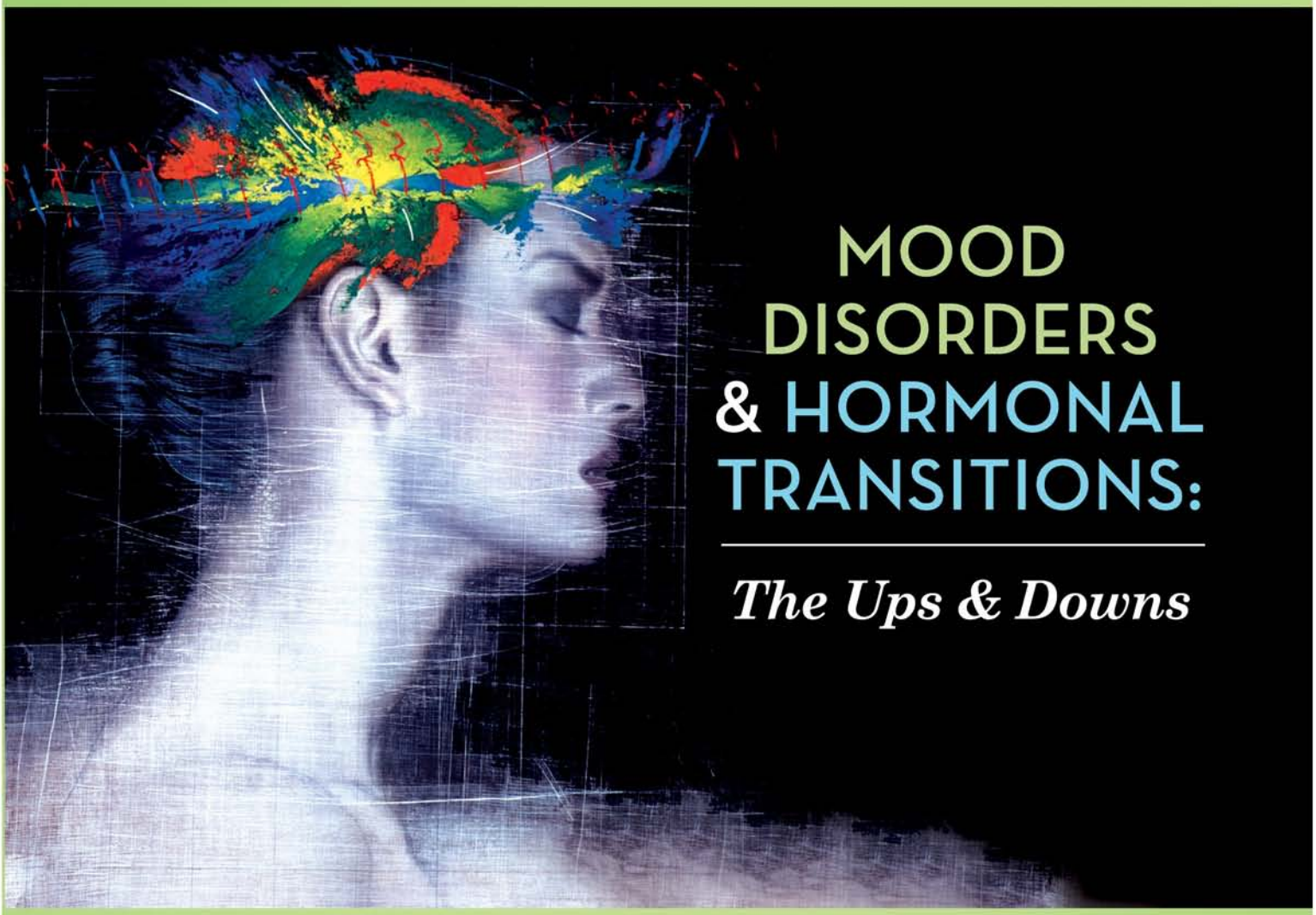

MOOD DISORDERS & HORMONAL TRANSITIONS:

The Ups & Downs

SOCIETY FOR
WOMEN'S HEALTH RESEARCH

Scientific Report Series: Understanding the Biology of Sex Differences:

Report on the Society for Women's Health Research-National Institute of Mental Health Roundtable on Mood Disorders and Hormonal Transitions

