

The Perimenopause and Mood Disorders

Khursheed Khine, MD, Jamie A. Luff, MD,

David R. Rubinow, MD, and Peter J. Schmidt, MD

Focus Points

- The perimenopause is defined on the basis of menstrual cycle irregularity and elevated plasma follicle-stimulating hormone levels.
- Abnormalities of plasma hormone secretion do not distinguish perimenopausal women with and without depression.
- Randomized controlled trials have demonstrated the short-term (6–8 weeks) antidepressant efficacy of estradiol treatment in perimenopausal women.

Abstract

Is there a relationship between perimenopausal reproductive function and the onset of mood disorders? The perimenopause is a time of considerable variability in reproductive function and, in some women, is associated with an increased susceptibility to depression. Whether the variability in ovarian hormone secretion during the perimenopause has any causal role in the development of depression remains unclear. Recent epidemiologic data confirm that the perimenopause is a time of increased susceptibility to the onset of depression. Additionally, although similar to major depressive disorder in phenomenology, course, and family and personal history of mood disorder, perimenopausal depression may be distinguished by an antidepressant response to estradiol therapy. This article presents background information relevant to the controversy surrounding the putative relationship between reproductive aging and mood disorders, reviews the endocrinology of the perimenopause, and describes several emerging methodologic issues that may help reconcile conflicting findings in past observational studies and recent randomized controlled trials. Studies examining the prevalence, presentation, and treatment response characteristics of mood disorders occurring during the perimenopause are described as well. The article concludes with recommendations for the evaluation and treatment of women with perimenopausal depression.

Introduction

A potential relationship exists between the onset of affective disorders in women and the reproductive events of the perimenopause. Elucidation of this relationship requires description of the following: the background for the controversy surrounding reproductive senescence and mood disorder; the endocrinology of this phase of a woman's life, and emerging methodologic issues that may resolve discrepant findings between previous observational studies and recent randomized controlled trials (RCTs).

Studies examining the prevalence, presentation, and pathophysiology of mood disorders occurring during the perimenopause are presented as well. Finally, recommendations on the clinical evaluation and management of these conditions are provided.

While it is important to distinguish between the perimenopause and postmenopause, many older studies failed to do so. For simplicity, this article will use the term perimenopausal depression to refer to depression that presents at the end of reproductive life.

Background

Medical literature from the 19th century contains numerous case reports describing the onset of mood and behavioral disorders in women during midlife and reproductive senescence.^{1,2} These early observations led to speculations about the role of ovarian steroids in brain function and psychiatric illness—speculations supported by the anecdotal reports of the psychotropic actions of ovarian extracts. Nonetheless, a debate ensued in the psychiatric literature regarding the nature of these mood and behavioral disturbances and their connection to reproductive aging.

Prior to publication of the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition,³ several investigators performed more systematic examinations of mood disorders occurring in association with midlife and reproductive senescence. These studies were unable to confirm the existence of involuntional melancholia (ie, melancholia occurring in old age), nor were they able to identify epidemiologic evidence for an increased prevalence of major depressive disorder (MDD) during the perimenopause. Thus, the earlier debate over the appropriate classification of involuntional melancholia changed to skepticism about its existence as a distinct condition. Moreover, these findings suggested that hormonal events did not underlie mood disorders occurring during midlife and reproductive senescence.

The evidence against the uniqueness of depression at the end of reproductive life (ie, similar symptomatology and prevalence to that seen in premenopausal depression) is far from

Continued on page 44

Drs. Khine and Luff are clinical fellows and Dr. Rubinow is clinical director and chief in the Behavioral Endocrinology Branch at the National Institute of Mental Health in Bethesda, Maryland.

Dr. Schmidt is chief of the Unit on Reproductive Endocrine Studies in the Behavioral Endocrinology Branch at the National Institute of Mental Health.

Disclosure: Drs. Khine and Luff have received material support from Watson Pharmaceuticals. Dr. Rubinow is a consultant to Servier and Vela, and has received research support from Watson. Dr. Schmidt is a consultant to Zynx and has received material support from TAP pharmaceuticals and Watson.

Please direct all correspondence to: David R. Rubinow, MD, National Institute of Mental Health, 10 Center Dr MSC 1276, Bldg. 10, Room 3N238, Bethesda, MD 20892-1276; Tel: 301-496-9675; Fax: 301-402-2588; E-mail: rubinowd@intra.nimh.nih.gov.

