

The Metabolic Syndrome:

Impact on women and considerations for treatment

► Cynthia K. Sites, MD, and Shauna L. McKinney, MD

Introduction

Metabolic Syndrome (MetS) refers to a constellation of factors that increase an individual's risk of cardiovascular morbidity and mortality as well as type 2 diabetes mellitus (T2DM). The term MetS is relatively new but appears to have been initially defined, in a formal way, by the Swedish physician Eskil Kylin. In 1923, Dr Kylin reported on a metabolic disorder characterized by hypertension, hyperglycemia, and hyperuricemia.¹ More recently, in 1988, Gerald Reaven

and his colleagues identified a clustering of risk factors that they coined Syndrome X.² Reaven was among the first to suggest that insulin resistance and obesity were directly linked to this clustering of metabolic risk factors that predispose an individual to cardiovascular disease (CVD) and T2DM.

In the late 1990s, the World Health Organization formally defined MetS but the criteria that appear to have gained the widest acceptance are those set forth by the National Cholesterol Education Program (NCEP) Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III).³ The American As-

sociation of Clinical Endocrinology (AACE) and the International Diabetes Foundation (IDF) have also defined MetS based on their differing opinions regarding what constitutes the absolute thresholds for the various criteria, such as waist circumference or lipid level.

There is also a lack of agreement regarding which of the criteria are most clinically relevant to provide a diagnosis of MetS. Nevertheless, each organization agrees on 4 distinct criteria for making the diagnosis of MetS. These include central adiposity, hypertension, glucose intolerance, and dyslipidemia. **TABLE 1** shows the most widely used criteria as defined by NCEP-ATP III, including new ethnic-specific criteria.⁴

Importance of diagnosis

It has been suggested that the importance of diagnosing MetS is to identify and reduce or negate its effects on the development of CVD and T2DM. The value of collating these individual risk factors into a single entity appears to be its ability to assist the clinician in identifying and intervening in that segment of the population at increased risk of CVD (eg, coronary heart disease [CHD], peripheral

Cynthia K. Sites, MD, Shauna L. McKinney, MD
Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility
University of Alabama at Birmingham
Birmingham, Alabama

CONTINUED ON PAGE S3

S2 From the editor

■ Nanette F. Santoro, MD

S8 Is the risk of depression greater during menopause?

■ Veronica Harsh, MD, Peter J. Schmidt, MD, David Rubinow, MD

PRESIDENT G. David Adamson, MD
PRESIDENT-ELECT R. Dale McClure, MD
VICE PRESIDENT William E. Gibbons, MD

IMMEDIATE PAST PRESIDENT
Steven J. Ory, MD

PAST PRESIDENT Joseph S. Sanfilippo, MD, MBA

SECRETARY Catherine Racowsky, PhD

TREASURER Stuart S. Howards, MD

EXECUTIVE DIRECTOR Robert W. Rebar, MD

CHIEF OPERATING OFFICER
Nancy R. Frankel, BS, MBA

SCIENTIFIC DIRECTOR
Andrew R. La Barbera, PhD, HCLD

DIRECTORS

Owen K. Davis, MD

Dolores J. Lamb, PhD

Richard J. Paulson, MD

Elizabeth E. Puscheck, MD

Richard H. Reindollar, MD

William D. Schlaff, MD

ASRM AFFILIATE SOCIETY PRESIDENTS

Michael P. Diamond, MD (SREI)

Tommaso Falcone, MD (SRS)

Mark D. Hornstein, MD (SART)

Jay I. Sandlow, MD (SMRU)

EDITOR

Nanette F. Santoro, MD

Professor and Director

Division of Reproductive Endocrinology
Department of Ob/Gyn and Women's Health
Albert Einstein College of Medicine
Bronx, New York

EDITORIAL BOARD

Kurt T. Barnhart, MD, MSCE

Associate Professor, Obstetrics
and Gynecology and Epidemiology
Senior Scholar, Center for Clinical
Epidemiology and Biostatistics

University of Pennsylvania Medical Center
Penn Fertility Care
Philadelphia, Pennsylvania

Morris Notelovitz, MD, PhD

Consultant, Adult Women's Health and Medicine
Boca Raton, Florida

Cynthia K. Sites, MD

Associate Professor

Department of Obstetrics & Gynecology
University of Alabama at Birmingham
Birmingham, Alabama

DIRECTOR OF COMMUNICATIONS

Mitzi Mize, MS

MANAGING EDITOR

Jennifer Price, MA

*The ASRM is pleased to acknowledge the generous
contribution of Wyeth Pharmaceuticals toward
the publication of this newsletter.*

Wyeth

COPYRIGHT © 2008

American Society for Reproductive Medicine

1209 Montgomery Hwy., Birmingham, AL 35216
(205) 978-5000 • asrm@asrm.org • www.asrm.org

*Views and opinions published in Menopausal Medicine
are not necessarily endorsed by the ASRM.*



Is menopause associated with an increased risk of depression?

New, thought-provoking data presented by Drs Harsh, Schmidt, and Rubinow describe the prevalence and presentation of depression in women during perimenopause and menopause in this issue of Menopausal Medicine.

Many of us expected the latest observational studies to show that women with prior hormonal-related depression would comprise the chief risk pool for perimenopausal and menopausal depression. Instead, 3 observational studies suggest a complex picture: The Harvard Study of Moods and Cycles, The Penn Ovarian Aging Study, and The Study of Women's Health Across the Nation (SWAN) indicate that many of the women who have major depression do not have a prior history.

Perhaps clinicians should view their patients in a new light. Why? Because we often assume that women of a certain age are able to detect the signs and symptoms that suggest they may have menopause-related depression. Evidently, that is not the case. Patients who experience new onset of depression may lack the vocabulary to accurately communicate their symptoms and resultant distress. Clinicians need to look beyond the superficial symptoms that patients may mention in order to make the correct diagnosis.

In this issue, Drs Sites and McKinney explore another complex relationship between menopause and the metabolic syndrome. They discuss how each symptom of the metabolic syndrome—increased blood pressure, elevated insulin levels, excess body fat around the waist, or abnormal cholesterol levels—develop gradually in an aging individual. Menopause and its accompanying loss of estrogen worsen these components.

We need to help our menopausal patients meet the challenge of preventing central adiposity. Physical activity and dietary control of fat and total caloric intake are the cornerstones of current treatment. Again, the clinician must help patients recognize their health risks and encourage the necessary, often difficult lifestyle modifications and medications needed to live a longer, healthier life.

