



In This Issue

Pregnancy and SSRI's

- Is There a Risk to the Newborn?

Hormones and Mental Health

- Where Do We Stand in the Post-WHI Era?

New Research at the CWMH

- Who is at Risk for Depression During Pregnancy?

Ongoing CWMH Research

Dear Readers,

It is a pleasure to publish this first issue of the **Center for Women's Mental Health Newsletter**. The newsletter provides a range of information including discussion of new research findings in women's mental health and how such investigations inform day-to-day clinical practice. Despite the growing number of studies being conducted in women's health, the clinical implications of such work are frequently controversial, leaving patients with questions regarding the most appropriate path to follow.

The CWMH Newsletter complements the extensive resources on our website, www.womensmentalhealth.org. Providing these resources to patients and their doctors so that individual clinical decisions can be made in a thoughtful and collaborative fashion dovetails with the mission of our Center.

We hope you find this inaugural issue informative and we welcome your feedback.

Sincerely,
Lee Cohen, MD

Mission Statement

The mission of **The Center for Women's Mental Health** is to provide state-of-the-art evaluation and treatment to women who suffer from a spectrum of psychiatric disorders, including premenstrual dysphoric disorder, mood and anxiety disorders during pregnancy and the postpartum period, and peri- and post-menopausal depression. At the Center, internationally renowned clinician-researchers focus on the diagnosis, treatment and prevention of psychiatric disorders affecting women. Providing accurate information to patients and caregivers informs and improves care.

The Reproductive Psychiatry Resource and Information Center was developed as a means of providing up-to-date information to patients and caregivers in the rapidly evolving field of women's mental health. The primary goals of this internet-based resource are to disseminate current research findings in this field, to help women make informed decisions regarding their care, and to facilitate collaborative decision-making between patients and their caregivers.

Pregnancy and SSRIs: Is There a Risk to the Newborn?

The increasing number of reproductive-age women taking antidepressants has raised concerns about the potential risks of using these medications during pregnancy. 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. These concerns are not new. Twenty years ago, case reports suggested that maternal use of tricyclic antidepressants near the time of delivery was associated with problems in the newborn such as difficulty feeding, restlessness, or jitteriness.

Several recent studies have suggested that exposure to SSRIs at the time of delivery may be associated with poor perinatal outcomes. This concern was first raised by Chambers and colleagues who reported an association between third-trimester use of fluoxetine (Prozac) and an increased risk of neonatal complications and higher rates of admission to the special care nursery ([Chambers 1996](#)). Several other studies have also shown increased rates of admission to the special care nursery among SSRI-exposed infants ([Casper 2003](#), Pearson 2001, [Cohen 2000](#)). Nonetheless, the clinical relevance of admission to the special care nursery in non-blinded series is unclear ([Cohen 2000](#)).

Another study compared neonatal outcomes following *in utero* exposure to tricyclic antidepressants and SSRIs using a large database from a group-model HMO. There was an association between third-trimester exposure to SSRIs and lower Apgar scores, decreased gestational age, and lower birth weight; these differences were not observed among tricyclic-exposed newborns ([Simon 2002](#)). Several other studies also observed lower Apgar scores in SSRI-exposed infants ([Casper 2003](#), [Laine 2003](#), [Kallen 2004](#)); however, not all studies have demonstrated differences in APGAR scores between exposed and non-exposed infants ([Suri 2004](#), Pearson 2001). It is reassuring to note that in these studies that demonstrated lower Apgar scores, the difference in Apgar scores between exposed and non-exposed infants was small (less than 1 point) and average Apgar scores in the exposed children remained high (above 7). Clinically a score of 7 or greater at 5 minutes suggests that the baby's condition is good to excellent.

In a prospective, controlled, follow-up study ([Laine 2003](#)), neonatal outcomes were assessed in 20 mothers taking 20 to 40 mg of either citalopram or fluoxetine and in 20 controls not receiving any psychotropic medication. The newborns were assessed during the first 4 days of life and at 2 weeks and 2 months of age. In exposed infants, symptoms of "serotonergic overactivity" were observed more frequently than in non-exposed controls. The most prominent symptoms observed in the newborns included tremor, restlessness, and increased muscle tone. These symptoms resolved over the next 1 to 4 days, and there were no observed differences between the exposed and non-exposed infants at 2 weeks and 2 months. Similarly, Simon and colleagues reported that from 6 months on, significant differences between exposed and non-exposed groups were not evident, despite the differences noted at birth. Exposure to SSRI or tricyclic antidepressants was not associated with developmental delays through age 2.