Continued from page 41

conclusive in refuting the existence of a perimenopause-related mood syndrome. Several authors have described differences between women with perimenopausal versus premenopausal depressions. Stenstedt⁴ and Brown and colleagues⁵ both reported involuntional-onset depression to be associated with a lower family history of depression than that observed in patients with early-onset depression. A study by Weissman⁶ demonstrated that the percentage of women with first-onset depression was higher in perimenopausal and postmenopausal women than in younger women; the increased years at risk for depression in the older women would have suggested the contrary. Thus, while perimenopausal MDDs do not appear to be phenomenologically distinct, evidence suggests that they may differ from earlier-onset depressions with respect to family history and age of first depressive episode. Further, epidemiological and even phenomenological similarity does not entail causal identity. It is not unusual in medicine for phenomenologically similar disorders to have different precipitants or causes. For example, meningitis in both the neonate and infant may present with fever, vomiting, and drowsiness, yet different pathogenic organisms are typically involved with each age group.

The presupposition that perimenopause-related affective syndromes are melancholic depressions is an additional confound that may have interfered with the identification and characterization of other affective syndromes (eg, atypical depression) occurring at this time. In fact, as described below, both historical and recent reports of mood disorders during the perimenopause are more consistent with a neurasthenia or minor depression.

Reproductive Endocrinology of the Perimenopause

The menopause has been defined as the permanent cessation of menstruation resulting from loss of ovarian activity. The postmenopause is characterized endocrinologically by tonically elevated gonadotropins (follicle stimulating hormone [FSH], luteinizing hormone) secretion, persistently low levels of ovarian steroids (estradiol, progesterone), and relatively low (50% decrease compared to younger age groups) androgen secretion.^{7,8}

The perimenopause has been defined as the transitional period from reproductive to nonreproductive life.^{9,10} As the perimenopause progresses, ovarian follicular depletion occurs, the ovary becomes less sensitive to gonadotropin stimulation, and a state of relative hypoestrogenism occurs. In addition, gonadotropin secretion is elevated across the menstrual cycle, ovulatory cycles are fewer, and menstrual cycle irregularity ensues.¹¹ However, in contrast to the postmenopause, episodic (not tonic) gonadotropin secretion is present and both ovulation and normal (or at times increased) estradiol secretion may occur.^{12,13} The late perimenopause is characterized endocrinologically by persistent elevations of plasma FSH, sustained menstrual cycle irregularity with periods of amenorrhea, and hypoestrogenism. The levels of several other hormones that may also impact on mood and behavior decrease with aging concomitant with changes in reproductive function. These hormones include androgens (testosterone and androstenedione),^{7,8,13,14} which begin to decline when a person is in their 20s and reach peak decline during a person's late 40s and 50s; dehydroepiandrosterone (DHEA)¹⁵; and insulin-like growth factors and binding proteins.^{15,16}

Not only is there evidence suggesting the importance of distinguishing between peri- and postmenopausal women with respect to treatment response characteristics, but studies have also identified that the perimenopause has distinct endocrine sub-phases, with the early perimenopause (eg, high gonadotropin levels and increased estradiol secretion) differing from the late perimenopause (eg, high gonadotropin levels and decreased estradiol secretion).^{12,13} Thus, investigators have attempted to develop criteria to define the phases of reproductive senescence. These criteria will facilitate the collection of more homogeneous samples, aiding understanding of the interaction between the stage of ovarian decline, aging, and a variety of physiological endpoints. For example, the Stages of Reproductive Aging Workshop criteria for reproductive, perimenopausal (menopausal transition), and postmenopausal years developed by Soules and colleagues¹⁷ define the early perimenopause to include women with menstrual cycle irregularity (defined as

a variable cycle length that differs from normal by more than 7 days) and elevated plasma FSH secretion. During the late perimenopause there is a continued elevation of FSH in conjunction with two or more skipped cycles and a period of amenorrhea lasting 60 days. This could include up to 1 year of amenorrhea, at which time the woman has entered the early stages of postmenopause.