In these, as in so many other cases, clinicians must take on the role of educator as well as physician. We can never assume that our patients know too much.

Nanette F. Santoro, MD

vascular disease, and stroke) and T2DM.

The question has been raised as to whether the risk of atherosclerotic CVD associated with MetS is greater than the sum of its risk factors. Epidemiologic studies strongly suggest that multiple risk factors, such as those that comprise MetS, raise an individual's health risks more than the sum of the accompanying single risk factors.⁵ Additionally, several metabolic risk factors (prothrombotic state, proinflammatory state, and elevated triglycerides) are not included in standard algorithms but undoubtedly are independent risk factors for cardiovascular events. Since MetS is often progressive and culminates in CVD and T2DM, the syndrome's long-term risk is likely underestimated at any one time. It seems, then, that the risk accompanying MetS is greater than the sum of its measured components.⁵

MetS vs 10-year risk assessment

MetS, however, is not a reliable tool for global risk assessment for atherosclerotic CVD in the short term (such as 10-year risk). It does not account for all of the risk factors involved in the standard risk-prediction algorithms (age, gender, total cholesterol, and smoking status). Thus, algorithms such as the Framingham risk scoring system better determine a 10-year risk assessment.⁵ The British Regional Heart Study showed that MetS was inferior to the Framingham Risk Score in predicting total CHD or major CVD over 20 years but was superior in predicting T2DM.⁶ Jassal et al examined the sex-specific contributions of MetS and microalbuminuria to CVD and CHD mortality.⁷ In their cohort, they found that microalbuminuria and MetS together was a more powerful predictor of CVD mortality than either alone in women but not in men. This study provided new evidence

that screening for microalbuminuria in older women (>40 years) may identify those at high risk of CVD mortality beyond that conferred by risk factors included in MetS.⁷

The CVD and MetS connection

CVD is the number one cause of mortality in women. Studies have shown an association between the diagnosis of MetS and an increase in an individual's risk for CVD.⁸ The San Antonio Heart Study highlighted gender differences in CVD risk in patients diagnosed with MetS. The hazard ratios for cardiovascular mortality in patients with ATP III-defined MetS were 4.6 (95% confidence interval [CI], 2.35-9.21) in women and 1.82 (95% CI, 1.14-2.91) in men. Clear gender-specific differences have been shown in MetS prevalence, presentation, and risk, with women having more negative CVD outcomes.⁸⁻¹⁴ Of great interest is whether the diagnosis of MetS in menopausal women is affected by events that occurred in their reproductive years. Unique modifiers of MetS exist for women and may include pregnancy, lactation, gestational diabetes mellitus (GDM), preeclampsia, hormonal contraceptive use, polycystic ovarian syndrome (PCOS), and menopause.⁹

Prevalence

According to the US Census 2000 data, METs is present in 47 million residents.¹⁵ Although the age-adjusted prevalence was similar in men (24%) and women (23%), gender equality was lost when comparisons were made within ethnic groups.⁹ Whereas Caucasian women were found to have a lower prevalence of MetS than do Caucasian men, this trend did not hold true for either African American or Mexican American women.¹⁵ The Census 2000 data revealed that 57% more African American women and 26% more Mexican American women

TABLE 1

NCEP-ATP III Guidelines for Diagnosis of MetS

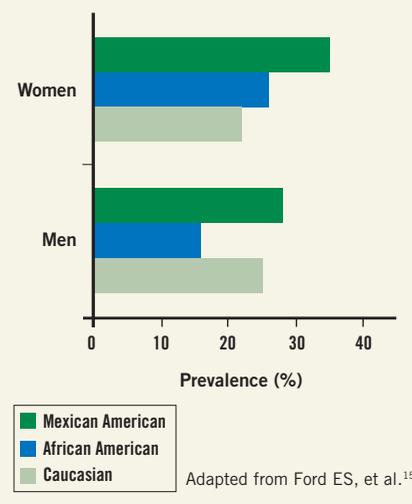
Risk factor	Threshold level for diagnosis
Abdominal obesity (waist circumference)*	
Men	>102 cm (>40 inches)
Women	>88 cm (>35 inches)
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL

Diagnosis is established when ≥3 of these risk factors are present.

*Ethnic-specific criteria for abdominal obesity in Asians is >90 cm in men and >80 cm in women.⁴

FIGURE 1

Racial, Ethnic, and Gender Differences in the Prevalence of MetS



have MetS than do males in the same ethnic group (FIGURE 1).⁹

When the National Health and Nutrition Examination Survey (NHANES) data from 1988-1994 was compared with NHANES data from 1999-2000, it was noted that the age-adjusted prevalence of MetS increased by 23.5% among women ($P=.021$) and

2.2% among men ($P=.831$). Based on the increasing prevalence of MetS in women, it appears that the similarity in age-adjusted prevalence between men and women, regardless of ethnicity, will likely be lost over time.⁹ Ford et al evaluated the causes of the increasing prevalence of MetS among women in the United States and found that increases in blood pressure, waist circumference (surrogate for central adiposity), and triglycerides have occurred.¹⁶

The American Heart Association (AHA) reports that 1 out of every 2 women will develop some form of CVD during their lifetime.¹³ As previously stated, CVD is the number one killer of women in the United States and has been estimated to affect approximately 42 million US women over the age of 20. It is disconcerting to think that two-thirds of cardiac deaths (66%) occur without individual awareness of the risk of CVD. To gain some perspective regarding the significance of CVD in women, the 2008 update of the AHA Heart Disease and Stroke Statistics showed that 1 in 30 female deaths were attributed to breast cancer, whereas 1 in 2.6 women died of CVD.¹³ Put another way, CVD claims more lives each year than the next 5 leading causes of death (cancer, Alzheimer's disease, chronic respiratory disease, accidents, and diabetes mellitus) combined.¹³

Presentation of MetS in women Obesity

Abdominal obesity, or central adiposity, is the manifestation of increased visceral storage of adipose tissue and is most highly associated with MetS.^{11,17} Clinically, obesity most recently has been defined by the body mass index (BMI) which is simply the person's weight (kilograms) divided by their squared height (meters²) [BMI <24.9, normal weight; >25 but <29.9, overweight; and >30, obese].

