

Depression During Pregnancy

Out of every 10 women who are pregnant, one or two have symptoms of major depression. Women who have been depressed before are at higher risk.

Depression is a serious medical condition. It poses risks for the woman and her baby. But a range of treatments are available. These include counseling, psychotherapy, support groups, therapy with light, and medications. Individual therapy is highly recommended.

It is usually best for a team of health care professionals to work with a pregnant woman who is depressed or who has a history of depression. Team members include:

- The provider who is caring for her during her pregnancy
- A mental health professional
- The provider who will take care of the baby after birth

Together, the team and the woman decide what is best for her and her baby. The team can connect her to support groups, help her consider counseling and psychotherapy, and assess the need for light therapy or medication.

Often a pregnant woman wonders whether antidepressant drugs, such as Zoloft and Prozac, will harm her baby or herself. There are no simple answers. Each woman and her health care providers must work together to make the best decision for her and her baby. The drugs used to treat depression have both risks and benefits.

IMPORTANT: If you are taking an antidepressant and find that you are pregnant, do not stop taking your medication without first talking to your health provider. Call him or her as soon as you discover that you are expecting. It may be unhealthy to stop taking an antidepressant suddenly.

What Is Depression?

Depression is an illness that involves the body, mood and thought. It affects the way a woman feels about herself and the way she thinks about things. This article addresses two types of depression:

Major depression: This serious illness interferes with a person's ability to work, study, sleep, eat and enjoy oneself. It may appear once in a person's life, but more often occurs several times.

Dysthymia: This is a less severe type of depression. Persons with this illness have long-term symptoms. They are able to conduct day-to-day activities, but they don't always function well or feel good. They may also have episodes of major depression.

Depression carries serious risks for the pregnant woman and her baby. These risks include:

- Poor weight gain
- Use of drugs or alcohol to self-medicate
- Suicidal Thoughts and/or Suicide
- Poor nutrition

The above symptoms can lead to premature birth, low birth weight and developmental problems. In addition, depressed mothers are often less able to care for themselves or their children, or to bond with their children.

What Are the Symptoms of Depression?

A woman who is depressed feels sad or “blue” and has other symptoms that last for two weeks or longer. The other symptoms include the following:

- Trouble sleeping
- Sleeping too much
- Lack of interest
- Feelings of guilt
- Loss of energy
- Difficulty concentrating
- Changes in appetite
- Restlessness, agitation or slowed movement
- Thoughts or ideas about suicide

Things other than depression can cause some of these symptoms. For instance, changes in appetite and trouble sleeping are common in pregnancy. Some medical conditions, such as anemia and hypothyroidism, can cause a pregnant woman to lack energy.

If you have any of these symptoms, talk to your health care provider. He or she will check to see what might be causing your symptoms. You need to be checked for depression if symptoms continue and interfere with your daily life and if your provider rules out other medical conditions.

Treatments

Depression can be treated in several ways. Support groups may help. Some women go to therapy or counseling with a mental health professional (such as a social worker, psychotherapist or psychiatrist).

Some people suffer from a type of depression that comes on during the fall or winter, when there is less sunlight. This is called Seasonal Affective Disorder (SAD). This condition can be treated with light therapy. In her home, the patient looks into a box with special light bulbs. To avoid injury to her eyes, she looks at the lights indirectly. Typically, the patient does this from 15 minutes to two hours every day. The health provider may recommend a different number of minutes over time.

Mental health professionals often talk with women about the risks and benefits of antidepressants.

Two Main Groups of Antidepressants

The most studied antidepressants can be categorized into one of two groups.

Group 1: Selective serotonin uptake inhibitors (SSRIs). This group of drugs includes:

- Prozac (fluoxetine)
- Zoloft (sertraline)
- Celexa (citalopram)

- Lexapro (escitalopram)
- Paxil (paroxetine) – not recommended in pregnancy (see below)
- Effexor (venlafaxine) – not actually an SSRI, but has similar serotonin effects

Group 2: Tricyclic antidepressants (TCAs). This group of drugs includes:

- Elavil (amitriptyline)
- Tofranil (imipramine)
- Pamelor (Aventyl, nortriptyline)

Like many drugs, antidepressants can have side effects. SSRIs usually have fewer side effects than TCAs. Women differ in the type and seriousness of the side effects that they have.

