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MGH Center for Women's Mental Health

Reproductive Psychiatry Resource and Information Center

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Dear Readers:

We are very pleased to bring you this February issue of our newsletter from the Center for Women's Mental Health. Previous issues are available on our website at <http://www.womensmentalhealth.org/>

This issue describes several studies among the growing number of recent reports regarding antidepressant use during pregnancy. While it is becoming clearer that pregnancy is not protective with respect to risk for depression, at least one study described in this issue notes the extent to which depression during pregnancy remains untreated. Another study addresses the critical question of long-term neurobehavioral sequelae of fetal exposure to antidepressants. Both studies provide information which patients and clinicians weigh as they make individual decisions about using these agents during pregnancy.

Multiple reports describe the growing numbers of people approaching midlife and for women the relevant concerns regarding the array of symptoms that may accompany the transition to menopause. The current issue highlights a report regarding the increased risk for major depression during the perimenopause and how associated vasomotor symptoms accentuate this risk.

One of the goals of the Center is to provide critical current information for patients and care providers in the rapidly changing field of women's mental health. This current newsletter describes rapidly emerging findings across studies in women's mental health and represents an effort to bridge the gap between data emerging from new investigations across reproductive psychiatry and the clinical implications of such studies.

Sincerely,

Lee S. Cohen, MD

Depression During Pregnancy is Often Not Treated

While pregnancy has traditionally been considered a time of emotional well-being, recent data indicate that about 10% to 15% of women experience clinically significant depressive symptoms during pregnancy. Furthermore, women with a history of major depression appear to be at high risk for recurrent illness during pregnancy particularly in the setting of antidepressant discontinuation. In a recent study researchers from the University of Michigan report that while depression affects many women during pregnancy the majority of women suffering from this illness do not receive adequate treatment.

In this study, 1837 pregnant women from several hospital-based obstetrics clinics were surveyed using a standardized questionnaire screening for depression, the Center for Epidemiological Studies-Depression Scale (CES-D). 294 of the women were identified as being at risk of depression. High risk was defined as: (a) having a CES-D score of > 16, a score suggestive a major depression, (b)

reporting depressive symptoms with the last six months, or (c) recent use of an antidepressant. 276 women were assessed using the Structured Clinical Interview for DSM-IV to confirm the diagnosis of major depression and the Beck Depression Inventory-II to assess depression severity. Information regarding current and past psychiatric treatment was also collected.

Among the women at high risk for depression, only 20% were receiving some type of depression treatment. About half of the women received a combination of medication and psychotherapy/counseling, 21% took antidepressants alone, and 31% were treated with psychotherapy alone. Only 43% of those taking antidepressant medications received adequate treatment - antidepressant used at the recommended dose for at least six weeks. Among women meeting criteria for major depression at the time of interview, 33% were receiving depression treatment. In this group, only 11% received adequate treatment with an antidepressant. Women were more likely to receive treatment if they had a history of major depression prior to conception, a history of psychiatric treatment or greater depression severity. Having a current episode of depression did not predict use of treatment.

These findings indicate that while depression is relatively common during pregnancy most women at risk for this illness do not receive any type of treatment. Of greater concern is the fact that even when depression is suspected most women do not receive adequate treatment. Low rates of treatment may reflect concerns regarding the use of antidepressants during pregnancy; however, women receiving psychotherapy alone did not receive treatment of adequate intensity. The mean number of sessions received in the preceding three months was two. Most studies demonstrating the efficacy of therapy recommend treatment to occur on a weekly basis during the acute phase. This study underscores the need for effective strategies for the detection of depression during pregnancy but also points to the need for greater efforts to ensure adequate treatment of women at high risk for depression.

Ruta Nonacs, MD PhD

[Flynn HA, Blow FC, Marcus SM. Rates and predictors of depression treatment among pregnant women in hospital-affiliated obstetrics practices. General Hospital Psychiatry, Vol. 28, No. 4, July-August 2006, pp 289-29. | PDF |](#)

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Evaluating the Long-Term Effects of Prenatal Antidepressant Exposure

Over the last decade information has accumulated regarding the safety of antidepressants taken during pregnancy. While much research has addressed the effect of antidepressant drugs on risk for congenital malformation, less research has focused on the long-term effects of prenatal antidepressant exposure.

