MASSACHUSETTS GENERAL HOSPITAL
55 Fruit Street
Boston, MA 02114
617.726.2000

MGH Center for Women's Mental Health

Reproductive Psychiatry Resource and Information Center

In This Issue

Dear Readers,

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

This issue describes several recently reported studies regarding the safety of antidepressant use during pregnancy. Given the prevalence of depression in reproductive age women and the frequency of anti-depressant use in this population, these new studies have significant implications for women who suffer from depression and who are either planning to conceive or who are pregnant.

Part of the mission 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 newsletter attempts 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

New Research from the CWMH: Relapse of Major Depression during Pregnancy

Over the last decade, the number of reproductive-age women treated for depression has increased significantly. Given the incomplete information available regarding the reproductive safety of many antidepressant medications, many women choose to discontinue pharmacologic treatment during pregnancy. However, several studies estimate that about 10 to 15% of women suffer from depression during pregnancy (O'Hara et al, 1990; Evans et al, 2001). A recent study from the Center for Women's Mental Health indicates that the risk for depression is particularly high among women with histories of major depression (Cohen et al, 2006).

In this study, a total of 201 pregnant women were recruited from three sites: the Perinatal and Reproductive Psychiatry Clinical Research Program at Massachusetts General Hospital, the UCLA Pregnancy & Postpartum Mood Disorders Program and the Emory Women's Mental Health

Program. All of the participants had a history of major depression prior to conception. They were considered eligible if they were currently or recently (<12 weeks prior to last menstrual period) treated with an antidepressant and were euthymic for at least 3 months prior to conception. All women were recruited prior to 16 weeks' gestation and were followed prospectively using longitudinal psychiatric assessments on a monthly basis across pregnancy.

The mean age of the participants was 34.1 years. Approximately 90% were married and more than half reported completing a college education. The mean age at first onset of depression was 18.8 years (SD = 6.8), with approximately half the sample reporting first onset of mood disorder prior to 18 years of age. The women in the sample were noted to have highly recurrent depression, with 44% reporting 5 or more prior episodes. Comorbid psychiatric illness was noted in 93 women (53% of the sample). The most common comorbid diagnoses were anxiety disorders (35%) and eating disorders (17%).

Of the 201 participants, 13 miscarried, 5 electively terminated their pregnancy, 12 were lost to follow-up prior to completion of pregnancy, and 8 chose to withdraw from the study. The main outcome measure was relapse of major depression as defined using the Structured Clinical Interview for DSM-IV Diagnosis (SCID) criteria. Among the 201 women in the sample, 86 (43%) experienced a relapse of major depression during pregnancy. Of the 82 women who maintained antidepressant treatment throughout pregnancy, 21 (26%) relapsed compared with 44 (68%) of the 65 women who discontinued medication. Women who discontinued medication were 5 times as likely to relapse as compared to women who maintained their antidepressant treatment across pregnancy (hazard ratio, 5.0; 95% confidence interval, 2.8-9.1; P<.001).

This study also examined whether certain demographic and clinical variables predicted risk for relapse during pregnancy. No statistically significant association was noted between depressive relapse and race, education level, or baseline antidepressant treatment. However, there was a trend for married women to be somewhat protected against relapse of depression compared with single women (HR, 0.4; 95% CI, 0.1-1.3; P = .13). Women who were older than 32 years were noted to have a 60% reduction in risk for relapse compared with younger women (<32 years; HR, 0.4; 95% CI, 0.2-0.8; P = .01). Risk of illness was greater in women with a longer duration of depressive illness of (> 5 years; HR, 2.7; 95% CI, 1.5-4.7; P = .009) and in those with a history of more recurrent depressive illness (>4 episodes; HR, 3.6; 95% CI, 1.9-7.0; P<.001).

These findings have important clinical implications. While several certain studies have raised concern regarding the use of antidepressants during pregnancy (see Summer 2005 and Winter 2005 Newsletters), this study suggests that women who discontinue treatment are at extremely high risk for recurrent illness. Pregnancy does not appear to be protective with respect to risk of relapse of major depression. Women with histories of depression should be informed of their risk of depressive relapse during pregnancy following antidepressant discontinuation. Given this information, some women with more recurrent or severe depressive illness may choose to maintain antidepressant therapy during attempts to conceive and during pregnancy in order to limit their risk of illness.

Ruta Nonacs, MD PhD

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SSRIs and Persistent Pulmonary Hypertension of the Newborn

Literature accumulated over the last decade supports the use of certain selective serotonin reuptake inhibitors (SSRIs) and the older tricyclic antidepressants during pregnancy, indicating no increased risk of congenital malformation in children exposed to these medications during the first trimester of pregnancy. Still, questions remain regarding the purported risk for "toxicity" in newborns exposed to antidepressants around the time of labor and delivery (see Fall 2004 and Spring 2005 Newsletters). In addition, a recent study published in the New England Jounal of Medicine has linked SSRI use during late pregnancy to an increased risk of persistent pulmonary hypertenstion in the newborn (Chambers 2006).