Mood Disturbances Occurring During the Perimenopause and Reproductive Senescence

Although the postmenopause has not been associated with an increased risk for developing depression in women,¹⁸⁻²² depressive symptoms have been observed more frequently in perimenopausal women compared with postmenopausal women in some longitudinal, community-based studies.^{22,23}

Similarly, community-based surveys^{24,25} of the prevalence of affective syndromes (conditions meeting standardized diagnostic criteria) have observed patterns of morbidity consistent with those reported in the surveys examining mood symptoms. Several epidemiologic studies^{24,25} examining gender- and age-related differences in the 6-12-month prevalence of MDD lasting 6-12 months reported no increased prevalence of MDD in midlife women (approximately 45-55 years of age). In contrast, a recent multisite study by Weissman and colleagues²⁴ identified an increased hazard rate for the onset of depression in the cohort of women (but not men) 45-50 years of age. The Study of Women's Health Across the Nation (SWAN)²⁶ employed a measure of "psychological distress" as a proxy for the syndrome of depression by requiring that core depressive symptoms (sadness, anxiety, and irritability) persist for 2 weeks. Similar to the studies of depressive symptoms, SWAN's initial cross-sectional survey observed that perimenopausal women reported significantly more psychological distress than either pre- or postmenopausal women (defined by self-reported menstrual cycle status).²⁶ Moreover, the increased psychological distress appeared independent of the presence of vasomotor symptoms. These data, therefore, provide additional evidence supporting the role of the perimenopause, but not the postmenopause, in the development of mood disorders.

There is also evidence that anxiety disorders, although less common than depressive disorders, are experienced by a considerable number of perimenopausal women²⁷ and that the frequency of episodes may increase during the perimenopause (Ellen Freeman, MD, oral communication, 2003). New onset panic disorder in the perimenopause has been observed anecdotally and may be responsive to estrogen therapy; however, in the authors' experience, the frequent comorbidity of perimenopausal panic disorder and hot flashes and their shared symptomatology make it difficult to readily separate the two phenomena. Thus, estradiol treatment may be effective for panic attacks; however, it is unclear if this improvement is secondary to relief of hot flashes (which may trigger as well as mimic panic attacks) or due to the direct effects of estradiol on panic disorder. Moreover, hot flashes and panic improve after treatment with selective serotonin reuptake inhibitors (SSRIs), suggesting a potential shared pathophysiology as well as treatment response characteristics.

In summary, epidemiological studies examining the prevalence of both affective symptoms and syndromes have documented that the majority of postmenopausal women do not experience a MDD associated with this phase of life. On the other hand, several community-based and clinic-based surveys suggest that the perimenopause is relevant to the development of affective disorders²⁶⁻²⁸ and that a substantial number of perimenopausal women do, in fact, experience a clinically significant affective syndrome.

Emerging Methodological Concepts

Several new methodological issues have emerged reflecting, in part, efforts to reconcile substantial differences in the results of observational studies and RCTs of hormone replacement therapy (HRT). These issues comprise several explanations for differential responses of both behavioral and physiologic measures to changes in hormones (either endogenous or exogenous) across individuals, including phase of reproductive senescence (ie, late perimenopause or early menopause versus 5 years past last menses), presence of menopausal symptoms, the duration of hypogonadism

prior to receiving HRT, and genetic polymorphisms that underlie differences in steroid responsivity.

A differential response to estradiol in depression was reported by Appleby and colleagues²⁹ and Montgomery and colleagues,³⁰ with perimenopausal but not postmenopausal women responding to estrogen therapy under RCT conditions. These observations were confirmed by several recent RCTs employing standardized psychiatric diagnostic interviews to establish the presence of depression.³¹⁻³³ Similarly, a literature review and meta-analysis by Yaffe and colleagues³⁴ concluded that the benefits of HRT on cognitive function were limited to perimenopausal women compared with postmenopausal women and suggested that the beneficial effects of HRT were secondary to the concurrent improvement in menopausal symptoms. A subsequent meta-analysis of a similar literature performed by LeBlanc³⁵ confirmed Yaffe's suggestion and observed that the presence of symptoms (eg, hot flashes, sleep disturbance, or mood disturbance) predicted a beneficial effect of HRT on cognition. Similarly, studies in both animals and humans suggest that a short but not long duration of hypogonadism prior to initiation of estrogen therapy is associated with beneficial effects on both measures of cognition³⁶⁻³⁸ and atherosclerotic plaque formation.^{39,40} These findings are consistent with the observed differences in treatment response between perimenopausal or recently menopausal and older postmenopausal women.^{28,41,42} Additionally, these findings introduce the concept of the critical window for the efficacy of HRT. For example, nonhuman primate studies have shown that initiation of HRT is associated with cardioprotection when administered immediately after oophorectomy but not after 30 months (approximately 6 human years).³⁹ This critical window construct has been proposed as an explanation for some of the discrepant findings between the observational studies (many of which included younger, more symptomatic women) and the recent RCTs related to the Women's Health Initiative,⁴³⁻⁴⁵ which principally included older asymptomatic women.⁴⁶ Finally, independent of stage of reproductive life or duration of hypogonadism, several studies employing both plasma lipid levels and