BMI, however, does not account for the actual distribution of fat mass in an individual; it is this distribution of fat, one's "body composition," which determines metabolic risk.¹⁸ Abdominal visceral fat is thought to be the most deleterious from a metabolic standpoint, with abdominal subcutaneous fat imposing an intermediate risk. Notably, lower extremity adiposity may actually confer "metabolic protection."¹⁹ Visceral fat, when compared to subcutaneous fat, is less sensitive to the action of insulin and causes the body to undergo lipolysis, releasing free fatty acids into the circulation; this ultimately leads to elevated serum levels of cholesterol and low-density lipoprotein (LDL), known to be independent risk factors for CVD.¹⁹

Premenopausal women tend to have a gynoid or "pear" shape, characterized by fat accumulation in the subcutaneous gluteal/femoral regions (buttocks/hips). It has been suggested that with the loss of estrogen at menopause, a woman's body shape begins to change and becomes more android, or "apple" in appearance. Although menopausal women are noted to have an increase in total body fat, with adipose distribution occurring between both visceral and subcutaneous depots, it is the visceral depot that preferentially gains a greater percentage of total fat.¹⁸ Older women gain approximately 1 pound of weight per year in the aging process, which is occurring simultaneously with menopause. Studies show that women with an android body composition (increased central adiposity) have an increased risk of cardiovascular mortality and associated metabolic abnormalities such as glucose intolerance, insulin resistance, increased risk of T2DM, and dyslipidemia.^{20,21}

Central adiposity has been quantified in a variety of ways, including

dual x-ray absorptiometry (DXA) and computed tomography (CT). Although both DXA and CT can provide accurate measures of central adiposity, these modalities are labor-intensive, time-consuming, costly, and of limited availability in the office setting. Waist circumference has been shown to directly predict MetS²² and act as a surrogate marker for central adiposity. Waist circumference greater than 88 cm (34 inches) in a female satisfies the MetS criterion as defined by the ATP III.

Over the past 20 years, the percentage of women with abdominal obesity has increased from 47.0% to 61.3% ($P<.001$).²³ The San Antonio Heart Study presents data that suggest that increases in BMI and waist circumference increase the risk of developing MetS to a greater degree in women than in men.²² Thus it appears that both the aging process and menopause result in an increase in total body fat as well as a change in body composition, which favors the development of MetS.

Hypertension

Hypertension increases the risk of CVD; its prevalence increases as a woman ages. Studies have shown an increase in hypertension in menopausal women even after correcting for age and body weight.¹⁴ The prevalence of hypertension in menopausal women also exceeds that of age-matched men.^{10,24} There are several physiologic mechanisms that help to explain this phenomenon of increasing blood pressure in menopausal women.

It is known that estrogen prevents the conversion of angiotensin I to angiotensin II and decreases the sensitivity of angiotensin receptors, which favors vasodilatation.²⁵ With declining estrogen levels at menopause, the conversion of angiotensin I to angiotensin II is increased. Both

plasma renin activity and sympathetic activity are also increased, which favors vasoconstriction and results in increased blood pressure.¹² Estrogen also enhances nitric oxide synthesis, promoting vasodilatation. In an estrogen-deficient state (menopause), this blood pressure-lowering mechanism would be lost. Thus, menopause may promote hypertension, contributing to MetS and the risk of CVD.

Glucose intolerance

Insulin resistance is defined as the inability of insulin to promote the uptake of glucose into skeletal muscle. Many investigators have suggested that insulin resistance is of greater significance than obesity in the pathogenesis of MetS.¹² However, insulin resistance is directly related to obesity, and hyperglycemia increases with increasing body fat.¹² Overt diabetes increases the risk of atherosclerosis to a greater degree in women than in men, secondary to worsening lipid profiles. Women with diabetes have greater increases in triglycerides and LDL with lower levels of high-density lipoprotein (HDL) compared to diabetic men.¹² Of note, premenopausal diabetic women have the same cardiovascular risk profile as diabetic men. With the decline in estrogen at menopause, women have a greater degree of insulin resistance. However, insulin sensitivity and glucose intolerance are not entirely explained by a woman's hormonal status. There are now data showing that weight gain in women is a stronger predictor of impaired glucose tolerance than is menopausal status.¹²

Dyslipidemia

Premenopausal women have higher HDL levels than their age-matched male counterparts and, thus, are less likely to satisfy this criterion of MetS. Estrogen deficiency is associated with a more atherogenic lipid profile and

is thought to be responsible for the increased CVD seen in menopausal women.¹² The decline in estrogen is known to result in increased triglycerides and increased total and LDL cholesterol, with a concomitant decline in HDL cholesterol. Thus, the increase in dyslipidemia after menopause increases the risk of development of MetS.

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a disorder that is diagnosed in approximately 5% of reproductive age women. The accepted criteria for diagnosing PCOS are still undergoing debate. PCOS is defined in women with oligo- or anovulation, clinical or laboratory evidence of hyperandrogenism, and the exclusion of other endocrine disorders. Ultrasonographic finding of "multicystic ovaries" has recently been added to the criteria for PCOS.²⁶ The etiology of PCOS has not been elucidated fully at this time. Patients with PCOS are known to have many of the characteristics of MetS, including obesity, glucose metabolism abnormalities, and dyslipidemia. The prevalence of MetS in women with PCOS is twice as high as that of the age- and BMI-matched controls. Women with PCOS also have a higher risk of T2DM and hypertension. Central obesity and dyslipidemia (including low serum HDL levels) are routinely found in women with PCOS. Thus, the diagnosis of PCOS during a woman's adolescent and reproductive years places her at an increased risk of MetS throughout her lifetime.¹²

Treatment options for menopausal women with MetS

Lifestyle interventions

The increasing prevalence of obesity in menopausal women would seem to suggest that weight loss is a straightforward means of preventing MetS.