Persistent pulmonary hypertension of the newborn (PPHN) is a cardiovascular syndrome typically occurring in full-term or near-term infants. After birth, the infant's pulmonary vascular resistance fails to decrease; and blood is shunted away from the lungs and is therefore not fully oxygenated, causing hypoxemia in the newborn. PPHN is usually seen shortly after birth, typically within 12 hours of delivery. Infants present with respiratory distress and, in the worst cases, require assisted ventilation. PPHN occurs in approximately one in 700 births and is often seen when there is an underlying lung disease, such as hyaline membrane disease or meconium aspiration syndrome; however, PPHN may also occur in the absence of underlying lung disease. Maternal factors associated with PPHN include cesarean section, antenatal use of non-steroidal anti-inflammatory agents (NSAIDs), and tobacco use (van Marter 1996).

Based on a previous report suggesting a higher than expected number of cases of PPHN in infants exposed to fluoxetine during pregnancy (Chambers 1996), the investigators used a case-control design to evaluate risk factors for PPHN, focusing on exposure to NSAIDs and SSRIs. The authors identified 637 infants with possible PPHN from 97 institutions in four metropolitan areas (Boston; Philadelphia; San Diego, California; and Toronto). Diagnosis of PPHN was confirmed in 377 infants by review of the medical records by a neonatologist blinded to the mother's medication status. A control group of 836 women and their infants was also identified. Rates of participation were 73% in the PPHN group and 71% in the control group. The mothers were interviewed using a structured questionnaire within six months of delivery by a study nurse who was unaware of the study hypothesis.

The use of SSRIs at any time in pregnancy was not significantly associated with PPHN. However, when the comparison was stratified according to the timing of exposure in pregnancy, the use of an SSRI antidepressant after the 20th week of gestation was significantly associated with PPHN (adjusted odds ratio, 6.1; 95 percent confidence interval, 2.2 to 16.8). Although body mass index, diabetes, NSAID use, and smoking have been identified as maternal factors associated with PPHN, controlling for these potential confounders did not significantly attenuate the association between SSRI use and PPHN. Neither the use of SSRIs before the 20th week of gestation nor the use of non-SSRI antidepressants at any time during the pregnancy was associated with an increased risk of PPHN.

It is difficult to reconcile these findings with other studies investigating neonatal outcomes in infants exposed to antidepressants in utero. There have been reports of adverse events in exposed infants, most commonly symptoms of jitteriness, sleep disturbance, feeding problems, and excessive crying. There have also been reports of respiratory distress (usually tachypnea or rapid breathing); however, the observed symptoms were relatively mild, transient, and did not require specific medical intervention, suggesting that these cases were not PPHN, a more serious complication with significant morbidity. The only study to report cases of PPHN was from the authors of the current study (Chambers 1996). Clearly further investigation is warranted to clarify the association between SSRI use and PPHN.

These findings are likely to generate significant anxiety among child-bearing women who suffer from depression. About 10% to 15% of women in the general population suffer from depression

during pregnancy. The risk is particularly high in women with histories of depression who discontinue antidepressants during pregnancy. Women considering the use of antidepressants during pregnancy must be made aware of this risk but it must be weighed against the risks of untreated illness in the mother. To avoid or withhold antidepressants during pregnancy places these women - and their children - at risk. Depression in the mother is not a benign event and, when left untreated during pregnancy, has been associated with poor neonatal outcomes, including preterm birth, low birthweight, and lower Apgar scores. If we assume that these findings are correct, the risk is still relatively small; the authors estimate the risk of PPHN to be less than 1% in infants exposed to SSRIs in utero. Thus many women with more severe or recurrent illness may elect to continue treatment with SSRIs during pregnancy, acknowledging that the risks associated with untreated depression are greater than the risks of SSRI use.

Ruta Nonacs, MD, PhD

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Van Marter LJ, Leviton A, Allred EN, et al. Persistent pulmonary hypertension of the newborn and smoking and aspirin and nonsteroidal anti-inflammatory drug consumption during pregnancy. Pediatrics 1996;97:658-63. | PDF |

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Withdrawal Symptoms in Newborns Exposed to SSRIs

A recent report suggests that newborns exposed to selective serotonin reuptake inhibitors (SSRI) antidepressants such as Prozac, Zoloft, Celexa and Paxil may be at risk for developing withdrawal symptoms after delivery (Levinson-Castiel 2005). However, the investigators also noted that the symptoms usually disappeared within 48 hours and did not require medical intervention.