What Research Tells Us About Antidepressants

It is challenging to study and understand the risks of any drug given to pregnant women. During pregnancy, two patients—the mother and the fetus—are exposed to the drug. Medications that are safe for a woman are sometimes risky for a fetus. Because of this, researchers have not studied many drugs during pregnancy.

It is unethical to test a drug on a pregnant woman since we don't know how it might affect the fetus. Researchers get most of their information by studying drugs that have been approved for women who are not pregnant and that are then taken by pregnant women. Often these women are not aware that they are pregnant.

Several drugs have been used for many years without any obvious signs of serious risk to the baby. But some researchers have reported that some antidepressants may have increased risks. SSRIs are a newer group of drugs than TCAs. Researchers are continuing to study them.

Research has clearly shown that women who are not pregnant and are depressed are very likely to become ill again if they stop taking their medications. A recent study in 2006 suggests that the risk of depression relapse is high in pregnant women who discontinue their antidepressant during pregnancy.

Here are some other things that research tells us about the risks and benefits of taking SSRIs during pregnancy.

During Pregnancy:

- One study in 2006 found that pregnant women with major depression are very likely to become ill again during their pregnancy if they stop taking their medication. A depressed woman may have trouble taking care of herself during pregnancy. This could threaten the health of the fetus.
- Many studies have found no link between antidepressants and serious malformations in newborns. But in 2005, the U.S. Food and Drug Administration (FDA) issued a warning about Paxil based on several studies. The warning said that taking the drug during the first three months of pregnancy may increase the risk of birth defects, particularly heart defects. Scientists do not yet know enough to draw a firm conclusion. Women and their health care providers should weigh the risks and benefits of using Paxil during pregnancy. But in general, Paxil is not advised during pregnancy.

- In one study in 2006, three of 60 infants exposed to SSRIs for the complete pregnancy had major congenital anomalies, including ventricular septal defect, hydronephrosis, and cleft palate (see below for more specific information).
- Two large studies in the June 28, 2007 issue of *The New England Journal of Medicine* found that despite some significant associations, any increase in birth defects associated with exposure to SSRIs is "likely to be small in terms of absolute risk." There was a small increased risk for right ventricular outflow tract lesions with Paxil and a small increased risk for septal defects with Zoloft (see below for more specific information).
- According to a three-country study in the November 2008 issue of the *British Journal of Clinical Pharmacology*, women who took Prozac during the first three months of pregnancy gave birth to four times as many babies with heart problems as women who did not and the levels were three times higher in women taking Paxil. International researchers from Israel, Italy and Germany followed the pregnancies of 2,191 women – 410 who had taken Paxil during pregnancy, 314 who had taken Prozac and 1,467 controls who hadn't taken either of the drugs. Although some of the conditions were serious, others were not severe and resolved themselves without the need for medical intervention. The team suggested that women on Prozac should be given a fetal echocardiogram in their second trimester to diagnose possible heart anomalies. Other antidepressants were not studied (see below for more specific information).
- In September 2009, *The British Medical Journal (BMJ)* reported that women who used Zoloft or Celexa early in pregnancy faced increased risk for septal heart defects in their offspring. Researchers examined data on more than 490,000 infants born in Denmark between 1996 and 2003. They found that women who filled prescriptions for Zoloft and Celexa (but not other SSRIs) during their first trimester were significantly more likely to have children with septal heart defects (but not other malformations) than those who didn't use SSRIs (odds ratios: 3.2 and 2.5, respectively). The authors note that the absolute risks for septal heart defects were low: 0.9% in children exposed to at least one SSRI and 2.1% in those exposed to more than one. The editorialist concludes: "Clinicians and patients need to balance the small risks associated with SSRIs against those associated with undertreatment or no treatment" (see below for more specific information).
- In July 2011, Finnish investigators (Malm and colleagues) performed a retrospective national cohort study of maternal SSRI use and incidence of major congenital anomalies (including pregnancy terminations performed because of severe malformations) to evaluate outcomes in 6976 offspring with first-trimester SSRI exposure in comparison with 628,607 unexposed offspring. Overall, adjusted risk for major congenital anomalies was not significantly different in exposed and unexposed offspring. They reported that although *relative* risks for certain anomalies are elevated with SSRI use, *absolute* risks are low. For example, excess risk for a major cardiovascular anomaly attributable to SSRI use is 37 additional cases per 10,000 women. For women who use SSRIs during early pregnancy, second-trimester ultrasound imaging to evaluate for anomalies is advisable.
- In an article published July 4, 2011, Lisa Croen and colleagues examined fetal SSRI exposure in 298 children with medical-record diagnoses of autism spectrum disorders (ASDs) and 1507 control children. Children whose mothers received at least one antidepressant prescription in the year before delivery were considered exposed (20 case mothers and 50 control mothers). This study indicates a possible association between SSRI exposure and childhood ASD, which can be explained as either a two- to threefold increase in risk or as an increase from 1% to 2-3%. Although the study was carefully done, its findings need to be replicated. Prescription use was not