TABLE 2

Recommended Treatment Options for MetS

Lifestyle interventions

Weight reduction

Increased physical activity

Smoking cessation

Pharmacologic interventions

Antihypertensives

Lipid-lowering agents

Antidiabetic agents

One simply must create a negative energy balance; that is "burn more, eat less," but this is quite difficult in practice. Estrogen deficiency brings about changes in fat distribution that increase the risk of MetS, T2DM, and CVD. The AHA published evidence-based guidelines in 2007 for CVD prevention in women. The cornerstone is lifestyle interventions, including smoking cessation, dietary modifications that "result in weight loss," and an increase in physical activity. CVD risk can be reduced by as much as 82% by maintaining a healthy diet and body weight while engaging in regular physical activity. Dietary recommendations include a diet low in both saturated and transaturated fat as well as a carbohydrate-controlled diet. Many of the risk factors associated with MetS are attenuated with weight loss. The Diabetes Prevention Program demonstrated that reducing body weight by only 7% was associated with a 58% reduction in T2DM.³⁰

Pharmacologic interventions

Targeted interventions can address other major risk factors, such as insulin resistance, elevated blood pressure, and an abnormal lipid profile. Lowering of blood pressure with antihypertensive agents effectively reduces CVD risk in women. The

TABLE 3

Recommended Treatment Options for MetS

Botanicals

Russian tarragon

Anthrocyanins

Supplements

Soy isoflavones

Chromium picolinate

pharmacologic treatment of dyslipidemia with fibrate or statin therapy is also beneficial in women for prevention of heart disease. For example, when a practitioner prescribes a statin for the treatment of hypercholesterolemia, it is recommended that use of the medication be combined with lifestyle changes such as diet and exercise, which will affect other risk factors. In addition, there is some evidence to suggest that statins, which are known to reduce inflammation, may also increase adiponectin levels (marker of insulin sensitivity),³¹ so in this way, other risk factors may be treated as well (TABLE 2).

A meta-analysis published in 2006 demonstrated global improvement in the individual components of MetS in menopausal women receiving hormone therapy (HT).³² A reduction in abdominal obesity, insulin resistance, and new-onset diabetes as well as improvement in the lipid profile and blood pressure in menopausal women receiving HT was noted. Menopausal women with T2DM who received HT were also found to experience an improvement in their insulin resistance and fasting glucose levels. However, this meta-analysis was limited in that various hormone preparations and doses were combined for analysis. Also, criterion measures were not

used to assess body fat distribution and insulin sensitivity.

In a 2-year, randomized trial of postmenopausal women without diabetes, combined estrogen/progestin did not significantly affect visceral fat, subcutaneous abdominal fat, total body fat, or lean body mass. The trial used CT scans to assess body fat distribution and euglycemic hyperinsulinemic clamps to measure insulin sensitivity. Insulin sensitivity worsened by 17%, but this was reversed after discontinuing HT.³³ It is important to remember that HT is not currently indicated for prevention of chronic disease, including CVD and MetS.

Future treatment for MetS

In the future, postmenopausal women may have new options for preventing MetS. Supplementation with soy isoflavones reduces the gain in subcutaneous abdominal fat in postmenopausal women.³⁴ Chromium picolinate supplementation attenuates body weight gain and visceral fat accumulation, while improving insulin sensitivity and glucose control in patients with T2DM.³⁵ Studies in rodents report that some botanicals may also improve components of MetS. Specifically, the botanical Russian tarragon reduces cholesterol and blood glucose levels. In addition, the botanical anthrocyanin (found in berries) improves insulin sensitivity, reduces fat deposition, and improves fatty acid uptake and oxidation in peripheral tissues.³⁶

Further studies are needed on these supplements and botanicals in perimenopausal and postmenopausal women before definitive recommendations can be made on their use in the prevention of MetS, optimal doses, and long-term safety (TABLE 3).

Summary

Many features of MetS arise or worsen with the onset of menopause. Estrogen deficiency has been shown to negatively impact many of the criteria used to diagnose MetS. Estrogen deficiency appears to play a role in increasing central adiposity with or without actual weight gain. Menopausal women have a higher incidence of hypertension, dyslipidemia, and insulin resistance.

MetS is an increasingly prevalent disorder known to significantly enhance the risk of developing cardiovascular disease and diabetes. The syndrome is defined by a constellation of cardiac risk factors that include obesity, atherogenic dyslipidemia, hypertension, and insulin resistance. There are several unique features of MetS in women. An insulin-resistant state associated with both PCOS and increased abdominal fat may contribute to the development of MetS and increase cardiovascular risk. Menopause heralds a decline in circulating estrogen levels, which may increase cardiovascular risk through effects on adiposity, lipid metabolism, and prothrombotic state.

The key elements involved in managing MetS are dietary and lifestyle modification. Managing individual cardiac risk factors with the use of antihypertensive and lipid-modifying agents is also appropriate. Although HT could have beneficial effects on the components of MetS, current recommendations do not include HT for either primary or secondary prevention of CVD or for prevention of MetS. In the future, some supplements and botanicals (soy isoflavones, chromium picolinate, Russian tarragon, and anthrocyanins) may provide alternatives for preventing MetS in menopausal women.

Disclosures

Drs Sites and McKinney have no financial relationships to disclose.