cognitive outcome measures suggest that the effects of sex steroids may be influenced by the presence of polymorphisms in specific steroid receptors.⁴⁷⁻⁴⁹

The evidence that younger perimenopausal but not older postmenopausal women respond to estrogen therapy suggests that those mood disorders occurring in perimenopausal women are caused by changes in hormones (eg, withdrawal or fluctuations) rather than prolonged sex steroid deficiency. The possibility that it is the change or acute withdrawal from ovarian steroids that is relevant in the pathophysiology of these conditions suggests several mechanisms that may be involved in the onset of mood disorders. Alternatively, since the perimenopause may be associated with prolonged and increased estradiol secretion, it is possible that these increased levels of estradiol compromise central nervous system function.⁵⁰

Role of Estradiol Therapy in Perimenopausal Depression

Investigations of plasma levels of gonadal steroids in women with perimenopause-related depression have identified no consistent abnormality of reproductive endocrine function that distinguishes this disorder. Nonetheless, the relevance of changes in pituitary-ovarian function to depression during the perimenopause is suggested by two findings: first, in some perimenopausal depressed women, mood symptoms improve concurrently with the restoration of ovarian function⁵¹; second, estradiol therapy may have mood-enhancing effects in perimenopausal women with depression.

Controlled studies employing synthetic forms of estrogen in the treatment of depression have yielded mixed results. Estrogen has been reported to improve mood (albeit inconsistently)⁵²⁻⁵⁴ in the following samples: perimenopausal and postmenopausal women reporting depressive symptoms^{30,55,56}; postmenopausal women with depression unresponsive to traditional antidepressant therapy⁵⁷; and nondepressed menopausal women not experiencing hot flashes.⁵⁸

Schmidt and colleagues³¹ examined the therapeutic efficacy of estradiol replacement in 34 women (approximately 50% of whom had no prior history of depression) with perimenopausal

depression under double-blind, placebo-controlled conditions. After 3 weeks of estradiol, depression rating scale scores were significantly decreased compared to baseline scores and significantly lower than scores in the women receiving placebo. A full or partial therapeutic response was seen in 80% of subjects on estradiol and in 22% of those on placebo, consistent with the observed effect size (0.69) in a recent meta-analysis of studies examining estrogen's effects on mood.⁵⁹ The therapeutic response to estrogen was observed in both MDD and minor depression as well as in women with and without hot flashes. These data suggest that estrogen's effect on depression is not solely a product of its ability to reduce the distress of hot flashes.

These findings are consistent with data from Montgomery and colleagues³¹ and Saletu and colleagues⁵⁵ suggesting the beneficial effects of estrogen on mood in perimenopausal women reporting depressive symptoms. Two recent studies^{32,33} have extended these observations. Soares and colleagues³² reported a significant and beneficial effect of estrogen replacement compared to placebo in women with perimenopause-related MDD (as defined by the Primary Care Evaluation of Mental Disorders—a self-administered diagnostic instrument)⁶⁰ and, additionally, reported that baseline plasma estradiol levels did not predict response to estrogen treatment.³² Morrison and colleagues³³ observed that estrogen was no more effective than placebo in postmenopausal depressed women, in contrast to previous results in perimenopausal women. These data emphasize that the stage of reproductive senescence may predict response to estrogen, as originally reported by Appleby and colleagues.²⁹ Thus, perimenopausal women who are undergoing changes in reproductive function may be more responsive to estrogen than postmenopausal women, whose hormonal changes have long since stabilized.