confirmed, diagnoses were from medical records and not psychiatric interviews, and factors such as tobacco, alcohol, and drug use were not controlled for. Mothers of children with ASD were significantly older and children with ASD were more likely to have low birth weight and gestational age under 37 weeks at delivery. Also, distinguishing the role of medication exposure from the role of the underlying disorder which necessitated the treatment is important. In this first-of-a-kind study, they found (only) a modest association between use of an SSRI in pregnancy and autism. The baseline risk of autism is 1% of the general population; if these data are true (and, more importantly, replicated), the risk is elevated to 2-3% of children developing autism, meaning 97-98% do not develop autism. The absolute risk is still small. There's also the consideration of the effect of stress and/or untreated depression or anxiety and the effect of that on the fetus.

During Delivery:

- **Neonatal Abstinence Syndrome (NAS):** Some babies born to mothers who are taking SSRI antidepressants show signs of "withdrawal." For instance, they may have breathing or feeding problems. Their movements may be jerky. Some have irritability, abnormal crying and tremor. There have been reports of some seizures and intubations, but no deaths. NAS can affect 10-30% of neonates exposed to SSRI's. Health providers who care for newborn babies are aware of these risks and can provide treatment. Symptoms usually subside from 48 hours to a few days. It is important for the baby's provider to know ahead of time that the mother has taken antidepressants during pregnancy (see below for more specific information).
- **Persistent Pulmonary Hypertension of the Newborn (PPHN):** In 2006, Chambers and colleagues published an article in the *New England Journal of Medicine* linking SSRI use in late pregnancy (after 20 weeks) to an increased risk of PPHN. Based on these findings, the "Usage in Pregnancy" section on the labels for SSRI antidepressants was updated to include the following warning: "Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN)." Since that time, other reports have been published which have examined the association between SSRI's and PPHN. Thus far, there have been a total of seven studies evaluating the association between PPHN and SSRI exposure. Three of these studies showed no association between SSRI exposure and PPHN. Four other studies showed an increased risk of PPHN in SSRI-exposed infants, with an estimated odds ratio ranging from 2.4 to 6.1. (This means an absolute risk of 2-12 per 1000 vs. a background risk of 1-2 per 1000 in the general population). Based on these studies, the FDA has issued a revision warning: "FDA has reviewed the additional new study results and has concluded that, given the conflicting results from different studies, it is premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN. FDA will update the SSRI drug labels to reflect the new data and the conflicting results." The authors of a review examining this data point out that many factors associated with depression (rather than exposure to an antidepressant) may account for the association, such as obesity, smoking, premature birth and cesarean section – all of which are more common in women with depression (see below for more specific information).
- One study in the August 2007 issue of *The American Journal of Psychiatry* followed 90 pregnant women, and found that compared with lower SSRI doses, higher SSRI doses were significantly associated with earlier birth. Yet a second study in the August 2007 issue of *Psychosomatic Medicine* found that women with higher anxiety were significantly more likely to have spontaneous preterm birth than less anxious women (see below for more specific information).