References

1. Kendall DM, Harmel AP. The metabolic syndrome, type 2 diabetes, and cardiovascular disease: understanding the role of insulin resistance. *The American Journal of Managed Care* 2002;8:S635-53; quiz S54-7.
2. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595-607.
3. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.
4. Liu J, Grundy SM, Wang W, Smith SC, Jr, Vega GL, Wu Z et al. Ethnic-specific criteria for the metabolic syndrome: evidence from China. *Diabetes Care* 2006;29:1414-6.
5. Grundy SM. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. *Journal of the American College of Cardiology* 2006;47:1093-100.
6. Wannamethee SG. The metabolic syndrome and cardiovascular risk in the British Regional Heart Study. *International Journal of Obesity* (2005) 2008;32 Suppl 2:S25-9.
7. Jassal SK, Langenberg C, von Muhlen D, Bergstrom J, Barrett-Connor E. Usefulness of microalbuminuria versus the metabolic syndrome as a predictor of cardiovascular disease in women and men >40 years of age (from the Rancho Bernardo Study). *The American Journal of Cardiology* 2008;101:1275-80.
8. Sarafidis PA, McFarlane SI, Bakris GL. Gender disparity in outcomes of care and management for diabetes and the metabolic syndrome. *Current Diabetes Reports* 2006;6:219-24.
9. Bentley-Lewis R, Koruda K, Seely EW. The metabolic syndrome in women. *Nature Clinical Practice* 2007;3:696-704.
10. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension* 1995;25:305-13.
11. Grundy SM, Brewer HB, Jr, Cleeman JJ, Smith SC, Jr, Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004;109:433-8.
12. Paul S, Smith L. The metabolic syndrome in women: a growing problem for cardiac risk. *The Journal of Cardiovascular Nursing* 2005;20:427-32.
13. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N et al. Heart disease and stroke statistics-2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008;117:e25-146.
14. Tremolieres FA, Pouilles JM, Cauneille C, Ribot C. Coronary heart disease risk factors and menopause: a study in 1684 French women. *Atherosclerosis* 1999;142:415-23.
15. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002;287:356-9.
16. Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. Adults. *Diabetes Care* 2004;27:2444-9.
17. Deedwania PC. Metabolic syndrome and vascular disease: is nature or nurture leading the new epidemic of cardiovascular disease? *Circulation* 2004;109:2-4.
18. Carr MC. The emergence of the metabolic syndrome with menopause. *The Journal of Clinical Endocrinology and Metabolism* 2003;88:2404-11.
19. Van Pelt RE, Jankowski CM, Gozansky WS, Schwartz RS, Kohrt WM. Lower-body adiposity and metabolic protection in postmenopausal women. *The Journal of clinical endocrinology and metabolism* 2005;90:4573-8.
20. Garaulet M, Perez-Llomas F, Baraza JC, Garcia-Prieto MD, Fardy PS, Tebar FJ et al. Body fat distribution in pre- and post-menopausal women: metabolic and anthropometric variables. *The journal of nutrition, health & aging* 2002;6:123-6.
21. Steinbaum SR. The metabolic syndrome: an emerging health epidemic in women. *Progress in cardiovascular diseases* 2004;46:321-36.
22. Han TS, Williams K, Sattar N, Hunt KJ, Lean ME, Haffner SM. Analysis of obesity and hyperinsulinemia in the development of metabolic syndrome: San Antonio Heart Study. *Obesity research* 2002;10:923-31.
23. Li C, Ford ES, McGuire LC, Mokdad AH. Increasing trends in waist circumference and abdominal obesity among US adults. *Obesity* (Silver Spring, Md) 2007;15:216-24.
24. Harrison-Bernard LM, Raji L. Postmenopausal hypertension. *Current hypertension reports* 2000; 2:202-7.
25. Fisman EZ, Tenenbaum A, Pines A. Systemic hypertension in postmenopausal women: a clinical approach. *Current hypertension reports* 2002;4:464-70.
26. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Human reproduction* (Oxford, England) 2004;19:41-7.
27. Azziz R. How prevalent is metabolic syndrome in women with polycystic ovary syndrome? *Nature clinical practice* 2006;2:132-3.
28. Soares EM, Azevedo GD, Gadelha RG, Lemos TM, Maranhao TM. Prevalence of the metabolic syndrome and its components in Brazilian women with polycystic ovary syndrome. *Fertility and sterility* 2008;89:649-55.
29. Coviello AD, Legro RS, Dunaif A. Adolescent girls with polycystic ovary syndrome have an increased risk of the metabolic syndrome associated with increasing androgen levels independent of obesity and insulin resistance. *The Journal of clinical endocrinology and metabolism* 2006;91:492-7.
30. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England journal of medicine* 2002;346:393-403.
31. Inami N, Nomura S, Shouzu A, Omoto S, Kimura Y, Takahashi N et al. Effects of pitavastatin on adiponectin in patients with hyperlipidemia. *Pathophysiology of haemostasis and thrombosis* 2007;36:1-8.
32. Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. *Diabetes, obesity & metabolism* 2006;8:538-54.
33. Sites CK, L'Hommedieu GD, Toth MJ, Brochu M, Cooper BC, Fairhurst PA. The effect of hormone replacement therapy on body composition, body fat distribution, and insulin sensitivity in menopausal women: a randomized, double-blind, placebo-controlled trial. *The Journal of clinical endocrinology and metabolism* 2005;90:2701-7.
34. Sites CK, Cooper BC, Toth MJ, Gastaldelli A, Arabshahi A, Barnes S. Effect of a daily supplement of soy protein on body composition and insulin secretion in postmenopausal women. *Fertility and sterility* 2007;88:1609-17.
35. Martin J, Wang ZQ, Zhang XH, Wachtel D, Volaufova J, Matthews DE et al. Chromium picolinate supplementation attenuates body weight gain and increases insulin sensitivity in subjects with type 2 diabetes. *Diabetes care* 2006;29:1826-32.
36. Cefalu WT, Ye J, Zuberi A, Ribnicky DM, Raskin I, Liu Z et al. Botanicals and the metabolic syndrome. *The American journal of clinical nutrition* 2008;87: 481S-7S.

Is the risk of depression greater during the menopause?

► Veronica Harsh, MD, Peter J. Schmidt, MD, and David Rubinow, MD

Introduction

This review focuses on the relationship between the onset of depression and events surrounding the menopausal transition. First, background information will be provided on depressive disorders, including their prevalence, impact, diagnostic methodologies, course and treatment outcome. We then review the current literature that relates to the following three questions:

- 1) Is there an increased risk of depression during the menopausal transition?
- 2) Are there identifiable risk factors for the onset of depression during the menopausal transition?
- 3) Is depression during the menopausal transition associated with abnormalities of ovarian hormone secretion?

Background

Prevalence of depression

Major and minor depression are prevalent forms of depressive illness. Major depression has an estimated lifetime prevalence of approximately 20% in women and affects women twice as often as men.¹ The lifetime

prevalence of minor depression is estimated to be comparable, if not greater than, that of major depression.² There is considerable overlap between the clinical characteristics of major and minor depressions of moderate severity including family history, course (i.e., both major and minor depressions occur in the same individual over their lifetime),³ as well as several biological characteristics. Indeed, minor depressions not only contribute to a substantial disability on their own but also increase a person's risk for developing more severe forms of depressive illness. Finally, both major and minor depressions can present as mood disorders during reproductive endocrine transitions, such as the postpartum period and the menopause transition.

Impact of depression

The World Health Organization has determined that major depression is a leading source of years of life lived with disability worldwide⁴ and is associated with multiple forms of disability involving social function, work productivity, physical health, and emotional functioning,⁵ as well as higher rates of marital dissatisfaction and divorce. The estimated annual expenditure for major depression in the United States is \$83 billion in workplace, mortality, and direct treatment costs.⁶

In addition to the functional disability that is directly attributed to major and minor depressions, adverse medical sequelae of depression have been identified, including increased risks of cardiovascular disease, Al-

zheimers' disease, premature ovarian failure, osteoporosis, and the metabolic syndrome. Depression might also represent a modifiable risk factor for the onset of some of these medical conditions. For example, if depression exists as a comorbid condition, it will increase the morbidity and mortality of several medical illnesses including heart disease.⁷ Finally, several studies have identified a substantially increased health care utilization cost associated with a variety of medical conditions when they are comorbid with depression.