In this study, published in the Archives of Pediatrics & Adolescent Medicine, 60 infants exposed to SSRIs during pregnancy and 60 non-exposed infants were assessed using the Finnegan scale, an objective rating used to assess the severity and resolution of neonatal abstinence symptoms. Of the 60 SSRI-exposed infants, 37 were exposed to paroxetine, 12 to fluoxetine, 8 to citalopram, 2 to venlafaxine, and 1 to sertraline. Elevated Finnegan scores were observed in 30% (n=18) of neonates exposed to SSRIs. None of the non-exposed infants had elevated scores. Of the 60 exposed neonates, 8 showed severe and 10 showed mild withdrawal symptoms. The most commonly observed symptoms were tremor, increased muscle tone, sleep disruption, gastrointestinal disturbance and high-pitched crying. In the infants who exhibited severe symptoms, the symptoms were most severe within 2 days after birth. No infants with symptoms required any specific medical treatment.

Several other reports have demonstrated similar symptoms in infants exposed to SSRIs in utero (reviewed in the Newsletter: Fall 2004). While the investigators carrying out this study suggest that these symptoms represent a withdrawal phenomenon, others have hypothesized that they reflect serotonergic hyperstimulation (Laine 2003). It should also be noted that infants born to mothers with untreated depression are at higher risk for adverse neonatal outcomes than those born to non-depressed mothers (Zuckerman 1990, Misri 2004), suggesting that it may be the underlying illness - rather than the medications used to treat the disorder - that is associated with poor neonatal outcomes.

Reassuringly, the reported adverse events appear to be relatively mild and short-lived and rarely require any type of medical intervention. Furthermore, there is no indication of longer-term problems in children exposed to SSRIs during pregnancy (Laine 2003, Nulman 2002). Clearly further research is essential, but pending more controlled study, appropriate vigilance of exposed newborns after delivery is good clinical practice. It is unclear at this point if discontinuing or lowering the dosage of the mother's antidepressant shortly before delivery will reduce the risk of neonatal toxicity; however, it is clear that this type of intervention may significantly increase the risk of recurrent depression in the mother. Given the adverse effects of maternal depression on the child, maintaining mood stability in the mother should remain the highest priority.

Ruta Nonacs, MD PhD

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Patient Corner: Use of Paxil during Pregnancy

Q. I have taken Paxil for about six years for depression and obsessive-compulsive disorder. I have tried several times to stop the medication but the symptoms come back within a few weeks of stopping the medication. My husband and I are now planning a pregnancy, and my obstetrician tells me that I cannot take Paxil during pregnancy. Are there any other options?

A. Several recent studies have raised concerns regarding the use of paroxetine (Paxil) during pregnancy. (These studies have been reviewed in detail in the Newsletter: Winter 2005.) In an unpublished report from GlaxoSmithKline, the manufacturer of paroxetine as Paxil (see communication, GlaxoSmithKline, December 2005), data derived from an HMO claims database demonstrated a 1.8-fold increase in overall risk of malformations and a trend toward an increased risk for cardiovascular malformations (odds ratio of 1.54) in paroxetine-exposed infants. A recent report from the Swedish Medical Birth Registry, including 822 infants exposed to paroxetine, also demonstrated a 1.8-fold increased risk of cardiovascular malformation in paroxetine-exposed children. Infants exposed to other SSRIs did not have an increased risk of cardiac or other defects (Hallberg 2005).

In a case control study, investigators from the University of British Columbia, Vancouver analyzed data from the National Birth Defects Prevention study (Alwan et al, 2005) and found an association between exposure to an SSRI during the first trimester and a three-fold increased risk of omphalocele. The strongest effect was observed with paroxetine, which was associated with a 6.4-fold increase in risk for this defect. (Omphalocele, an abnormality in which the infant's

intestines or other abdominal organs protrude from the navel, occurs in approximately 1 out of every 4,000 births.)

These recent findings of increased risk with prenatal paroxetine exposure are inconsistent with earlier findings. While there is clearly a need for more thorough analysis of the existing data, these reports, taken together, may signal an increase in risk of malformations in children exposed to paroxetine. However, it is important to put this risk in perspective. Even if we assume the associations from the new case-control study are true, a 6.4-fold increase in risk for omphalocele translates into an absolute risk of only 0.16% (approximately 2 out of every 1,200 births). The overall risk of cardiovascular malformation is estimated to be about 1.5%. Absolute risk is of far greater clinical value than relative risk and should be taken into consideration when making decisions regarding the use of antidepressants during pregnancy.