- A study published in October 2008 in the journal *Human Reproduction* found that "depression in pregnant women could help explain the growing problem of preterm delivery." A total of 791 women completed the screening and delivered a live baby. Overall, after accounting for other factors that might play a role, women with significant depressive symptoms were nearly twice as likely to deliver a baby preterm — or before 37 complete weeks' gestation — than those without significant depressive symptoms. The more severe the women's depression, the greater their risk of delivering preterm, the study found. The authors speculate that depression during pregnancy might interfere with placental hormones that help maintain a healthy pregnancy and ensure that labor doesn't start too early (see below for more specific information).
- A study published in March 2009 in the *American Journal of Psychiatry* found that SSRI use in late pregnancy correlated with an elevated risk of gestational hypertension and preeclampsia. Researchers interviewed 5912 mothers of nonmalformed live babies within 6 months of delivery regarding their use of prescribed and over-the-counter medications (see below for more specific information).
- Another study in March 2009 in the *American Journal of Psychiatry* prospectively followed 238 pregnant women and found that both untreated depression and continuous SSRI treatment in pregnant women are associated with increased rates of preterm birth (see below for more specific information).
- In a study published in October 2009 in the *Archives of Pediatric Adolescent Medicine*, Danish investigators evaluated 57,000 pregnancies. They found that in utero SSRI exposure was associated with excess risk for preterm delivery and related complications, but not for lower birth weight or smaller head circumference (see below for more specific information).

After Delivery:

- Some researchers have studied children whose mothers took antidepressants. They have found no link to serious problems with language, behavior or intelligence.
- There has been no data reported on long term effects of antidepressants on the baby's well being. So far, there is no evidence of long term effects.

Choosing an Antidepressant

This decision is difficult because we don't know all the answers. No drug is entirely safe. A woman and her health care team must look at her case and carefully weigh:

- The risks and benefits of various drugs
- The risks and benefits of other types of treatment
- The risk of untreated depression for the woman and her baby

Choosing an antidepressant needs to be done on a case by case basis. Of note, the literature changes frequently in this area.

Important Points

- Make sure that you are being followed closely by both your psychiatrist and an Ob/Gyn
- Take prenatal vitamins and folic acid

- Have your thyroid, blood count and other lab work checked to rule out medical reasons for low mood or energy
- It is a good idea to deliver your baby in a hospital versus at home by a midwife, as they can adequately monitor and assess any possible delivery complications
- Stress reduction techniques and individual therapy (at least weekly) are both encouraged
- It is always a good idea to be on the lowest number of medications possible, and on the lowest dose necessary
- With any medication during pregnancy, start low and go slow

The Latest Research

There are a variety of studies which show a small risk of increased side effects or birth defects in *newborns who have been exposed to SSRIs during pregnancy or delivery*. Below are the most recent studies.

In Utero SSRI Exposure is Associated with Excess Risk for Preterm Delivery:

In a prospective population-based study, Danish investigators evaluated delivery outcomes of 57,000 pregnancies from August 1989 through November 2006. Women were categorized into three cohorts: those who received at least one SSRI during pregnancy (329); those with histories of psychiatric illness who did not receive SSRIs during pregnancy (4902); and those who reported no histories of psychiatric illness (51,770).

Adjusted analysis showed that risk for preterm delivery in women treated with SSRIs was twice that of untreated women with histories of psychiatric illness and those with no histories of psychiatric illness. Infants exposed to SSRIs in utero were more likely to have 5-minute APGAR scores <7 compared with infants of women without psychiatric histories (odds ratio, 4.4) as well as infants of those with untreated psychiatric illnesses (OR, 6.6). Risk for admission to the neonatal intensive care unit (NICU) was more than twofold higher in SSRI-exposed infants than in unexposed infants. Mean head circumference and birth weight were similar among groups after adjusting for gestational age and other potential confounders.

Although these results point to associations between in utero SSRI exposure and certain adverse perinatal outcomes, events such as low APGAR scores and NICU admissions have many causes; thus, SSRI exposure might not be the crux of this issue. Indeed, pregnant women who received SSRIs were more likely to smoke; moreover, NICU-admitted infants had various diagnoses (e.g., jitteriness, seizures, respiratory problems, infections, jaundice, hypoglycemia), not all of which can be attributed to SSRI withdrawal. Thus, these findings should not be considered definitive, and decisions to treat depressed pregnant patients with SSRIs should be made based on benefits as well as risks.

Archives of Pediatric Adolescent Medicine. 2009 Oct; 163: 949.

Zoloft and Celexa are Linked to Septal Heart Defects in Offspring:

Women who use the antidepressants Zoloft or Celexa early in pregnancy face increased risk for septal heart defects in their offspring, *BMJ* reports online. Researchers examined data on more than 490,000 infants born in Denmark between 1996 and 2003. They found that women who filled prescriptions for sertraline and citalopram (but not other SSRIs) during

their first trimester were significantly more likely to have children with septal heart defects (but not other malformations) than those who didn't use SSRIs (odds ratios: 3.2 and 2.5, respectively).