Criteria for the diagnosis of depression

Depression is both underdiagnosed and undertreated. Standardized criteria for diagnosing both major and minor depression have been developed to distinguish depressive symptoms (i.e., sadness), which may be multidetermined, from depressive syndromes (i.e., major or minor depression), which have particular familial patterns, biological features, and treatment response characteristics. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV)⁸ specifies selected core symptoms of depression (five for major depression and three for minor depression), which must be present for at least two weeks, be associated with clinically significant distress or impairment in social or occupational functioning, and not be caused by medications, a medical condition (e.g., hypothyroidism), or bereavement (TABLE 1). Structured diagnostic

Veronica Harsh, MD, Peter J. Schmidt, MD

Behavioral Endocrinology Branch, National Institute of Mental Health, NIH, DHHS
Bethesda, Maryland

David Rubinow, MD

Department of Psychiatry, University of North Carolina, Chapel Hill,
Chapel Hill, North Carolina

This work was written as part of Drs Schmidt and Harsh's official duties as government employees. The views expressed in this article do not necessarily represent the views of the NIMH, NIH, HHS, or the United States government.

interviews are employed in research studies to establish the presence of a diagnosis of depression (e.g., SCID9), and modifications of these diagnostic instruments have been developed to screen patients for the presence of depression in medical settings. For example, recent studies employing the PRIME-MD10 as a screening instrument identified rates of mood disorder in women of approximately 31% in primary care clinics and 13% in gynecologic clinics.

In addition to the symptoms of depressive illness listed in **TABLE 1**, a considerable proportion of depressed outpatients experience somatic symptoms including fatigue, generalized musculoskeletal pain, and weakness. Multiple somatic complaints have been observed in up to 50% of depressed men and women, with a greater proportion of depressed women reporting somatic complaints than depressed men.¹¹ Somatic symptoms occurring in the context of a depressive illness are clinically important since their presence could delay the diagnosis of depression, delay appropriate treatment, and may be associated with differential treatment response characteristics. Clinicians once believed that somatic symptoms caused depression; however, these symptoms also may be a manifestation of, rather than a cause of, depression.¹¹ Thus, depression (even minor depression) accompanied by somatic symptoms, as may occur in women who develop depression during the menopause transition and who also report hot flashes, should not be presumed to reflect an “appropriate” reaction to disturbing somatic symptoms.

Course and treatment of depression

The occurrence of an episode of depression will increase an individual’s risk of developing recurrent episodes of depression. Thus, appropriate treat-

TABLE 1

DSM-IV core symptoms of major and minor depressive episodes

- (1) Depressed mood most of the day
- (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day
- (3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite
- (4) Insomnia or hypersomnia
- (5) Psychomotor agitation or retardation
- (6) Fatigue or loss of energy
- (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional), not merely self-reproach or guilt about being sick
- (8) Diminished ability to think or concentrate, or indecisiveness
- (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

In major depression, five (or more) of the above symptoms are present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms is either depressed mood or loss of interest or pleasure. Symptoms 1 – 8, if present, should be present nearly every day. The same criteria are used for minor depression except only two symptoms need to be present.

Adapted from the American Psychiatric Association 1994⁸

ment could reduce future recurrences. Estimates of the length of a major depressive episode range from an average of four to eight months,¹² with one study reporting that 50% of episodes of major depression remit within three months, regardless of treatment.¹² However, in approximately 20% of patients with major depression, the episodes become chronic (i.e., the duration of illness exceeds two years).¹²

Treatments for both major and minor depression include psychotherapy (time-limited focused cognitive or interpersonal therapy), antidepressant medications, and other somatic therapies (e.g., electroconvulsive therapy for severe major depression).

In contrast to public perceptions that antidepressants are over-prescribed, recent epidemiologic evidence suggests that only 43% of people with depression in the U.S. seek and receive treatment, and only 20% receive minimally adequate treatment (defined as either receiving an appropriate antidepressant agent for at least two months plus at least four visits to any medical doctor, or psychothera-

py involving at least eight visits to a health care professional lasting an average of at least 30 minutes).¹³ Indeed, patients with major depression are nearly as likely to receive care from a non-health care provider (e.g., religious or spiritual advisor), who generally would be less able to administer standard effective therapies than would a psychiatrist. The standard of practice for treatment of depression is full symptom remission with restoration of premorbid function; however, remission rates after a first antidepressant trial are low. In The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, persons receiving first line selective serotonin reuptake inhibitors (SSRIs) had a remission rate of only 28% to 33% and a response rate (defined as a 50% reduction in pretreatment symptoms of depression) of 47%.¹⁴

Is there an increased risk of depression during the menopausal transition?

The majority of women do not develop depression during the menopausal

al transition (MT). Nonetheless, four community-based studies have documented that some women are at an increased risk of depression during the MT.¹⁵⁻¹⁹ First, the Study of Women's Health Across the Nation (SWAN) observed, in an initial cross-sectional survey, that women in the MT reported significantly more "psychological distress" than either premenopausal or postmenopausal women (defined by self-reported menstrual cycle status). Second, a longitudinal study by Freeman, et al.¹⁶ found an increased risk of clinically significant depression (defined by elevated CES-D scale scores and the PRIME MD10) during the MT compared with the premenopause or postmenopause, and this association remained after adjusting for several variables, including past history of depression, severe premenstrual syndrome, poor sleep, and hot flashes. Third, Cohen, et al.¹⁷ in a longitudinal study of women who had no history of depression observed that the incidence of new-onset depression (defined by SCID-IV) in the MT was nearly twice that observed in the premenopause (adjusted OR = 1.8). Finally, Freeman, et al.¹⁸ in a similar study of women with no history of prior depression demonstrated, a 2½ times greater rate of new onset depression during the menopausal transition, compared with women who remained premenopausal. These data notwithstanding, the majority of women in these studies remained asymptomatic throughout the perimenopause.

In summary, epidemiological studies have documented that the majority of perimenopausal and postmenopausal women do not develop depression. However, community- and clinic-based surveys suggest that the MT is relevant to the development of affective disorders and that a substantial number of perimenopausal women experience clinically significant depression.

Are there identifiable risk factors for the onset of depression during the menopause transition?

Several epidemiologic studies have surveyed the presence of depressive symptoms in women at midlife and have identified several variables associated with depression, including the following:²⁰

- Previous episodes of depression
- Longer duration of the MT (defined by menstrual cycle irregularity) presence of hot flashes
- Retrospective reports of premenstrual dysphoria (PMD) or postpartum depression (PPD)
- Stressful life circumstances
- Complaints of poor health
- History of smoking
- Disturbed sleep
- Reduced parity
- Being unmarried

Most of these factors also are associated with an increased risk of developing depression during other stages of life (i.e., past history of depression, stressful life events, reports of premenstrual dysphoria or postpartum depression, smoking and sleep disturbance) and, therefore, are not specific to depression during the MT. Finally, several proposed risk factors such as insomnia, increased stress, and complaints of poor health, may be symptoms of, but are not necessarily a cause of, a current depressive episode.