Clinical Management

From both research and clinical perspectives, the assessment of perimenopause-related depression should include a careful history focused on several phenomena: (1) the prominence of the affective and behavioral symptoms relative to somatic symptoms such as hot flashes or vaginal dryness; (2) the presence of any past history of

depression or hypomania, in order to compare the similarity of current symptoms with those of previous episodes; (3) possible comorbid or preexisting conditions; (4) the temporal relationship between the severity of mood symptoms and possible changes in menstrual cycle function (regular to irregular); (5) the frequency of estrogen-sensitive somatic symptoms, such as hot flashes, which may predict the effectiveness of estrogen replacement in treating mood and behavioral symptoms; (6) the current social and vocational context; (7) other symptoms that may impact on self-esteem and that may be responsive to estrogen replacement, such as urinary incontinence or sexual dysfunction (due to urogenital changes); (8) potential risk factors for osteoporosis, which may suggest the potential need for estrogen replacement; and (9) the presence of contraindications to estrogen replacement, such as a personal or family history of breast cancer.

The differential diagnosis of perimenopause-related depression includes the following: dysphoria secondary to hot flash-induced dysomnia; depression secondary to adverse or stressful life events; recurrent depression; and medical illness presenting as depression. Reproductive status may be characterized by serial plasma FSH or estradiol levels to confirm the presence of the perimenopause and to track improvements in mood if they occur in relation to changes in pituitary-ovarian hormone secretion.

The decision to prescribe estradiol for perimenopausal depression must further be informed by associated risks and the availability of alternative treatments (such as DHEA, phytoestrogen, or testosterone supplementation). The Women's Health Initiative Study^{43,45,61} demonstrated that continuous administration of one form of estrogen (conjugated estrogens) in combination with one form of progesterone (medroxyprogesterone acetate) is associated with an increased risk of dementia, heart attacks, stroke, blood clots, and breast cancer, particularly when administered many years after menopause.^{43,45,61} Thus, the potential risks for cardiovascular morbidity and breast cancer after prolonged estrogen therapy appear to offset the benefits of estrogen therapy as a first-line treatment for depression. Additionally, several adequate treatments for depression exist, and, there-

fore, the first-line medication for perimenopausal women presenting with depression is a traditional antidepressant, such as an SSRI. Indeed, recent reports documenting the therapeutic benefits of SSRIs in hot flashes support a more prominent role for these medications in the management of perimenopausal depression. Nonetheless, treatment of depression with estradiol could be considered under the following circumstances: (1) as a treatment alternative for ambulatory depressed patients who fail to respond to a conventional first-line intervention (approximately 50%)⁶²; (2) women who refuse to take psychotropic agents or who otherwise prefer treatment with estradiol; (3) women who will undertake treatment with estradiol for other acute symptoms (eg, hot flashes) and who, therefore, could delay treatment with antidepressants until determining whether estradiol treatment was sufficient. While estradiol treatment is no longer appropriate for prophylaxis, it is still reasonably prescribed for acute symptoms and syndromes, including depression.

In addition to the possible antidepressant efficacy of estrogen in perimenopausal depression, some but not all⁶³ studies have suggested that the response of peri- (Soares and colleagues, oral communication, 2001) and postmenopausal women^{64,65} to some antidepressants (ie, SSRIs) may be enhanced by the use of estrogen replacement. Consequently, if not otherwise contraindicated, estrogen augmentation may be of value in the treatment of perimenopausal depressed women who ostensibly are antidepressant nonresponders. Finally, progestin may induce a dysphoric state in some women receiving estrogen therapy. However, progestin-induced dysphorias are not uniformly experienced in all women, nor are predictors of the dysphoric response known. Thus, progestins should not be contraindicated in the presence of an antidepressant response to estradiol in a depressed perimenopausal woman (and are advised in women with a uterus).

Alternative hormonal treatment strategies include DHEA available over-the-counter, phytoestrogens, selective estrogen receptor modulators (SERMs), and testosterone supplementation. The potential roles in perimenopausal depression for phytoestrogens and

SERMs remain to be investigated, whereas DHEA appears to have an anti-depressant effect in some women.⁶⁶ Reports of testosterone's effects on libido suggest the use of this strategy to augment libido in some women (at midlife or during the perimenopause) with decreased libido despite treatment with either SSRIs or estradiol therapy. As in other types of depression, psychotherapy is an important adjunct to pharmacologic or hormonal interventions and can prove crucial in women for whom the menopause holds negative meaning (eg, a hysterectomy can be a traumatic loss for some women) and in those who have significant life stressors and poor social supports.