In a landmark study from Irena Nulman and her colleagues at the MOTHERISK program in Toronto, a cohort of children exposed either to tricyclic antidepressants (n=80) or to fluoxetine (n=55) during pregnancy was followed prospectively for up to seven years. Outcomes in these children were compared to outcomes in a group of 84 non-exposed controls. At birth there were no differences between the two groups in terms of weight, height, head circumference, rates of perinatal complications, or incidence of major malformations. The children were examined between 16 and 86 months of age using specialized rating instruments; no significant differences between exposed and non-exposed children were observed across a number of variables, including IQ, language, temperament, behavior, reactivity, mood, distractibility, and activity level.

A subsequent study from the same group followed a group of children exposed to fluoxetine (n=40) or tricyclic antidepressants (n=47) for the entire duration of the pregnancy. In the first study, many of the

children were exposed to antidepressants only during the first trimester. As in the first study, no differences were observed between exposed and non-exposed children examined between 15 and 71 months of age. Of note, children exposed to longer or more frequent episodes of maternal depression after delivery had lower scores on measurements of IQ and language, indicating that exposure to maternal depression may be more deleterious than prenatal exposure to medications.

A new study from Dr. Shaila Misri and her colleagues at the University of British Columbia has prospectively examined the relationship between prenatal antidepressant exposure and behavior in a group of 4-year-old children. In this study, outcomes were compared between children with prenatal exposure to SSRIs (n=22) and children of healthy, non-depressed mothers with no medication exposure (n=14); both groups were initially enrolled during pregnancy and were evaluated again when their children were four years old. The mothers were treated for depression and/or anxiety and took the following SSRIs: fluoxetine (n=5), paroxetine (n=14), and sertraline (n=3). Nine of the women also took clonazepam in conjunction with the SSRI. Standardized parent and caregiver questionnaires including the Child Behavior Checklist and a clinical measure of mother-child interactions (scored by a blinded rater) were used to assess levels of internalizing behaviors, i.e. depression, anxiety, withdrawal. Maternal mood and anxiety levels were assessed using the Hamilton Rating Scales for Anxiety and Depression.

Levels of internalizing behaviors, as reported by parents and other caregivers and as rated by a clinician, did not differ significantly between 4-year-old children with and without prenatal SSRI exposure. Although the study was small in size, the results are encouraging. Like the two previous studies from the Motherisk program, these findings support the hypothesis that *in utero* exposure to SSRI antidepressants has no long-term negative effects on the child. While these studies are reassuring, these data are preliminary. Furthermore, it should be noted that effects of antidepressant exposure may appear later in a child's life. Clearly further investigation into the long-term neurobehavioral effects of prenatal exposure to antidepressants as well as other psychotropic medications is warranted.

While medication exposure was not associated with increased levels of internalizing behaviors in the current study, the authors observed a relationship between maternal mood and anxiety and internalizing behaviors in their children. Mothers with higher levels of depression and anxiety at the time of evaluation reported more internalizing behaviors in their children than mothers who did not have symptoms of depression or anxiety. These findings are consistent with a large number of previous reports in the medical literature documenting the negative impact of maternal depression on children. It is noteworthy that in this study all of the 22 mothers who used antidepressants during pregnancy continued to take them four years later and that despite treatment over half of the women had clinically significant symptoms of depression or anxiety at the time of evaluation. This suggests that for many women who decide to use antidepressants during pregnancy depression is a recurrent or chronic illness. Moreover these findings indicate that exposure to relapsing or chronic maternal depression or anxiety may have a more significant impact on child well-being than exposure to antidepressants *in utero*. Other studies have also suggested that depression itself may produce certain physiologic changes during pregnancy that may have long-term consequences for the child (Bonari 2004).