SSRIs were not associated with major malformations overall but were associated with septal heart defects (odds ratio 1.99, 95% confidence interval 1.13 to 3.53). For individual SSRIs, the odds ratio for septal heart defects was 3.25 (1.21 to 8.75) for Zoloft, 2.52 (1.04 to 6.10) for Celexa, and 1.34 (0.33 to 5.41) for Prozac. Using more than one type of SSRI was associated with septal heart defects (4.70, 1.74 to 12.7). The absolute increase in the prevalence of malformations was low—for example, the prevalence of septal heart defects was 0.5% (2315/493 113) among unexposed children, 0.9% (12/1370) among children whose mothers were prescribed any SSRI, and 2.1% (4/193) among children whose mothers were prescribed more than one type of SSRI.

The authors and an editorialist (both with ties to SSRI manufacturers) note that the absolute risks for septal heart defects were low: 0.9% in children exposed to at least one SSRI and 2.1% in those exposed to more than one. The editorialist concludes: "Clinicians and patients need to balance the small risks associated with SSRIs against those associated with undertreatment or no treatment."

The British Medical Journal. 2009 Sep 23; 339: b3569.

Untreated Depression and Continuous SSRI Use are Both Associated with Increased Rates of Preterm Birth:

These researchers prospectively observed 238 pregnant women; 131 had neither depression nor SSRI treatment, 14 had continuous major depression but no SSRI treatment, 48 had continuous SSRI treatment, 22 had "partial depression" (i.e., ≥ 1 depression-free trimesters) and no SSRIs, and 23 had partial SSRI treatment (≥ 1 SSRI-free trimesters). Untreated depressed women sustained markedly significantly worse depressive symptoms than other women. Rates of preterm birth (i.e., birth <37 weeks of gestation) exceeded 20% in the untreated depression and continuous SSRI groups, compared with 4% to 9% in the other three groups. Most preterm births occurred between weeks 34 and 37. A greater percentage of infants in the continuous SSRI group had 5-minute Apgar scores of 7 or less than in the nondepressed, SSRI-unexposed group. However, the groups did not differ in risk for admission to a neonatal intensive care unit; incidence of minor birth anomalies; or mean birth weight for gestational age, length, or head circumference.

American Journal of Psychiatry. 2009 Mar; [e-pub ahead of print].

SSRI Use in Late Pregnancy is Linked to Gestational Hypertension and Preeclampsia:

Researchers interviewed 5912 mothers of nonmalformed live babies within 6 months of delivery regarding their use of prescribed and over-the-counter preparations starting 2 months before pregnancy and diagnoses of hypertension, preeclampsia, or toxemia during pregnancy. Hypertension was considered gestational if first diagnosed after 20 weeks of pregnancy.

Among 5731 women without pregestational hypertension, 9.4% developed gestational hypertension and 2.7% developed preeclampsia. The rate of preeclampsia was 15.2% among 92 women who continued SSRI treatment after the first trimester, 3.7% among 107 women who discontinued SSRIs, and 2.4% among 5532 women not receiving SSRIs in this time period. Among 68 women taking non-SSRI antidepressants (including 16 on serotonin-

norepinephrine reuptake inhibitors), 19.1% developed gestational hypertension and 5.9% developed preeclampsia. After adjustment for many potential confounders (e.g., demographics, diabetes, smoking, prepregnancy body-mass index, use of non-SSRI antidepressants, and gravidity), the relative risks for gestational hypertension alone and for preeclampsia were, respectively, 1.30 and 1.37 in women who discontinued SSRI use before the second trimester and 1.41 and 4.86 in those who continued SSRI treatment.

American Journal of Psychiatry. 2009 Mar; 166(3):320-8.