Roundtable Participants
Lee Cohen, M.D., Massachusetts General Hospital
Ellen W. Freeman, Ph.D., University of Pennsylvania
Hadine Joffe, M.D., M.S.c, Massachusetts General Hospital
David R. Rubinow, M.D., University of North Carolina at Chapel Hill
Peter J. Schmidt, M.D., National Institute of Mental Health
Zachary Stowe, M.D., Emory University School of Medicine
Adele C. Viguera, M.D., M.P.H., Massachusetts General Hospital
Kimberly Yonkers, M.D., Yale University School of Medicine

Women undergo hormonal changes involving increases and decreases in levels of reproductive steroids, such as estrogens and progesterone, during key lifecycle transitions: first menstrual period, pregnancy, childbirth, perimenopause, and menopause. Many women navigate these hormonal transitions with minimal mood disturbances. However, for some women a normal hormonal transition may trigger mild to severe mood disorders such as mild depression, bipolar disorder, or major depression. Postpartum depression affects 10-15 percent of women any time from a month to a year after childbirth.[1] Its cause remains unknown. Researchers suspect that the dramatic shifts in hormone levels during pregnancy and immediately afterward may result in chemical changes in the brain leading to the condition. Similarly, the perimenopause transition increases risk of depression.[2]

Scientists know that changes in reproductive steroids affect brain functioning. However, nothing conclusive from basic affective neuroscience directly defines what causes depression and mood disorders for women during these lifecycle transitions. There are key research questions that still need answers:

- How is it that reproductive steroids can trigger a depression or mood disturbance, and why only in some individuals?
- How and why do some women develop premenstrual syndrome but not others?
- What produces the different responses to the same steroid signals that occur during the menstrual cycle?

Depression and mood disorders in women provide an unprecedented opportunity to learn about the neurobiology of affective regulation and depression. Researchers continue to uncover this complicated neurobiology by mapping out the neurocircuitry of hormonal activity at the intracellular level.

The Society for Women's Health Research and the National Institute for Mental Health convened a thought leaders' roundtable to discuss current efforts to understand the effects of hormonal transitions, specifically pregnancy and postpartum, and perimenopause, on the occurrence of mood disorders in women.

LESSONS LEANED FROM BASIC SCIENCE

Research in basic affective neuroscience is laying the groundwork for understanding the complicated and pervasive relationship between the brain and reproductive steroids: estrogens, androgen, and progesterone. The brain both controls estrogen release through the hypothalamus-pituitary-gonadal (HPG) axis and responds to estrogen produced by the ovaries, released from estrogen receptors throughout the brain, and produced in the brain from the aromatization of testosterone.

David Rubinow, M.D., Professor and Chair of Psychiatry at the University of North Carolina at Chapel Hill, asserted that depression and mood disorders in women provide the best opportunity available today to learn about the neurobiology of

affective regulation and depression. He noted that reproductive steroids alter sensitivity (to other stimuli) of neural circuits that influence behavior and act as behavioral switches. These hormones affect cellular communication in the brain by regulation of gene transcription; by both indirect and direct effects on ion channel activity; by modulating signal transduction, and by directly and indirectly modulating receptors. The effects of reproductive steroids on the brain vary with (a) changes in the levels of hormones and their receptor proteins and (b) changes in the rate of hormone synthesis and metabolism. Intracellular modulators of hormone effects include co-regulatory molecules and histones.

According to Rubinow, the "one receptor-one action" model of hormone action has been overturned by the robust evidence for action of steroid hormones through both nuclear and membrane receptors, and by the mounting evidence for the role of co-regulators in modulation of hormone action. Rubinow argued that the same hormone may simultaneously exert opposite effects on the same system (e.g., cell survival), and these effects can change with time. More research in this area is needed to understand why women respond differently to the same hormonal stimuli. Contextual factors, such as the environment, genetic susceptibility, perception, prior experience, etc., are key variables that mediate these individual differences in response. According to Rubinow, context also depends on the network of interacting proteins and how they are modified.