Depression during the MT could be caused by the accompanying endocrine or physiologic events (e.g., vasomotor symptoms). However, neither of these phenomena would explain why depression occurs in only some women and, therefore, the risk of depression related to these events is not uniform. Alternatively, the onset of depression could reflect a vulnerability to developing recurrent depression in women with a past depression or in those women with a past reproductive endocrine-related

depression (e.g., PMD, PPD). The relationship between depression during the menopause transition and these potential risk factors has been examined in several recent studies. First, as stated earlier, 3 community-based longitudinal studies have prospectively followed women with no prior history of depression and observed risks of depression that are approximately 2- to 2½-fold greater during the menopause transition compared with the premenopause. Similarly, in a longitudinal study by Schmidt, et al.,²¹ a similar percentage of incident depressions occurred in women with no prior history of depression (6/20), as in those with a past history (3/9) (small sample size notwithstanding). Nor did the three women with histories of PPD develop depression during the MT, suggesting that the presence of one episode of a reproductive endocrine-related mood disorder (i.e., PPD) does not predict the uniform occurrence of depression during a subsequent hormonal transition (i.e., the MT). Similarly, a cross-sectional study found no association between the onset of major or minor depression during the puerperium and the development of depression during the MT.²² Schmidt, et al.,²¹ used daily symptom ratings to prospectively evaluate self reports of the onset of premenstrual dysphoria in women entering the MT and found that PMD rarely accompanied depression in these women. Nonetheless, recent cross-sectional data²³ suggest a higher than expected co-occurrence of prospectively confirmed PMD and perimenopausal depression. In this study, women who developed depression during the MT (n = 70) (and who were not amenorrheic) were significantly more likely to meet criteria for PMD than an asymptomatic matched comparison group (n = 35) (21% compared with 3%). Thus, PMD is neither a uniform accompaniment nor a necessary ante-

cedent of depression during the MT; however, the presence of PMD could be a risk factor for the development of depression during the MT as suggested by Freeman, et al.¹⁸

Hot flushes often accompany the MT and are associated with depression during this phase of life. Consistent with the domino or cascade theory, hot flushes are hypothesized to disturb sleep and, therefore, contribute to daytime mood symptoms. However, as stated earlier, only some women develop depression during the MT, and not all of those who do experience hot flushes. Indeed, data from both cross-sectional²² and longitudinal studies¹⁶⁻¹⁸ demonstrate that hot flushes and the MT are independent risk factors for depression. Thus, in contrast to the “domino” or “cascade” hypothesis, existing evidence suggests that hot flushes appear to be neither a necessary nor a sufficient accompaniment of depression during the MT, and depression cannot be dismissed as epiphenomenal to hot flushes.

Finally, stressful life events are a frequent accompaniment of depression and, in some depressed subjects, may contribute to its onset. Stressful events have been reported in association with depressive symptoms at midlife as well as in women with major and minor depression during the MT.^{17, 24} However, women with depression during the MT do not report a greater number of exit events (i.e., personal losses) than asymptomatic perimenopausal women.²⁴ Thus, although stressful events are an accompaniment of both midlife depression and depression during the MT, there is no evidence to support the concept that depression at this time in a woman's life is caused by the “empty nest” syndrome.

In summary, many factors accompany depression during the MT; however, none is uniformly present in these depressed women. Our inability

to identify predictors of the onset of depression may reflect the small sample sizes of depressed women examined. Future efforts will clarify whether specific factors exist that predict or increase the risk of developing depression during the MT, independent of those factors that increase a woman's risk for depression at other times across the life cycle.

Is depression during the menopausal transition associated with abnormalities of ovarian hormone secretion?

The stage of the MT during which depressions occur could suggest a pathophysiologic role for hormonal events surrounding the final menstrual period. For example, the late MT is characterized by estradiol “withdrawal” relative to either the later postmenopause or the early perimenopause.²⁵ In a prospective study, we followed a group of asymptomatic premenopausal women until 6 to 12 months after their last menstrual period and observed a clustering of both new-onset and recurrent depressive episodes during the 24 months surrounding the final menstrual period, relative to the 31 years used as a comparison period. Thus, the timing of the observed depressive episodes suggests an endocrine trigger that is related to the later stages of reproductive aging (i.e., estradiol withdrawal and/or recent onset of prolonged hypogonadism).

No consistent abnormalities of basal ovarian or adrenal hormones have been identified in women with perimenopausal depression compared with asymptomatic controls. Thus, women with depression during the MT are not distinguished from non-depressed perimenopausal women by being more estrogen deficient. Nonetheless, the changes in pituitary-ovarian function characteristic of the MT appear to be relevant

to the onset of depression in some women, as mood symptoms may change concurrently with FSH levels²⁶ and estradiol therapy (ET) improves mood symptoms in perimenopausal depressed women.^{27,28}

In a longitudinal study, we observed several women with depression who presented to the NIMH midlife clinic and whose plasma FSH levels declined over six weeks, concurrent with spontaneous improvements in mood.²⁶ We found that incremental declines in FSH levels paralleled improvements in depression symptom scores in this group of women whose initial symptom scores decreased by at least 50% during this six-week period.

An association between the endocrine events related to the MT and the onset of depression is also indirectly supported by reports of the mood-enhancing effects of estradiol in depressed perimenopausal women. Recently, three double-blind, placebo-controlled trials examined the efficacy of ET in perimenopausal and postmenopausal women with major and minor depressions.²⁷⁻²⁹ First, the therapeutic efficacy of estradiol (i.e., 17 beta estradiol alone) was demonstrated²⁷ by significantly decreased depression rating scale scores in women after three weeks of estradiol compared with baseline scores and compared with scores in the women receiving placebo. We observed a full or partial therapeutic response in 80% of perimenopausal women on estradiol compared with 22% of those on placebo,²⁷ consistent with the observed effect size (.69) in a meta-analysis of studies examining estrogen's effects on mood.³⁰ These findings were replicated in a separate double-blind, randomized, controlled trial by Soares, et al.²⁸ However, a similar trial in older depressed women, who were 5-10 years postmenopausal, failed to observe a significant antidepressant effect of ET compared with placebo.²⁹

In addition to trials of ET as monotherapy in depressed perimenopausal and postmenopausal women, several studies evaluated ET as an augmentation strategy.³¹ The best evidence to date (albeit limited to open trials) supports ET's efficacy as an augmentor of SSRIs in perimenopausal women only.^{32,33}

Finally, the evidence that younger perimenopausal women respond to ET, but not older postmenopausal depressed women, suggests that the mood disorders occurring in the MT are caused by changes in hormones (e.g., withdrawal or fluctuations) rather than prolonged ovarian steroid deficiency.