Prozac and Paxil Have Been Linked With an Increased Risk of Heart Anomalies:

Women who took the antidepressant fluoxetine (Prozac) during the first three months of pregnancy gave birth to four times as many babies with heart problems as women who did not and the levels were three times higher in women taking paroxetine (Paxil). Although some of the conditions were serious, others were not severe and resolved themselves without the need for medical intervention, according to a three-country study in the November 2008 issue of the *British Journal of Clinical Pharmacology*. Researchers have advised women taking the drugs to continue unless they are advised to stop by their doctor or consultant. But they are being urged to give up smoking, as the study also found that more than ten cigarettes a day was associated with a five-fold increase in babies with major heart problems. The team has also suggested that women on fluoxetine should be given a fetal echocardiogram in their second trimester to diagnose possible heart anomalies. International researchers from Israel, Italy and Germany followed the pregnancies of 2,191 women - 410 who had taken paroxetine during pregnancy, 314 who had taken fluoxetine and 1,467 controls who hadn't taken either of the drugs. Other antidepressants were not studied. "After we excluded genetic and cytogenic anomalies, we found a higher rate of major heart anomalies in the women who had been taking the antidepressants," says lead author Professor Asher Ornoy from the Israeli Teratology Information Service in Jerusalem, Israel. Women who smoked more than 10 cigarettes a day also had more babies with heart anomalies. Women taking paroxetine or smoking less than ten cigarettes a day also faced elevated risks, but not to the same extent.

British Journal of Clinical Pharmacology. 2008 Nov; 66.5:695-705.

Depression During Pregnancy Can Double the Risk of Preterm Delivery:

The study looked at 791 pregnant Kaiser Permanente members in San Francisco city and county from October 1996 through October 1998. Researchers interviewed the women around their 10th week of pregnancy and found that 41 percent of the women reported significant or severe depressive symptoms. The women with less severe depressive symptoms had a 60 percent higher risk of preterm delivery -- defined as delivery at less than 37 completed weeks of gestation -- compared with women without significant depressive symptoms, and the women with severe depressive symptoms had more than twice the risk. "Preterm delivery is the leading cause of infant mortality, and yet we don't know what causes it. What we do know is that a healthy pregnancy requires a healthy placenta, and that placental function is influenced by hormones, which are in turn influenced by the brain," said lead author Dr. De-Kun Li, a reproductive and perinatal epidemiologist at Kaiser Permanente's Division of Research in Oakland. The authors theorized that "depression during pregnancy might interfere with placental hormones that help maintain a healthy pregnancy and ensure that labor doesn't start too early."

Human Reproduction. 2008 Oct; on-line journal.

No Association Between 1st Trimester SSRI Use and Major Congenital Malformations:

Using large medical, demographic, and public drug insurance registries in Quebec, researchers focused on women with psychiatric diagnoses (mostly mood or anxiety disorders) and antidepressant use for at least 1 month in the year before pregnancy. Researchers compared first-trimester antidepressant exposure and duration in 2140 healthy infants and 189 infants with any major congenital malformation in the year after birth. Antidepressants commonly used were paroxetine (42%), sertraline (15%), and venlafaxine (13%). The risk for congenital malformation (8%, vs. the usual population rate of 3%) was unrelated to first-trimester antidepressant use, its duration, or therapeutic class.

British Journal of Psychiatry. 2008 May; 192:344.

Duration of Exposure to SSRI's Rather Than Timing of Dose Increased Risk for Side Effects:

Other researchers linked maternal and neonatal British Columbian health records to identify recipients of SSRI's (commonly, paroxetine, 39%; fluoxetine, 25%; or sertraline, 23%) during pregnancy and compared effects of early exposure only (first and/or second trimesters; n=1575) and of continued exposure (from first or second trimester through delivery; n=1925). Longer duration of exposure to SSRI's rather than timing increased the risks for lower birth weight, gestational age, weight for age, and for respiratory distress.

British Journal of Psychiatry. 2008 May; 192:338.

The Risks of Earlier Birth with SSRI Use:

Suri et al. prospectively followed 90 pregnant women (mean age, 33.8). Forty-nine had major depression and received antidepressant medication, predominantly SSRIs (44 received medication in the first trimester, and all received medication in the second and third trimesters); 22 had major depression but minimal or no antidepressant treatment during pregnancy; and 19 were not depressed. The groups had similar mean numbers of previous births, miscarriages, and abortions. Apgar scores and birth weights did not differ significantly among the groups. However, women receiving antidepressants gave birth approximately 1 gestational week earlier than the others (38.5 weeks vs. 39.4 weeks in depressed controls and 39.7 weeks in healthy controls), had higher rates of preterm birth (14.3% vs. 0% and 5.3%), and had infants who were more likely to require admission to special-care nurseries (21% vs. 9% and 0%; these were *not* neonatal ICUs). Compared with lower SSRI doses, higher SSRI doses were significantly associated with earlier birth.