Receptors for the key female reproductive hormones, estrogens, are found throughout the entire brain including prefrontal cortex, hypothalamus, neocortex, hippocampus, amygdala, striatum, and brain stem. The neurotransmitter systems involved in depression (serotonin, norepinephrine, dopamine, cetylcholine, GABA, glutamate) are regulated by the action of estrogen.[4,5]

Research suggests that women may have increased susceptibility to depression and mood disorders during two key lifecycle transitions: pregnancy and the postpartum period, and perimenopause. Approximately 10-15 percent of women experience postpartum depression. The risk of depression increases during perimenopause.[6] University of Pennsylvania researchers Freeman, Sammel, Lin, and Nelson found an increased risk of a first lifetime episode of depression during perimenopause.[7] Perimenopausal depression leads to a 50 percent increase in cardiovascular mortality.[8]

Research by Rubinow and his colleagues Peter Schmidt, M.D., and Karen Berman, M.D., identified the central effects of estrogen and progesterone in isolation by using by the gonadotropin-releasing hormone agonist leuprolide acetate to purposely turn off the ovarian cycle in healthy research subjects.[9] They found that communication between key brain regions involved in depression and affect regulation (the prefrontal cortex and the hippocampus) shut down when estrogen and progesterone production stopped. They also found that prefrontal cortical activation diminished.

Further evidence for the effects of hormones on mood came from a study by Schmidt, Nieman, and Rubinow that asked the question: If you shut off the ovarian cycle, can you eliminate the symptoms of premenstrual syndrome? Women with premenstrual syndrome have negative mood-related and somatic symptoms during the luteal phase of the menstrual cycle. These symptoms disappear at or soon after menstruation begins. After two to three months of ovarian suppression, the subjects' premenstrual symptoms were eliminated. The researchers concluded that when the reproductive hormones are shut off premenstrual syndrome disappears.[10]

Recommendations for the Direction of Future Research on Basic Affective Neuroscience

During discussion, the participants made the following recommendations for future research:

- There are key research questions on what causes depression and mood disorders during hormonal transitions that still need answers:
    - How is it that reproductive steroids can trigger a depression?
    - Why do reproductive steroids trigger a depression only in some individuals?
    - How and why do some women develop postpartum depression or premenstrual syndrome but not others?
    - What produces the different responses to the same steroid signals that occur during the menstrual cycle?

- To answer these questions, basic science researchers in neuroendocrinology must continue to map out the neurocircuitry of hormonal activity at the intracellular level. Future research should focus on identifying potential ways of changing receptor activity to regulate behaviors to minimize depression and mood disorders.

- Examining the effects of reproductive steroids on the central nervous system will help researchers to understand the means by which reproductive steroids can trigger mood changes in "susceptible" women, and the mechanisms underlying differential response to the same stimuli.

- Large-scale studies are needed to understand the clinical implications of basic research results. "We need a large enough sample of women with these disorders to study to have meaningful clinically significant results," Rubinow said. "This will allow for sufficient genome association studies to identify targets that can then be tested in animal models." Identifying the genes involves in depression and mood disorders will move the field forward.

- The field needs to standardize phenotypic measures that researchers collect from clinical trial participants. Then researchers need to map phenotypes to differences in metabolism, genetics, background, and environment; to whatever happens to be the most common source of variation.

- Increased communication between animal model researchers and affective neuroscientists will move the field forward.

DEPRESSION AND BIPOLOAR DISORDER IN PREGNANCY AND POSTPARTUM

Contemporary culture sets high expectations for a positive experience during pregnancy and childbirth. In reality, even under normal conditions pregnancy and childbirth are stressful life experiences. Sleep disturbances, fatigue, energy loss, appetite changes, and decreased concentration are common symptoms during pregnancy. Kimberly Yonkers, M.D., Associate Professor of Psychiatry at Yale University School of Medicine, reported that research suggests these normal symptoms are hormonally based.

One challenge in understanding depression during pregnancy and postpartum is distinguishing symptoms of depression from normal responses to the stressful experiences of pregnancy. More research is needed to distinguish normal responses to stress from symptoms major depressive disorder, to more clearly define who is ill and who is healthy.

Reproductive hormone levels change throughout pregnancy, leading to a variety of changes in mind and body. For example:

- Human chorionic gonadotropin (hCG), a hormone produced only during pregnancy, is linked to nausea symptoms. According to Yonkers, hCG levels peak early in pregnancy and decrease by the end of the first trimester;
- Increasing progesterone levels during pregnancy may influence concentration and energy levels; and
- Changing estradiol levels may influence a woman's general feeling of well-being.

