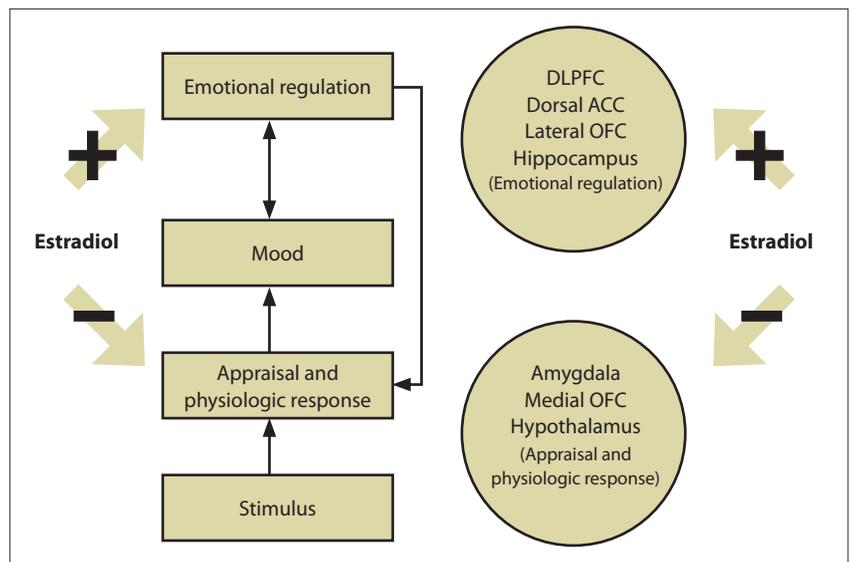
Gonadal steroid changes across the menopausal transition

Over a normal life span, women experience profound transitions and cyclic variability in hormone production and exposures. The cyclic variability of the reproductive years is bookmarked by prepubertal and postmenopausal lack

of cyclicality and hypoestrogenic states. These sweeping transitions are made over time and occur in stages.

The Stages of Reproductive Aging Workshop (STRAW) further defined the transitions that accompany loss of reproductive and ovarian function by including changes in hormone levels as well as menstrual cycle intervals.²³ According to STRAW criteria, the menopausal transition is characterized by variability in hormone production and the frequency of menstrual cycles prior to the final menstrual period (FMP). Hormone levels, including estradiol, can be erratic and unpredictable at this time, with estra-

FIGURE Role of estradiol in the processes underlying emotion perception



High levels of estradiol (E2) may support stable mood in premenopausal women. While the mechanisms through which estradiol may attenuate negative mood responses to negative stimuli remain to be fully investigated, recent neuroimaging studies suggest that estradiol may contribute to increased activity in brain areas related to emotional regulation and decreased activity in brain regions important for emotional appraisal and physiologic responses to negative stimuli. Estradiol has been reported to increase activity in brain areas with roles in emotion regulation, including the dorsal lateral prefrontal cortex (DLPFC),¹³ dorsal anterior cingulate cortex (dorsal ACC),¹⁴ lateral orbital frontal cortex (lateral OFC),¹⁴ and hippocampus.⁵ Estradiol has also been found to decrease activity in brain areas with roles in the appraisal of and physiologic response to emotional stimuli, including the amygdala,^{5,13} medial orbital frontal cortex (medial OFC),^{5,13,14} and hypothalamus.¹³

Adapted from Phillips ML, Drevets WC, Rausch SL, Lane R. Neurobiology of emotion perception I: the neural basis of normal emotion perception. *Biol Psychiatry*. 2003;54(5):504-514.

diol production finally decreasing significantly only 6 months prior to the FMP.²³ Postmenopause, indicated by lack of menstrual cycling, is divided into an early and a late phase based on length of time since the FMP. The early phase occurs within 5 years of the FMP.²³

This variability in ovarian hormones during the reproductive years and menopausal transition creates a dynamic environment for the functioning of mood regulatory brain systems that are influenced by these hormones.