Whether these symptoms represent a direct effect of exposure to antidepressant or a discontinuation syndrome is not clear. Investigators at the Motherisk Program at the University of Toronto reported that exposure to paroxetine (Paxil) late in pregnancy was associated with a significantly higher rate of transient neonatal complications among 55 paroxetine-exposed newborns, as compared to infants exposed to paroxetine early in pregnancy or to newborns with no paroxetine exposure ([Costei 2003](#)). Respiratory distress was the most commonly reported adverse event. The authors hypothesize that the unexpectedly high rate of symptoms in these newborns may be the neonatal equivalent of the discontinuation syndrome commonly seen in adults who develop a variety of somatic symptoms after rapidly stopping paroxetine.

One of the most significant shortcomings of these studies is that most did not use blind raters to make assessments of neonatal outcomes. Observations of newborn behavior and symptoms were made either by the physician or the mother. This runs the obvious risk of introducing a significant bias and may over-estimate the risk of adverse events in SSRI-exposed children. The decision to admit a newborn to a special care nursery may represent a reasonable precaution for an infant exposed to medication *in utero* and may not be an indication of a serious problem. In fact, the research from Pearson and colleagues at the Center for Women's Mental Health suggests that the duration of stay in the special care nursery was much shorter for the SSRI-exposed children than for non-exposed children, suggesting that they may have been admitted only for prudent observation.

Other methodologic limitations in the few studies addressing this issue lie in failure to assess maternal mood during pregnancy or at the time of delivery. Ample evidence exists that depression and/or anxiety in the mother may contribute to poor neonatal outcomes, including premature delivery and low birth weight. Thus, it is important to evaluate the contribution of maternal mood in studies designed to describe the effect of prenatal and peripartum exposure to SSRIs on neonatal outcomes.

Summarily, it is possible that the findings from these studies signal a potential problem. Reassuringly, the reported adverse events appear to be relatively 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](#), [Casper 2003](#), [Simon 2002](#), [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 a highest priority.

Lee S. Cohen, MD
Ruta Nonacs, MD, PhD

Hormones and Mental Health: Where Do We Stand in the Post-WHI Era?

Ms. S.J. is now 50 years old, and is facing a dilemma. Two weeks ago, her physician called, asking her to make an appointment to discuss her hormone treatment - "It is too risky," he told her. S.J. left her doctor's office somewhat confused, and unsure about her health. After all, she had spent quite a few years struggling with symptoms of depression, difficulty in concentrating, fatigue, and problems sleeping due to intense hot flushes; several unsuccessful trials with different psychotropic medications had left S.J. hopeless about her treatment. Around three months ago, she had initiated hormone replacement therapy (HRT) and had finally achieved some stability with combined use of antidepressants. Her quality of life had improved significantly. In addition, HRT was presented as an efficacious - and quite safe - strategy. Well, not anymore...

For many decades, women and health professionals were taught about the benefits of hormone replacement therapy (HRT). Essentially, HRT had been administered to alleviate physical symptoms associated with the menopausal transition (short-term use of HRT), and to help in preventing the clinical consequences of an estrogen-deficient state, including osteoporosis and cardiovascular disease (long-term use of HRT). More recently, the list of benefits of short-term HRT was expanded, incorporating preliminary but promising findings on mood and cognition. Nonetheless, results from large, prospective studies were highly desired, as they could provide more robust information on the risks and benefits of long-term HRT.

The recent findings derived from the *Women's Health Initiative Study* (WHI) have caused both disappointment and apprehension. This multi-center, randomized, placebo-controlled primary prevention trial was designed to follow more than 16000 healthy postmenopausal women for eight years but was closed early due to evidence of an increased risk for invasive breast cancer and cardiovascular events. The impact of HRT on "well-being" and sexual satisfaction was not significant. In addition, in a sub-group of subjects who had a higher risk for developing dementia (WHI Memory Study), HRT failed to prevent the development of cognitive deficits.

As a first reaction, physicians and patients felt betrayed, and many patients have decided to discontinue their HRT regimens. Still, others who did not abandon their prescription hormones are now questioning their current treatment and potential alternatives. Most women and their doctors are now facing a difficult situation: how should they deal with menopause-related physical and emotional symptoms? Is there a role for HRT in the post-WHI era?

The results from the WHI study should be carefully interpreted. In fact, various experts in the field have expressed their concerns about the WHI study limitations and the risk of generalizing its conclusions to all menopausal women. Clinicians should continue to consider many factors when advising peri- and post-menopausal women of their treatment choices.