A subset of women experience depression during pregnancy, and evidence suggests these women may have an underlying vulnerability to changing hormone levels, which then trigger the onset of symptoms. For example, women with a history of postpartum depression often have an increased stress response measured by higher levels of the stress hormone cortisol. Postpartum depression prevention research is almost nonexistent. The only two controlled studies of postpartum depression prevention with nortriptyline or sertraline showed mixed results.[14]

Preliminary results from the first 1,000 participants from the Yale Pink and Blue Study indicate that depression lessens as pregnancy progresses.[11] This study, funded by the National Institute of Child Health and Human Development, is a prospective cohort of 3,000 pregnant women that aims to determine if stress and related mood changes during pregnancy affect pregnancy outcomes. According to Yonkers, principal investigator of the study, women may adjust to higher levels

of reproductive hormones as a pregnancy progresses. This would explain why symptoms often worsen in the first trimester, improve in the second trimester, and again worsen in the third trimester as hormone levels change in preparation for labor.

A smaller population of women, those with bipolar disorder, faces significant challenges during pregnancy and postpartum. Bipolar disorder is a serious psychiatric condition that affects one to five percent of individuals in the United States.[15] Women with biopolar disorder are at increased risk of co-occurring illnesses and disability.[16] Pregnancy poses major challenges for treatment of bipolar disorder, and information to guide clinical care remains sparse.[17] The clinical management of bipolar disorder through pregnancy and postpartum calls for balanced assessments of maternal and fetal risks and benefits, according to Adele C. Viguera, M.D., Associate Director of the Perinatal and Reproductive Psychiatry Program at Massachusetts General Hospital.

Viguera recommends that clinicians view pregnant women with bipolar disorder the same way that neurologists treat pregnant women with epilepsy. In the field of neurology untreated seizures are considered dangerous to the fetus. Therefore women with epilepsy are often advised to continue taking their medications during pregnancy. Psychiatrists and other mental health professionals do not yet embrace this philosophy, workshop participants said, and women with bipolar disorder are often encouraged to stop taking their medications during pregnancy.

As is the case for major depression, there are many unanswered questions about pregnancy and bipolar disorder that are important for clinical care:

- What is the recurrence (relapse) risk for pregnant women with bipolar disorder?
- What are the predictors of risk?
- What is the impact of untreated maternal illness on the fetus?
- What is the reproductive safety data on antipsychotic medications?

One challenge in treating depression and bipolar disorder during pregnancy and postpartum is that the cultural value attached to protecting the fetus at all costs influences treatment decisions, according to Zachary Stowe, M.D., Associate Professor of Psychiatry and Behavioral Sciences and Gynecology and Obstetrics at Emory University School of Medicine. Clinicians and researchers "cannot tell patients unequivocally that taking medications during pregnancy poses toxic exposure for the unborn child" because of the lack of outcome studies on this topic, Stowe said. The scientific foundation to inform treatment decisions about medications and pregnancy is not yet available. Stowe said clinicians respond to this information gap by opting for an overcautious approach to care. In lieu of concrete data about medication effects on fetuses and nursing infants, most drug labels include broad and generic warnings to "consult your doctor if you are pregnant or breast feeding before using this medication."

"Choose your medicines wisely" is the first step in treating pregnant women, Stowe said. Medicine combinations can cause problems. However, research by Stowe and others suggests that significant amounts of medication cross the placenta from mother to unborn child.[12] Placental transfer of medications from mother to unborn child depends on more than just the dose or type of medication the mother takes, because the medication interacts with the receptors, enzymes, and other targets in the placenta and fetus, which may differ from those of the mother. Drug interactions that are not problematic for the mother may cause adverse effects in the fetus. For example, taking citalopram (an antidepressant drug), and valproic acid (an anticonvulsant and mood stabilizing drug) in combination causes the unborn child to receive twice the medication amount compared to when these medications are taken separately. To further complicate this issue, a commonly agreed upon definition of fetal exposures does not exist in the scientific literature.