American Journal of Psychiatry. 2007 Aug; 164:1206.

The Risks of Preterm Birth with Higher Anxiety:

Orr et al. prospectively examined rates of spontaneous preterm births (<37 weeks' gestation) among 1820 medication-free pregnant women reporting significant anxiety at a health clinic. The women self-rated their anxiety on a 6-point scale (median rating, 2). Results were adjusted for a host of potentially confounding factors, such as bleeding before the third trimester, drug use, employment, prior pregnancy outcomes, smoking, body-mass index, race, age, and education. Compared to women with self-rated anxiety of 3 or less, women with the two highest anxiety scores were significantly more likely to have spontaneous preterm delivery (adjusted odds ratios: score of 5, 1.70; score of 6, 2.73).

Psychosomatic Medicine. 2007 Jul/Aug; 69:566.

Low Risk of Birth Defects:

Two large studies in the June 28, 2007 issue of *The New England Journal of Medicine* indicate a few very small increases in risks for particular defects. Earlier studies have reported that use of SSRIs —especially paroxetine — during early pregnancy increases the incidence of cardiovascular birth defects markedly. These two large case-control studies challenge these findings.

Investigators from the U.S. and Canada identified 9622 infants with major birth defects, and 4092 controls without such defects, born between 1997 and 2002. No significant association was found between SSRI use in early pregnancy and congenital heart defects. However, there were small absolute increases in risks for anencephaly, craniosynostosis, and omphalocele with SSRI use, and all these risks — as well as the risk for ventricular outflow tract lesions — were increased most with paroxetine.

In a second study, funded in part by the manufacturer of paroxetine, 9849 infants with birth defects were compared with 5860 control infants born in five centers in the U.S. and Canada between 1993 and 2005. Use of SSRIs in early pregnancy was not associated with heart defects in general, but there was an increased risk for right ventricular outflow tract lesions with paroxetine and an increased risk for septal defects with sertraline. No evidence of increased risk was found for any other birth defects with paroxetine.

An accompanying editorial by Dr Michael F. Greene highlights the difficulties of interpreting the new findings. However, together with previous data, the results "[make] it clear that neither SSRIs as a group nor individual SSRIs are major teratogens on the order of thalidomide or isotretinoin," Dr. Greene writes. He concludes, "[A]ny increased risks of these malformations in association with the use of SSRIs are likely to be small in terms of absolute risks."

The absolute risk for right ventricular outflow tract lesions in the infant of a mother who uses paroxetine during pregnancy is likely less than 1%, and the risk for any congenital heart defect is unlikely to exceed 2%. These small risks must be weighed against the risks associated with discontinuing an SSRI during pregnancy.

New England Journal of Medicine. 2007 Jun 28; 2675-2683, 2684-2692, 2732-2733.

Neonatal Abstinence Syndrome (NAS):

About one-third of infants in a recent study who were exposed to antidepressants while in the womb experienced symptoms of neonatal abstinence syndrome, which include tremors, disturbed sleep, gastrointestinal problems, and hypertonicity.

Most of the symptoms occurred within the first 48 hours after birth, but the long-term effects of neonatal abstinence syndrome, if any, are unknown, according to a report in the February 2006 Archives of Pediatric and Adolescent Medicine.

Researchers from the Schneider Children's Medical Center of Israel studied 120 infants born at the Rabin Medical Center in Israel between January 2002 and August 2004.

Half of the infants in the sample were born to mothers who took one of the selective serotonin reuptake inhibitors (SSRIs) either through the entire pregnancy or during the last trimester.

Of the mothers who took SSRIs, 37 took paroxetine, 12 took fluoxetine, eight took citalopram, two took venlafaxine, and one took sertraline. The remaining 60 infants were born to mothers who did not take an SSRI during pregnancy.

Researchers assessed the infants' health with blood tests and by monitoring cardiorespiratory functioning and temperature. In addition, they used the Finnegan Scale, which measures symptoms of neonatal abstinence syndrome (NAS).

Of the 60 infants exposed to SSRIs in utero, 30 percent (18) exhibited symptoms of NAS. None of the infants in the control group exhibited symptoms of NAS.