Mood changes during the perimenopause and menopause

The perimenopause has been examined as a putative period of risk for depression, because the variability and eventual decrease in ovarian hormones during this stage may increase vulnerability to mood dysregulation. Indeed, longitudinal, community-based, and prospective studies have shown an increase in depressive symptoms during the perimenopause compared with both the pre- and postmenopausal periods. Some studies have reported that approximately 16% of perimenopausal women experienced at least one depressive episode.^{10,24}

In addition, the perimenopausal period has been associated with both increased recurrent depressive episodes and new-onset depressive episodes in women with no previous history of MDD.^{3,11,25,26} The increased risk for depressive symptoms and episodes may extend into early menopause.²⁴ However, as menopause continues, depression risk declines as circulating ovarian hormones stabilize at low levels.

The role of changing ovarian hormone levels in perimenopausal depression is likely mediated by brain

systems that are influenced by these hormones. The premenopausal stage is characterized by cyclic fluctuations in ovarian hormones. These regular cyclic patterns, however, are disrupted during the perimenopause and then resolve in the postmenopause as low levels of ovarian hormones stabilize.

The perimenopause may represent a period of increased vulnerability to depression because the brain systems involved in emotional processes and mood regulation are exposed to irregular variability in estradiol,³ resulting in a loss of estradiol's modulatory effects in these systems. This hypothesis is supported by the consistent finding that perimenopausal depression is not characterized by abnormal ovarian hormone levels,^{10,24,25,27} but is associated with an early perimenopause onset and prolonged transition to menopause.^{3,26}

Further, according to longitudinal studies that have followed women through the transition to menopause, depressive symptoms are increased in women who experience estrogen fluctuations^{3,25} and this increase is not fully accounted for by vasomotor symptoms related to menopause.¹¹

The perimenopausal period has been associated with both increased recurrent depressive episodes and new-onset depressive episodes in women with no previous history of MDD.

A prior history of premenstrual mood symptoms³ and postpartum depression²⁸ predicts the risk for perimenopausal depression. Thus, changes in mood related to ovarian hormone fluctuations may be a risk

factor for perimenopausal depression.

That most women undergo the hormonal changes that occur across the menstrual cycle and menopause and do not experience MDD indicates that these brain systems are able to adapt to gonadal hormone variations. However, a subgroup of women may have a reduced ability for the brain systems that are important for emotional processes to adapt to irregular ovarian hormone changes. These women may be vulnerable to mood dysregulation in response to the ovarian hormone irregularity that characterizes the perimenopause.

Effects of sex steroids on stress reactivity and mood after menopause

For most women, menopause represents a time of decreased depressive risk²; the brain systems important for emotional processing and mood regulation are no longer exposed to the effects of cycling ovarian hormones. However, the effects of postmenopausal hormone therapy on emotional processing and mood regulation remain unclear. Recent studies suggest that following menopause, the interaction with psychosocial stress may be an important factor in ovarian hormone effects on mood. Postmenopausal women appear to show greater sensitivity than premenopausal women in their physiologic response to stressful tasks; the difference has been ascribed to both age and hormonal status.²⁹ Studies of the effects of hormones on experimental stressors have found that various forms of estrogen appear to reduce some of the physiologic effects of mild laboratory-induced stress (eg, solving arithmetic problems).^{30,31}

Lindheim and colleagues showed that the greater biophysical response of postmenopausal women following stress was reduced after 6 weeks



of transdermal estradiol treatment.³² Estrogen treatment enhances parasympathetic responsiveness to experimental stress, suggesting reduced sympathetic activation.³³ Kajantie and Phillips³⁴ concluded that there is an increase in sympathoadrenal responsiveness after menopause that is attenuated with oral hormone therapy.