In addition to the lack of information on drug effects on the fetus, the impact of untreated maternal symptoms on pregnancy outcomes remains unknown. For example, if a woman has a history of major depression, will that result in a higher rate of pregnancy complications? Physicians do not know what type of exposure, such as medications, toxins, maternal stress or maternal mental illness, or what level of exposure leads to illness for pregnant women and their children.

Recommendations for the Direction of Future Research on Mood Disorders in Pregnancy and Postpartum

During discussion, the participants made the following recommendations for future research:

- The development of a pharmacogenetic profile that would be used to determine the risk of side effects and medication response during pregnancy would allow for individualized drug treatments based on the mother and fetus's genotype.

- Clinicians need the equivalent of a "glucose tolerance test" (the baseline test for diabetes) for mental illness in pregnancy. This test would allow researchers and clinicians to determine when symptoms of mental illness are severe enough to require intervention.

- Multi-site studies are needed to measure fetal exposures and the effects of such exposures on outcomes for newborns and to account for the heterogeneity of fetal reactions to different medications.

- More precise measures for the evaluation of symptoms are needed. Future research on pregnancy and depression needs to match symptoms with specific points in a pregnancy (i.e. number of weeks).

- Better measures for the postnatal environment with respect to nature, context, and quality of maternal parenting interaction as it influences the child's health outcomes are needed.

- More research on anxiety disorders, the most common psychiatric illness in women, is necessary. Understanding the role of anxiety in depression and mood disorders will accelerate research progress.

- Accessible registries of collected reproductive safety information on antidepressant, antipsychotic, and anticonvulsant medications are needed.

MOOD DISORDERS IN PERIMENOPAUSE

Peter J. Schmidt, M.D., of the National Institute of Mental Health, asserted that "it makes absolutely no sense to collapse the complicated series of hormonal events that make up the menopause transition (a process that may take on average five years and up to 15 years in some women), into a single event surrounding the last menstrual period." The association between depressed mood and hormonal changes during the transition to menopause remains controversial. The onset of depression in midlife women has been linked with numerous risk factors, including prior depression or postpartum depression, premenstrual dysphoria, frequency and severity of hot flashes, disturbed sleep, life stress, and poor health as well as perimenopause.

Recent studies have produced evidence that perimenopause is associated with increased vulnerability to depression. Studies by Lee Cohen, M.D., Ellen Freeman, Ph.D., and Joyce Bromberger, Ph.D., show approximately a two-fold increased risk of a first lifetime episode of depression for women during the menopause transition.[19-21] Schmidt reported data from a longitudinal study that found an association between depressive episodes (not associated with prior depression) and proximity to the last menstrual period.[22] The association of depression with perimenopause suggests a hormonal basis. However, there is only preliminary evidence of a direct relationship between estrogen changes and onset of mood problems. In a preliminary study, Schmidt found that estrogen therapy for perimenopausal depression had an acute effect of reducing subjects' scores on a depression scale. However, the mechanism and duration of this effect of estrogen is not known.[23]

The cause of menopause-associated depression is unknown. The co-occurrence of hot flashes, sleep disturbance, and depression suggests shared brain mechanisms or cascade effects according to Hadine Joffe, M.D., M.Sc., Director of

Endocrine Studies, Perinatal and Reproductive Psychiatry Clinical Research Program, Massachusetts General Hospital, Harvard Medical School. The cascade effects theory, or domino theory as it is also known, proposes that hormonal changes during perimenopause and menopause lead to hot flashes; hot flashes lead to sleep disturbances; and sleep disturbances lead to depression.

Researchers have suggested that hot flashes result from a central effect of estrogens on the thermoregulatory center of the hypothalamus, which is the part of the brain that links the nervous system to the endocrine system via the pituitary gland. Clinical evidence linking hot flashes with decreasing estrogen levels includes studies of women in natural menopause, women who have had their ovaries removed (surgical menopause), and women who take medications that decrease the production of estrogens or that block their effects. However, there is little laboratory evidence to link serum levels of estrogens with the frequency or severity of hot flashes.[24-26] Several studies have found a significant correlation between frequency and severity of hot flashes and sleep disturbance. [27-31] In addition, studies have found a correlation between hot flashes and depression.[32-36] However, these results do not distinguish between a causal cascade and a common mechanism for all three symptoms, and further research will be needed to understand the cause of perimenopausal depression.