When researchers measured severity of symptoms among the 18 NAS infants, they found that eight had severe symptoms and 10 had mild symptoms. Six of the eight infants with severe symptoms had been exposed to Paxil (paroxetine) in utero.

In addition, three of the infants exposed to SSRIs for the complete pregnancy had major congenital anomalies, including ventricular septal defect, hydronephrosis, and cleft palate. One of the newborns in the control group had hydronephrosis.

Gil Klinger, M.D., one of the study's investigators, told *Psychiatric News* that most of the mild symptoms in newborns subsided within a few days. "Of the severely affected infants, two had seizures, which resolved without intervention." Klinger is a senior neonatologist at Schneider Children's Medical Center.

Though none of the short-term symptoms were life-threatening, he said, "the long-term effects of SSRIs on newborns are unknown."

Klinger acknowledged that "depression also entails a risk to a pregnant woman and her fetus and should also be controlled—we are not recommending discontinuation of medications during pregnancy; however, sometimes SSRIs are given for very mild indications, and in these circumstances the risk-benefit ratio may not be in favor of giving antidepressants."

Archives of Pediatric Adolescent Medicine. 2006; 160:173-176.

Persistent Pulmonary Hypertension of the Newborn (PPHN):

In 2006, Chambers and colleagues published an article in the *New England Journal of Medicine* linking SSRI use in late pregnancy (after 20 weeks) to an increased risk of PPHN. Based on these findings, the "Usage in Pregnancy" section on the labels for SSRI antidepressants was updated to include the following warning: "Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN)."

Since that time, other reports have been published which have examined the association between SSRI's and PPHN. Thus far, there have been a total of seven studies evaluating the association between PPHN and SSRI exposure. Three of these studies showed no association between SSRI exposure and PPHN. Four other studies showed an increased risk of PPHN in SSRI-exposed infants, with an estimated odds ratio ranging from 2.4 to 6.1.

(This means an absolute risk of 2-12 per 1000 vs. a background risk of 1-2 per 1000 in the general population). Based on these studies, the FDA has issued a revision warning:

"FDA has reviewed the additional new study results and has concluded that, given the conflicting results from different studies, it is premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN. FDA will update the SSRI drug labels to reflect the new data and the conflicting results."

In a thorough review of the subject from Occhigrosso and colleagues, the authors point out many of the limitations of the studies to date:

- Case-control studies (such as the positive studies from Chambers and Kallen) tend to overestimate risk

- Prospective studies are smaller and are usually underpowered to detect an association between exposure and a relatively uncommon events such as PPHN

The authors also point out that many factors associated with depression (rather than exposure to antidepressant) may account for the association, and there has been no systematic examination of the role these factors may play.

- Obesity and smoking, established risk factors for PPHN, are more common in depressed women.
- Risk of PPHN is increased fourfold in babies born at 34–36 weeks' gestation. Untreated depression and treatment with SSRIs during pregnancy have been linked to reduced length of gestation.
- Cesarean section, a known risk factor for PPHN, is more common among women with depression.

Taking all of these studies into consideration, the data supporting an association between SSRI exposure and PPHN is weak. Cumulatively there were a total of 50 infants with PPHN among an estimated 25,000 infants exposed to SSRIs during pregnancy. It is important to note that even if we assume a modest increase in the risk for PPHN in this scenario, the absolute risk is extremely small and it may not justify avoiding or discontinuing antidepressants proximate to delivery. In women with histories of recurrent or severe depression, avoiding antidepressants increases the risk of antenatal and postpartum depression and thus may not be the safest option.

Herbal Products

Herbal products, such as St. John's Wort, vary in strength and quality from product to product. We need more research to help us know whether St. John's Wort is useful and safe for treating depression in pregnant women.

Resources

- The Organization of Teratology Information Services (OTIS), (866) 626-6847. Provides fact sheets on pregnancy and specific antidepressants, including Prozac and Zoloft.
http://otispregnancy.org/otis_fact_sheets.asp
- LACT MED: A website that gives the latest research about medications and breast feeding.
<http://www.toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>
- www.womensmentalhealth.org - Massachusetts General Hospital
- www.emorywomensprogram.org - Emory
- www.motherisk.org
- Parts of this handout were adapted from the following websites:
www.marchofdimes.com/pnhec/188_15663.asp
<http://pn.psychiatryonline.org/cgi/content/full/41/7/25>