Ruta Nonacs, MD PhD

[Position Statement of the Canadian Pediatric Society, Maternal Depression and Child Development, Paediatrics & Child Health 2004; 9\(8\): 575-583](#)

[Nulman I, Rovet J, Stewart DE, Wolpin J, Gardner HA, Theis JGW, Kulin N, Koren G: Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 1997; 336:258-262 | PDF |](#)

[Nulman I, Rovet J, Stewart DE, Wolpin J, Pace-Asciak P, Shuhaiber S, Koren G: Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. Am J Psychiatry 2002; 159:1889-1895 | PDF |](#)

[Misri S, Reebye P, Kendrick K, Carter D, Ryan D, Grunau RE, Oberlander TF. Internalizing behaviors in 4-year-old children exposed in utero to psychotropic medications. Am J Psychiatry. 2006 Jun;163\(6\):1026-32 | PDF |](#)

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Perimenopause May Be a Time of Risk for New-Onset Depression

The transition to menopause, also known as perimenopause, represents a time of reproductive hormonal changes for women. The average age of onset of menopause is 51 years with perimenopausal symptoms typically beginning 4-8 years before menopause. During the perimenopause the ovaries produce fluctuating levels of hormones and women experience irregular menstrual periods and a constellation of physical symptoms including night sweats and hot flashes. The transition to menopause has typically been considered a time when women may be more vulnerable to mood changes. There have been inconclusive data, however, as to whether women with no lifetime history of depression transitioning to menopause are at increased risk for developing an episode of major depression

In a recent study, Drs. Lee Cohen and Claudio Soares examined the association between the menopausal transition and first onset of major depression. This study was conducted as part of the Harvard Study of Moods and Cycles, a population-based prospective study of premenopausal women with and without a lifetime history of major depression. In this report, a cohort of premenopausal women (36-45 years of age) with no lifetime diagnosis of major depression (n = 460) was assessed. The Center for Epidemiologic Studies Depression Scale (CES-D) was used to screen for depressive symptoms over a period of up to 6 years.

Premenopausal women with no history of depression who entered the perimenopause were twice as likely to develop significant depressive symptoms when compared with women who remained premenopausal during the period of observation. The risk for depression was somewhat greater in women who reported vasomotor symptoms and was also increased among women who experienced negative life events proximate to this transition.

These findings indicate that among women with no history of depression transition into the menopause significantly increases the risk for depression. Further studies will help to determine whether other factors such as the presence of vasomotor symptoms, use of hormone therapy, presence of sleep disturbance and the occurrence of adverse life events may also affect a woman's risk for depression during the midlife.

Ruta Nonacs, MD PhD

[Cohen L, Soares C, Vitonis A, Otto M, Harlow B. Risk for new onset of depression during the menopausal transition: The Harvard Study of Moods and Cycles. Arch Gen Psychiatry. 2006;63:385-390 | PDF |](#)

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Patient Corner: Use of Wellbutrin (Bupropion) During Pregnancy

Q. I have been taking Wellbutrin SR (generic name: bupropion) for the last five years and am now thinking about getting pregnant. I have tried several times to come off the Wellbutrin, but the depression comes back within a few months. My OB suggested that I switch to Prozac, but the last

time I took Prozac it just didn't work for me. Is there any information regarding the safety of Wellbutrin in pregnancy?

A. There are data to support the use of certain antidepressants during pregnancy. Most of the research over the last decade has focused on the selective serotonin reuptake inhibitors (SSRIs) like fluoxetine (Prozac) and the older tricyclic antidepressants but there is some new data supporting the use of bupropion during pregnancy.

The most recent information from the Bupropion Pregnancy Registry maintained by the manufacturer GlaxoSmithKline includes data from 517 pregnancies involving first trimester exposure to bupropion. In this sample, there were 20 infants with major malformations. This represents a 3.9% risk of congenital malformation that is consistent with what is observed in women with no known teratogen exposure. (Health care providers may receive an updated report from GlaxoSmithKline by calling (800) 336-2176.) While this information regarding the overall risk of malformation is reassuring, earlier reports had revealed an unexpectedly high number of malformations of the heart and great vessels in bupropion-exposed infants.