Conclusion

The relationship between the onset of depressive illness and reproductive senescence has been a source of controversy. Epidemiologic and clinic-based studies that have distinguished between perimenopause (a time of considerable variability in ovarian hormone secretion) and postmenopause (a time when hormonal changes have long since stabilized) have suggested that in some middle-aged women perimenopause is associated with an increased vulnerability to depression. Additional support for this suggestion is provided by double-blind RCTs documenting the therapeutic efficacy of estradiol in perimenopausal depressed women but not in postmenopausal depressed women. Future efforts should abandon the all-or-none controversy and should be directed toward understanding the determinants and consequences of the variability that we see in the response to change in reproductive endocrine function; the response (therapeutic or adverse) to hormonal therapy; the impact of duration of hypogonadism; and the behavioral effects of the growing number of hormone receptor agonists and modulators. **PP**

References

- Conklin WJ. Some neuroses of the menopause. *Trans Am Assoc Obstet Gynecol.* 1889;2:301-311.
- Savage GH. Some mental disorders associated with the menopause. *Lancet.* 1893;2:1128.
- Diagnostic and Statistical Manual of Mental Disorders.* 3rd ed. Washington, DC: American Psychiatric Association; 1983.
- Stenstedt A. Involuntal melancholia: an etiologic clinical and social study of endogenous depression in later life, with special reference to genetic factors. *Acta Psychiatr Neurol Scand.* 1959;127:1-71.