Summary

For many years, the nature of the relationship between the menopause and depression has been controversial. Recent longitudinal studies focusing on the MT provide more consistent evidence that better defines this relationship. First, the majority of women do not develop a depressive disorder during the MT or early postmenopause. Second, a subgroup of women are at an increased risk of developing depression during the MT. For some women, these depressions occur for the first time in their lives. Finally, at present, few if any characteristics predict those women who are at risk of developing depression during the MT. Future studies should focus on documenting the number of women who are at risk and the markers of susceptibility for developing depression during the MT. Moreover, increasing evidence documenting the safety of ET in symptomatic perimenopausal women also suggests that a better understanding of both the potential risks and therapeutic benefits of ET in depression during the MT could lead to a viable alternative therapy to traditional antidepressants.

Disclosure

Dr Schmidt reports that he is Chair, Ethics Advisory Panel of The Endocrine Society. Drs Harsh and Rubinow report that they have no financial relationships to disclose.

References

- Kessler RC. Appendix table 1: lifetime prevalence of DSM-IV/WMH-CIDI disorders by sex and cohort. National Comorbidity Survey 2005; Available at: http://www.hcp.med.harvard.edu/ncs/ftpdir/table_ncsr_by_gender_and_age.pdf. Accessed September 7, 2006.
- Kessler RC, Zhao S, Blazer DG, Swartz M. Prevalence, correlates, and course of minor depression and major depression in the national comorbidity survey. *J Affective Disord* 1997;45:19-30.
- Judd LL, Rapaport MH, Paulus MP, Brown JL. Subsyndromal symptomatic depression: a new mood disorder? *J Clin Psychiatry* 1994;55:18-28.
- Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006;367:1747-1757.
- Papakostas GI, Petersen T, MahalY, et al. Quality of life assessments in major depressive disorder: a review of the literature. *Gen Hosp Psychiatry* 2004; 26:13-17.
- Greenberg PE, Birnbaum HG. The economic burden of depression in the US: societal and patient perspectives. *Expert Opin Pharmacother* 2005;6:369-376.
- Wassertheil-Smoller S, Shumaker S, Ockene J, et al. Depression and cardiovascular sequelae in postmenopausal women. The Women's Health Initiative (WHI). *Arch Intern Med* 2004;164:289-298.
- Diagnostic and statistical manual of mental disorders fourth edition. Washington, DC: American Psychiatric Association; 1994.
- First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV axis I disorders - patient edition. New York, N.Y.: Biometrics Research Department, New York State Psychiatric Institute; 1996.
- Spitzer RL, Williams JBW, Kroenke K, et al. Utility of a new procedure for diagnosing mental disorders in primary care: the PRIME-MD 1000 study. *JAMA* 1994;272:1749-1756.
- Halbreich U, Kahn LS. Atypical depression, somatic depression and anxious depression in women: are they gender-preferred phenotypes? *J Affective Disord* 2007;102:245-258.
- Spijker J, de Graaf R, Bijl RV, et al. Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Br J Psychiatry* 2002;181:208-213.
- Wang PS, Berglund P, Olfson M, et al. Failure and delay in initial treatment contact after first onset of mental disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62:603-613.
- Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 2006;163:28-40.
- Bromberger JT, Assmann SF, Avis NE, et al. Persistent mood symptoms in a multiethnic community cohort of pre- and perimenopausal women. *Am J Epidemiol* 2003;158:347-356.
- Freeman EW, Sammel MD, Liu L, et al. Hormones and menopausal status as predictors of depression in women in transition to menopause. *Arch Gen Psychiatry*

2004;61:62-70.

- Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition. The Harvard study of moods and cycles. *Arch Gen Psychiatry* 2006;63:385-390.
- Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry* 2006;63:375-382.
- Bromberger JT, Matthews KA, Schott LL, et al. Depressive symptoms during the menopausal transition: the study of women's health across the nation (SWAN). *J Affective Disord* 2007;103:267-272.
- Schmidt PJ. Mood, depression, and reproductive hormones in the menopausal transition. *Am J Med* 2005;118:545-585.
- Schmidt PJ, Haq NA, Rubinow DR. A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. *Am J Psychiatry* 2004;161:2238-2244.
- Steinberg EM, Rubinow DR, Bartko JJ, et al. A cross-sectional evaluation of perimenopausal depression. *J Clin Psychiatry*. In press 2008.
- Richards M, Rubinow DR, Daly RC, Schmidt PJ. Premenstrual symptoms and perimenopausal depression. *Am J Psychiatry* 2006;163:133-137.
- Schmidt PJ, Murphy JH, Haq NA, Rubinow DR, Danaceau M. Stressful life events, personal losses, and perimenopause-related depression. *Arch Womens Ment Health* 2004;7:19-26.
- Santoro N, Brown JR, Adel T, Skurnick JH. Characterization of reproductive hormonal dynamics in the perimenopause. *J Clin Endocrinol Metab* 1996;81: 1495-1501.
- Daly RC, Danaceau MA, Rubinow DR, Schmidt PJ. Concordant restoration of ovarian function and mood in perimenopausal depression. *Am J Psychiatry* 2003;160:1842-1846.
- 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, Cohen LS. 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, Ten Have T, et al. Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. *Biol Psychiatry* 2004;55:406-412.
- Zweifel JE, O'Brien WH. A meta-analysis of the effect of hormone replacement therapy upon depressed mood. *Psychoneuroendocrinology* 1997;22:189-212.
- Schneider LS, Small GW, Clary CM. Estrogen replacement therapy and antidepressant response to sertraline in older depressed women. *Am J Geriatr Psychiatry* 2001;9:393-399.
- Morgan ML, Cook IA, Rapkin AJ, Leuchter AF. Estrogen augmentation of antidepressants in perimenopausal depression: a pilot study. *J Clin Psychiatry* 2005;66:774-780.
- Cohen LS, Soares CN, Poitras JR, et al. Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report. *Am J Psychiatry* 2003;160:1519-1522.