Newhouse and colleagues demonstrated that, in postmenopausal women, estradiol treatment increased negative mood scores and impaired cognition after a psychosocial stress manipulation^{35,36} and that estradiol treatment produced significantly worse mood ratings after psychosocial stress manipulation and monoamine depletion. Interestingly, there was no interaction of estradiol treatment and the monoamine manipulation procedure. Estradiol thus appears to have effects on mood that are independent of monoamine systems.

These results suggest that premenopausal and postmenopausal women differ in their psychosocial stress response. While it is tempting to speculate that the changes in the hormonal milieu that occur during the menopause may alter the mood effects of estradiol on the brain, this hypothesis requires further investigation.

Newhouse and colleagues recently showed⁶ that emotion-related brain circuitry remains responsive to estradiol administration in postmenopausal women. Thus, alterations in brain cortical activity produced by differing circulating levels of hormones, such as estradiol and progesterone, may play a role in regulating how emotion-related brain structures respond to emotional stimuli and/or stressful events,^{13,14,37} even in older postmenopausal women. It appears that the administration of sex hormones to postmenopausal women at a plasma level consistent with the late follicular phase produces altera-

tions in the brain processing of stressful or emotional experiences.

Efficacy of hormone treatment on mood dysregulation

The efficacy of estrogen treatment for negative mood is likely modulated by age and menopausal status. The brain changes that allow for stable emotional processing in the postmenopause may alter the brain's ability to respond to subsequent estrogen or reverse the mood-regulatory effects of estrogen. Studies examining the antidepressant effects of estrogen during both the perimenopause and the postmenopause provide support for the hypothesis that the brain response to ovarian hormones changes with the menopause. In perimenopausal women who are experiencing large fluctuations in estradiol levels, estrogen treatment may provide a stable level to which the emotion and mood systems in the brain can adapt to maintain healthy functioning.

While it is tempting to speculate that the changes in the hormonal milieu that occur during the menopause may alter the mood effects of estradiol on the brain, this hypothesis requires further investigation.

Estradiol replacement therapy in perimenopausal women reduces autonomic and endocrine responses to laboratory stressors^{30,31} and decreases depression scores in women with perimenopausal depression.²² In contrast, studies of depression in postmenopausal women generally find that estrogen treatment has no beneficial mood effect in this group.⁴ Other studies suggest that estradiol during

the postmenopause may enhance negative mood response to emotional stimuli.^{7,35}

The lack of estradiol treatment efficacy on depressive symptoms may be due to changes in the brain's response to ovarian hormones that occur following the tonically hypogonadal state during menopause. During the postmenopause, the brain systems important for emotional processing and mood regulation may become adapted to low circulating estrogen levels and therefore respond to exogenous estradiol differently than in the premenopausal period. Or, these brain systems may experience treatment-induced increased estradiol levels as a perturbation.

Estrogen treatment may be beneficial for negative mood symptoms in perimenopausal and early menopausal women, whereas the same benefit is not generally seen after menopause has been established. Experimental evidence suggests that estrogen treatment in older postmenopausal women may increase arousal or sensory processing of negative emotional stimuli and be associated acutely with increased negative mood symptoms in response to psychosocial stress.³⁵

At doses sufficient to suppress the hypothalamic-pituitary-gonadal axis, estradiol alone or combined with progestins can mute chaotic hormonal signals and provide a predictable and constant exposure. Estradiol treatment may also augment the effect of selective serotonin reuptake inhibitors (SSRIs) in perimenopausal depression (for a general review of the treatment of perimenopausal depression, see Parry, 2010).³⁸

Low-dose combination oral contraceptives (OCs) can also be used in this circumstance if other medical conditions do not preclude their use.

Combination OCs may improve mood symptoms and also treat other clinical manifestations of the menopausal transition, such as autonomic symptoms, dysfunctional uterine bleeding, and dysmenorrhea, as well as provide contraception and protection against endometrial hyperplasia and carcinoma.

Although estradiol alone does not appear to have antidepressant effects, in limited circumstances, estradiol may enhance mood if used in combination with other treatments for depression. ■

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