Patients who are planning to conceive and are at significant risk for depressive relapse in the setting of antidepressant discontinuation may benefit from switching to an antidepressant for which there is more information supporting reproductive safety. These include fluoxetine and citalopram, as well as the older tricyclic antidepressants. However, some women may not be able to tolerate or may have an inadequate response to these alternative treatments; under these circumstances, they may elect to continue treatment with paroxetine, acknowledging that, while there may be some concerns regarding its use during pregnancy, the relative risk remains small. And this risk should be weighed against the risks associated with untreated illness in the mother.

Ruta Nonacs, MD PhD

Communication: "Dear Doctor" Letter from GlaxoSmithKline, December 2005

New FDA Guidelines concerning paroxetine during pregnancy (Issued September 2005)

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New Research from the CWMH: Menstrual Cycle Irregularity in Women with Bipolar Disorder

Preliminary reports have suggested that menstrual irregularity may occur more commonly in women with mood disorders than in the general population. What has been unclear, however, is whether these menstrual cycle irregularities reflect an underlying disruption of the hypothalamic-pituitary-gonadal (HPG) axis in women with mood disorders or are caused by the psychotropic medications used to treat these psychiatric disorders.In a recent study, Dr. Hadine Joffe of the Center for Women's Mental Health and her colleagues assessed the prevalence of menstrual cycle dysfunction in 3 groups of women: (1) with bipolar disorder, (2) with unipolar depression, or (3) with no psychiatric illness (Joffe 2006).

Subjects were drawn from two large studies which used the same questionnaires to collect data regarding a wide range of demographic and clinical variables, including menstrual history and age at onset of illness. Subjects with DSM-IV bipolar disorder (n=295) were derived from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Subjects with DSM-IV unipolar depression (n=245) or no psychiatric illness (n=619) were selected from the Harvard Study of Moods and Cycles. In this study, early-onset menstrual dysfunction was defined as menstrual cycle irregularity occurring within 5 years of the onset of menses and before the onset of psychiatric illness, either menstrual cycle length unpredictable within 10 days or menstrual cycle length < 25 days or > 35 days.

Early-onset menstrual cycle dysfunction was retrospectively reported to have occurred in 101/295 women with bipolar disorder (34.2%), 60/245 women with depression (24.5%), and 134/619 healthy controls (21.7%). After adjusting for age, body mass index, ethnicity, age at menarche, and marital, educational, and employment status, women with bipolar disorder were 1.7 times more likely to report early-onset menstrual cycle dysfunction than healthy controls (p=.01). Menstrual dysfunction was more common among women with type I bipolar disorder than in women with type II bipolar disorder.

Consistent with prior reports, this study indicates that women with bipolar disorder are more likely to report menstrual irregularities that women in the general population. In contrast, women with unipolar depression did not appear to be at greater risk for early-onset menstrual dysfunction. Because menstrual dysfunction occurred before the onset of illness in the women included in this study, it is possible to exclude medications as a possible cause of menstrual irregularities. These findings raise the possibility that the changes in neurotransmitter systems associated with bipolar disorder may also affect the functioning of the HPG axis.

Ruta Nonacs, MD PhD

Joffe H, Kim DR, Foris JM, Baldassano CF, Gyulai L, Hwang CH, McLaughlin WL, Sachs GS, Thase ME, Harlow BL, Cohen LS. Menstrual dysfunction prior to onset of psychiatric illness is reported more commonly by women with bipolar disorder than by women with unipolar depression and healthy controls. J Clin Psychiatry. 2006 Feb;67(2):297-304. | PDF |

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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: Kim Kelly at (617) 724-6540 or kkelly11@partners.org

Breastfeeding and Psychiatric Medications
Are you breastfeeding and taking psychiatric medications?
Contact: Juliana Mogielnicki at (617) 724-6989 or jmogielnicki@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: Juliana Mogielnicki at (617) 724-6989 or jmogielnicki@partners.org

Depression in Post-Menopausal Women
If you are a post-menopausal woman who is feeling depressed or down and has not had a menstrual period in the past year, you may be eligible to participate in a research study evaluating how a non-hormonal medication helps with depression and menopausal symptoms.
Contact: Brittny Somley at (617) 724-1181 or bsomley@partners.org

Menopause and Recent Discontinuation of Hormone Replacement Therapy
Do you have hot flashes? Have you tried Hormone Replacement Therapy and recently stopped it? Are your menopause-related symptoms still bothering you?
Contact: Maya Rydzewski at (617) 643-3078 or mrydzewski@partners.org.

Menopause, Mood, Sleeplessness, and Hot Flushes
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: Brittny Somley at (617) 724-1181 or bsomley@partners.org.

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