- Brown RP, Sweeney J, Loutsch E, et al. Involuntal melancholia revisited. *Am J Psychiatry.* 1984;141:24-28.
- Weissman MM. The myth of involuntal melancholia. *JAMA.* 1979;242:742-744.
- Adashi EY. The climacteric ovary as a functional gonadotropin-driven androgen-producing gland. *Fertil Steril.* 1994;62:20-27.
- Couzinet B, Meduri G, Lecce MG, et al. The postmenopausal ovary is not a major androgen-producing gland. *J Clin Endocrinol Metab.* 2001;86:5060-5066.
- Reame NE. Gonadotropin changes in the perimenopause. In: Lobo RA, ed. *Proceedings of the International Symposium on Perimenopause.* New York, NY: Springer-Verlag; 1997:157-169.
- Seifer DB, Naftolin F. Moving toward an earlier and better understanding of perimenopause. *Fertil Steril.* 1998;69:387-388.
- Judd HL, Fournet N. Changes of ovarian hormonal function with aging. *Exp Gerontol.* 1994;29:285-298.
- Santoro N, Brown JR, Adel T, et al. Characterization of reproductive hormonal dynamics in the perimenopause. *J Clin Endocrinol Metab.* 1996;81:1495-1501.
- Burger HG, Dudley EC, Hopper JL, et al. The endocrinology of the menopausal transition: a cross-sectional study of a population-based sample. *J Clin Endocrinol Metab.* 1995;80:3537-3545.
- Davis SR, Burger HG. Androgens and the postmenopausal woman. *J Clin Endocrinol Metab.* 1996;81:2759-2763.
- Morley JE, Kaiser F, Raum WJ, et al. Potentially predictive and manipulable blood serum correlates of aging in the healthy human male: progressive decreases in bioavailable testosterone, dehydroepiandrosterone sulfate, and the ratio of insulin-like growth factor 1 to growth hormone. *Proc Natl Acad Sci U S A.* 1997;94:7537-7542.
- Klein NA, Battaglia DE, Miller PB, et al. Circulating levels of growth hormone, insulin-like growth factor-I and growth hormone binding protein in normal women of advanced reproductive age. *Clin Endocrinol.* 1996;44:285-292.
- Soules MR, Sherman S, Parrott E, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). *Fertil Steril.* 2001;76:874-878.
- McKinlay JB, McKinlay SM, Brambilla D. The relative contributions of endocrine changes and social circumstances to depression in mid-aged women. *J Health Soc Behav.* 1987;28:345-363.
- Kaufert PA, Gilbert P, Tate R. The Manitoba project: a re-examination of the link between menopause and depression. *Maturitas.* 1992;14:143-155.
- Avis NE, Brambilla D, McKinlay SM, et al. A longitudinal analysis of the association between menopause and depression: results from the Massachusetts Women's Health Study. *Ann Epidemiol.* 1994;4:214-220.
- Matthews KA, Kuller LH, Wing RR, et al. Biobehavioral aspects of menopause: lessons from the healthy women study. *Exp Gerontol.* 1994;29:337-342.
- Matthews KA. Myths and realities of the menopause. *Psychosom Med.* 1992;54:1-9.
- Hunter M. The South-East England longitudinal study of the climacteric and postmenopause. *Maturitas.* 1992;14:117-126.
- Weissman MM, Leaf PJ, Tischler GL, et al. Affective disorders in five United States communities. *Psychol Med.* 1988;18:141-153.
- Kessler RC, McGonagle KA, Swartz M, et al. Sex and depression in the National Comorbidity Survey I: lifetime prevalence, chronicity and recurrence. *J Affect Disord.* 1993;29:85-96.
- Bromberger JT, Meyer PM, Kravitz HM, et al. Psychologic distress and natural menopause: a multiethnic community study. *Am J Public Health.* 2001;91:1435-1442.
- Hay AG, Bancroft J, Johnstone EC. Affective symptoms in women attending a menopause clinic. *Br J Psychiatry.* 1994;164:513-516.
- Stewart DE, Boydell K, Derzko C, et al. Psychologic distress during the menopausal years in women attending a menopause clinic. *Int J Psychiatry Med.* 1992;22:213-220.
- Appleby L, Montgomery J, Studd J. Oestrogens and affective disorders. In: Studd J, ed. *Progress in Obstetrics and Gynaecology.* Edinburgh, United Kingdom: Churchill Livingstone; 1981:289-302.
- Montgomery JC, Brincat M, Tapp A, et al. Effect of oestrogen and testosterone implants on psychological disorders in the climacteric. *Lancet.* 1987;1:297-299.
- Schmidt PJ, Nieman L, Danaceau MA, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol.* 2000;183:414-420.
- Soares CD, Almeida OP, Joffe H, et al. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry.* 2001;58:529-534.
- Morrison MF, Kallan MJ, Have TT, Katy IR, Tweedy K, Battistini M. Lack of efficacy of estradiol for depression in postmenopausal women: a randomized controlled trial. *Biol Psychiatry.* 2004. In press.
- Yaffe K, Sawaya G, Lieberburg I, et al. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA.* 1998;279:688-695.
- LeBlanc ES, Janowsky J, Chan BKS, et al. Hormone replacement therapy and cognition: systematic review and meta-analysis. *JAMA.* 2001;285:1489-1499.
- Zandi PP, Carlson MC, Plassman BL, et al. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County study. *JAMA.* 2002;288:2123-2129.
- Resnick SM, Henderson VW. Hormone therapy and risk of Alzheimer disease: a critical time. *JAMA.* 2002;288:2170-2172.
- Gibbs RB. Long-term treatment with estrogen and progesterone enhances acquisition of a spatial memory task by ovariectomized aged rats. *Neurobiol Aging.* 2000;21:107-116.
- Mikkola TS, Clarkson TB. Estrogen replacement therapy, atherosclerosis, and vascular function. *Cardiovasc Res.* 2002;53:605-619.
- Brownley KA, Hinderliter AL, West SG. Cardiovascular effects of six months of hormone replacement therapy vs. placebo: differences associated with years since menopause. *Am J Obstet Gynecol.* 2004. In press.
- Jaszmann L, van Lith ND, Zaat JCA. The perimenopausal symptoms: the statistical analysis of a survey: Part A. *Med Gynaecol Sociol.* 1969;4:268-277.
- Dennerstein L, Smith AMA, Morse C, et al. Menopausal symptoms in Australian women. *Med J Aust.* 1993;159:232-236.
- Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288:321-333.
- Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA.* 2003;289:2651-2662.
- Rapp SR, Espeland MA, Shumaker SA, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA.* 2003;289:2663-2672.
- Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on postmenopausal hormone therapy. *N Engl J Med.* 2003;348:645-650.
- Herrington DM, Howard TD, Hawkins GA, et al. Estrogen-receptor polymorphisms and effects of estrogen replacement on high-density lipoprotein cholesterol in women with coronary disease. *N Engl J Med.* 2002;346:967-974.