Scientists still know very little about what causes hot flashes. Between 60-80 percent of women experience hot flashes at some point during the menopause transition.[37] Anxiety is strongly associated with hot flashes in perimenopausal women, according to Ellen W. Freeman, Ph.D., Co-Director, Human Behavior and Reproduction Unit, Department of Obstetrics and Gynecology at University of Pennsylvania Medical Center. In Freeman's study, perimenopausal women with high anxiety were nearly five times more likely to report hot flashes compared to women with normal range anxiety levels.[38]

Recommendations for the Direction of Future Research on Perimenopausal Mood Disorders

- Studies of perimenopausal depression are needed to clearly identify the number of women affected, the individual risk factors, and the role of hormonal therapies in this condition.

- Research is needed to uncover the susceptibility markers that predict which women are at risk for developing depression during perimenopause. Identifying these susceptibility markers will allow clinicians and researchers to design better hormone therapies for women who develop depression at perimenopause and to more closely monitor women at high risk for depression.

- Research is needed to understand the role of depression in hot flashes and other menopausal symptoms, and the role of those symptoms in the etiology of perimenopausal depression.

- Studies are needed to determine whether perimenopausal depression differs from major depression or other hormonally related depressions.

- Research is needed to understand the underlying mechanisms by which a change in levels of estrogens during perimenopause may translate into a change in central nervous system function that then manifests in behavior changes (i.e. depression symptoms).

- Studies are needed to determine the efficacy of anxiety treatments on hot flashes and other menopausal symptoms.

- The role of anxiety disorders, the most common psychiatric illness in women, in depression and mood disorders needs to be addressed.

- Studies are needed to compare the risks and benefits of estrogen therapy with antidepressants to treat perimenopausal depression; to determine the efficacy of augmenting antidepressants with estrogen therapy; and to determine whether treatments that target mood and anxiety influence hot flash symptom response. Studies should attempt to identify the predictors of the therapeutic response to estrogen therapy.

GLOSSARY OF SELECTED TERMS

Affective neuroscience – the study of the neural mechanisms of emotion. This interdisciplinary field combines neuroscience with the psychological study of personality, emotion, and mood.

Affective regulation – the mechanisms by which the brain responds to environmental stimuli, evaluates the emotional significance of stimuli, and produces emotion or mood.

Histones – the chief protein components of chromatin, the complex of DNA and protein that makes up chromosomes. Histones act as spools around which DNA winds and they play a role in gene regulation.

Intracellular – inside the cell; used in contrast to extracellular, which is outside the cell, and intercellular, which is between cells.

Luteal phase – the latter phase of the menstrual cycle. Also referred to as "days past ovulation," it is part of the cycle that begins at ovulation and ends the day before the next period. It usually lasts 12-16 days and its duration is generally consistent within a woman's cycle.

Neurobiology – the study of cells of the nervous system and the organization of these cells into functional circuits that process information and mediate behavior. It is a subdiscipline of both biology and neuroscience.

Neurocircuitry – the brain's system of neurotransmitters that affect cognitive functioning.

ACKNOWLEDGEMENTS

The Society for Women's Health Research would like to acknowledge Cathy Roca, M.D., chief of women's programs at the National Institute of Mental Health for her assistance with the roundtable and Elizabeth Stillman for her work in preparing this report. The roundtable was supported by the Marjorie Kovler Fund and the Jennifer Mudd Houghtaling Postpartum Depression Foundation.