The benefits and safety of long-term use of HRT are now in question; research will undoubtedly increase in the search for safer alternatives. For those currently on HRT, it is important to remember that an abrupt treatment discontinuation could lead to the occurrence or reemergence of somatic symptoms, interfering with sleep pattern, physical well-being and most probably mood.

The short-term use of HRT (up to three to five years) has not been considered unsafe, and still is the most efficacious treatment for vasomotor symptoms (i.e., night sweats, hot flashes). Alternative treatments are not necessarily safe. Some of the so-called "natural" treatments for menopausal symptoms have a significant binding affinity for estrogen receptors, and may result in similar risks. Their use should be carefully considered, particularly in the presence of contraindications for using estrogen therapy. Recent studies suggest that antidepressants promote improvement of vasomotor symptoms, constituting an interesting alternative for menopausal women who experience depressive symptoms and vasomotor complaints.

Claudio N. Soares, MD, PhD

New Research at the Center for Women's Mental Health

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, recent studies estimate that about 10 to 15% of women suffer from depression during pregnancy, and risk for depression appears to be even higher among women with histories of mood disorder.

The Center for Women's Mental Health has been interested in this group of women with recurrent depression and in learning more about the course of their illness during pregnancy:

- Which women with histories of depression are at highest risk for recurrent illness during pregnancy?
- What interventions, both pharmacologic and non-pharmacologic, may be used to decrease the risk of depression during pregnancy?
- What are the effects of antidepressant usage during pregnancy on the child?

In a research study funded with a grant from the National Institutes of Mental Health, the Center for Women's Mental Health, in collaboration with the UCLA Pregnancy & Postpartum Mood Disorders Program and the Emory Women's Mental Health Program, will attempt to address many of these important questions. In this study, 260 women were followed across pregnancy. All of the women included in this prospective study had a history of major depression and were treated with antidepressants prior to pregnancy. A preliminary analysis of the first 207 women to complete this study suggest that:

- Among the women who elected to discontinue antidepressant treatment, almost two-thirds experienced depression during pregnancy.
- Women who discontinued treatment were 3.3 times as likely to relapse as the women who chose to remain on an antidepressant during pregnancy.
- Half of the women who relapsed did so during the first trimester.

These results clearly demonstrate that discontinuing treatment may not always be the best or safest decision. The data are now being analyzed in order to determine which women in this population are at highest risk for illness during pregnancy.

Ruta Nonacs, MD, PhD

Current Studies at the Center for Women's Mental Health

Bipolar Disorder and Pregnancy

Are you a pregnant woman with a history of bipolar disorder?

Contact: Juliana Mogielnicki

617-724-6989 or jmogielnicki@partners.org

Postpartum Depression

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

Contact: Kim Kelly,

617-724-6540 or kkelly11@partners.org

Breastfeeding and Psychiatric Medications

Are you breastfeeding and taking psychiatric medications?

Contact: Juliana Mogielnicki

617-724-6989 or jmogielnicki@partners.org

PMS and Depression

Do you experience symptoms such as depression, anxiety, and/or irritability before their period?

Contact: Hannah Gottschall

617-726-2912 or hgottschall@partners.org

PMS and Bipolar Disorder

Have you been diagnosed with bipolar disorder and have premenstrual worsening of mood symptoms?

Contact: Hannah Gottschall

617-726-2912 or hgottschall@partners.org

Menopause and Recent Discontinuation of Hormone Replacement Therapy

Do you have hot flashes? Tried Hormone Replacement Therapy and recently stopped it? Are your menopause-related symptoms still bothering you?

Contact: Revital Yehezkel

617-724-1181 or ryehezkel@partners.org

Perimenopause and Insomnia

Are you a perimenopausal woman with irregular periods? Having trouble falling asleep at night? Feeling tired?

Contact: Revital Yehezkel

617-724-1181 or ryehezkel@partners.org

Menopause: Hot Flashes, Sleeplessness and Mood Swings

Are you a menopausal woman aged 40-60 with frequent hot flashes, sleeplessness, and mood swings?

Contact: Revital Yehezkel

617-724-1181 or ryehezkel@partners.org

Neurobehavioral Outcome of Children Exposed to Psychotropics During Pregnancy

Are you a mother with a history of bipolar disorder who has children who were exposed to medication during pregnancy?

Contact: Juliana Mogielnicki

617-724-6989 or jmogielnicki@partners.org

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