To more carefully quantify the risk for cardiovascular malformation in bupropion-exposed infants, another study was conducted relying upon two large insurance claims databases ([Cole et al, 2006](#)). Outcomes were compared in three different groups: (1) women dispensed bupropion during the first trimester, (2) women dispensed other antidepressant during the first trimester, and (3) women dispensed bupropion after the first trimester. This retrospective cohort study including over 1200 infants exposed to bupropion during the first trimester did not reveal an increased risk of malformations in the bupropion-exposed group of infants nor did it demonstrate an increased risk for cardiovascular malformations. This study, however, did observe an increased risk of cardiovascular malformation in paroxetine-exposed infants; see Newsletter December 2005.

These data are complemented by a smaller prospective study from the Motherisk Program in Toronto ([Chun-Fai-Chan et al, 2005](#)). Women who were pregnant or planning a pregnancy and taking bupropion (n=136) were enrolled in the study and were contacted after delivery. There were 105 live births and no major malformations were reported. Compared to a group of women with non-teratogen exposures, there were no significant differences in birth weight or mean gestational age. In the bupropion group 20 women (14.7%) had miscarriages, which is higher than observed in the non-teratogen control group but is consistent with rates observed in women taking other antidepressants.

Given these data, bupropion may be an attractive option for women who have not responded well to fluoxetine or tricyclic antidepressants. Further studies are required to assess the risk of neonatal symptoms in bupropion-exposed infants and to better evaluate the long-term neurobehavioral effects of bupropion exposure.

Ruta Nonacs, MD PhD

[Updated preliminary report on bupropion and other antidepressants, including paroxetine, in pregnancy and the occurrence of cardiovascular and major congenital malformation.](#)

[Cole JA, Modell JG, Haight BR, Cosmatos IS, Stoler JM, Walker AM. Bupropion in pregnancy and the prevalence of congenital malformations. Pharmacoepidemiol Drug Saf. 9 August 2006](#)

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Current Research Studies

Premenstrual Dysphoric Disorder (PMDD)

The Center for Women's Mental Health is seeking women, between the ages of 18-49, who regularly experience symptoms of moodiness, sadness, irritability and/or anxiety before getting their menstrual period each month. Eligible women will be enrolled in a clinical research study of an investigational medication to possibly alleviate severe premenstrual symptoms.

Contact: Kate Silver-Heilman at (617) 643-3083 or ksilver-heilman@partners.org

Bipolar Disorder in Pregnancy

Do you have questions about bipolar disorder and anti-depressants or mood stabilizers during pregnancy? If you are pregnant and diagnosed with bipolar disorder (or manic depression), you may be eligible for this research study. Participants meet with research coordinators and psychiatrists who specialize in bipolar illness during pregnancy.

Contact: Marisa Johnson at (617) 726-2912 or mjohnson33@partners.org

Postpartum Depression

Are you a pregnant woman with a history of depression who is less than 36 weeks pregnant?

Contact: Viveka Prakash at (617) 724-6540 or vprakash@partners.org

Neurobehavioral Outcome of Children Exposed to Psychotropics During Pregnancy

Are you a mother with a history of bipolar disorder who has young children?

Contact: Viveka Prakash at (617) 724-6540 or vprakash@partners.org

Menopause, Mood, Sleeplessness, and Hot Flashes

Are you menopausal? Do hot flashes keep you awake at night? Do you have mood swings? If you are a 40-60 year-old menopausal woman who has hot flashes, mood swings, and difficulty sleeping, you may be eligible for an 8-week research study at Massachusetts General Hospital evaluating how estrogen and a sleep medication treat your menopausal symptoms. You will receive study medication and evaluations of your mood, hormone levels, hot flashes, and sleep at no cost.

Contact: Brittany Somley at (617) 724-1181 or bsomley@partners.org.

Menopause and Insomnia

If you are a menopausal woman, 40 years or older, with irregular or no menstrual periods in the past year, and has trouble sleeping at night, you may be eligible for a research study at Massachusetts General Hospital that evaluates the effectiveness of a sleeping medication for the treatment of your insomnia. You will receive study medications and evaluations of your sleep at no cost.

Contact: Kate Silver-Heilman at (617) 643-3083 or ksilver-heilman@partners.org

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