REFERENCES

1. National Institutes of Health. Understanding postpartum depression: common but treatable. Available at: http://newsinhealth.nih.gov/2005/December2005/docs/01features_02.htm
2. Cohen LS, Soares CN, Vitonis AF, et al. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Arch Gen Psychiatry 2006; 63(4): 385-90.
3. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994; 51: 8-19.
4. McEwen BS. Basic neurobiology of ovarian steroids: clinical implications. Dial Clin Neuroscience 2002; 4: 163-175.
5. McEwen BS, Alves SE. Estrogen actions in the central nervous system. Endocr Rev 1999; 20: 279-307.
6. Cohen LS, Soares CN, Vitonis AF, et al. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Arch Gen Psychiatry 2006; 63(4): 385-90.
7. Freeman EW, Sammel MD, Lin H, et al. Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry 2006; 63(4): 375-82.
8. Wassertheil-Smoller S, Shumaker S, Ocken J, et al. Depression and cardiovascular sequelae in postmenopausal women. The Women's Health Initiative (WHI). Arch Intern Med 2004; 164: 289-98.
9. Berman KF, Schmidt PJ, Rubinow D, et al. Modulation of cognition-specific cortical activity by gonadal steroids: A positron-emission tomography study in women. Proc Natl Acad Sci 1997; 94: 8836-8841.
10. Schmidt PJ, Nieman LK, Danaceau MA et al. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. New Engl J Med 1998; 338: 209-16.
11. Unpublished preliminary results from The Yale Pink and Blue Study funded by the National Institute of Child Health and Human Development (NICHD).
12. Devane C, Stowe Z, Donovan J et al. Therapeutic drug monitoring of psychoactive drugs. J Psychopharmacol 2006; (4 Suppl): 54-9.

13. National Institutes of Health. Understanding postpartum depression: common but treatable. Available at: http://newsinhealth.nih.gov/2005/December2005/docs/01features_02.htm
14. Two controlled studies of postpartum depression prevention: the nortriptyline and sertraline studies. [Dr. Stowe will provide author names and reference]
15. Yonkers, KA, Wisner, K, Stowe, Z et al. Management of bipolar disorder during pregnancy and postpartum period. Am J Psychiatry 2004; 161(4): 608-620.
16. Kessler RC, Chiu WT, Demler O, et al, Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62: 617-627.
17. Viguera, AC, Nonacs R, Cohen L, et al. Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. Am J Psychiatry 2000; 157(2): 179-184.
18. Viguera, AC, Cohen L, Baldessarini, RJ, et al. Managing bipolar disorder during pregnancy: weighing the risks and benefits. Can J Psychiatry 2002; 47(5): 426-436.
19. Freeman E W, Sammel M, and 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.
20. 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(4): 347-56.
21. Cohen LS, Soares CN, Vitonis AF, et al. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Arch Gen Psychiatry 2006; 63(4): 385-90.
22. 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(12): 2238-2244.
23. Schmidt PJ, Nieman L, Danaceau MA, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. Am J Obstet Gynecol 2000; 183(2): 414-420.
24. Freeman R. Physiology of hot flashes. Am J Hum Biol 2001; 13(4): 543-64.
25. Kronenberg F, et al. Menopausal hot flashes: thermoregulatory, cardiovascular, and circulating catecholamine and LH changes. Maturitas 1984; 6(1): 31-43.
26. Stearns V, et al. Hot flushes. Lancet 2002; 360(9348): 1851-61.
27. Freedman RR and Roehrs TA. Lack of sleep disturbances from menopausal hot flashes. Fertil Steril 2004; 82(1): 138-44.
28. Woodward S and Freedman RR. The thermoregulatory effects of menopausal hot flashes on sleep. Sleep 1994; 17(6): 497-501.
29. Savard J, Davidson JR, Ivers H, et al. The association between nocturnal hot flashes and sleep in breast cancer survivors. J Pain Symptom Manage 2004; 27(6): 513-22.
30. Freedman RR and Roehrs TA. Effects of REM sleep and ambient temperature on hot flash-induced sleep disturbance. Menopause 2006; 13(4): 576-83.
31. Erlik Y, Tataryn IV, Meldrum DR, et al. Association of waking episodes with menopausal hot flushes. JAMA 1981; 245(17): 1741-4.
32. 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(3): 214-20.
33. Joffe H, Hall JE, Soares CN, et al. Vasomotor symptoms are associated with depression in perimenopausal women seeking primary care. Menopause 2002; 9(6): 392-8.
34. Cohen LS, Soares CN, Vitonis AF, et al. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Arch Gen Psychiatry 2006; 63(4): 385-90.
35. Freeman EW, Sammel MD, Lin H, et al. Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry 2006; 63(4): 375-82.
36. 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 Affect Disord 2007; 103(1-3): 267-72.
37. Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. Am J Public Health 2006; 96(7): 1226-35.
38. Freeman EW, Sammel MD, Lin H, et al. The role of anxiety and hormonal changes in menopausal hot flashes. Menopause 2005; 12(3): 258-266.