

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.

Antidepressants During Pregnancy

The most studied antidepressants during pregnancy are the Selective Serotonin Reuptake Inhibitors (SSRIs). This group of drugs includes:

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

- Lexapro (escitalopram)
- Paxil (paroxetine) – not recommended in pregnancy (see below)

Like many drugs, antidepressants can have side effects. SSRIs usually have fewer side effects than older antidepressants and have been more studied in pregnancy. 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 and 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:

- In 2013, Kjaersgaard and colleagues did a large population-based study of 1,005,319 pregnancies using data obtained from four medical registries in Denmark. They found that antidepressant exposure during pregnancy is associated with a very small increased risk of miscarriage (RR 1.14) when compared to women who have no diagnosis of depression and are on no antidepressants. However, when they then compared them to women with a history of depression, no increased risk of miscarriage was found. Thus, this study showed that the risk of miscarriage is likely due to factors related to the maternal depression itself rather than to antidepressant use – as women with depression had the same risk of miscarriage whether they were taking an antidepressant or not. The lack of association between antidepressant use and miscarriage is consistent with a rigorous meta-analysis done by Ross and colleagues (2013) and with another large meta-analysis (of 1,279,840 pregnancies) done by Andersen and colleagues (Sept 2014) who did not find a significant association either.
- 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).
- 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).
- 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 risk for unexposed children was 0.5%. 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.
- Another study came out on April 19, 2013 in the *British Medical Journal* based on data collected in Sweden looking at the link between parental depression, maternal antidepressant use and autism. Dheeraj Rai et al. looked at 4,429 cases of autism spectrum disorder and 43,277 age and sex matched controls. In utero exposure to both SSRIs and non-selective monoamine reuptake inhibitors (tricyclic antidepressants) was associated with an increased risk of autism spectrum disorders, particularly without intellectual disability. Whether this association is causal or reflects the risk of autism with severe depression during pregnancy requires further research. However, even if we were to assume causality, antidepressant use during pregnancy is unlikely to have contributed significantly towards the dramatic increase in observed prevalence of autism spectrum disorders as it only explained *less than 1% of cases* in this sample.
- Two other studies came out confirming the lack of association between SSRIs and autism: (1) In a Nov. 15th, 2013 study, Sorensen et al. looked at 668,468 live births in Denmark 1996-2006. After controlling for important confounding factors, there was no significant association between prenatal exposure to antidepressant medication and autism spectrum disorders in the offspring. (2) Yet another study came out on Dec. 19th, 2013 in the *New England Journal of Medicine* where Hviid et al. looked at 626,875 live births in Denmark 1996-2005, with follow-up through 2009. They found that SSRI use during pregnancy was not associated with a significantly increased risk of autism spectrum disorders (fully adjusted rate ratio, 1.20; 95% confidence interval [CI], 0.90 to 1.61). Among women who received SSRIs before pregnancy but not during pregnancy, the corresponding fully adjusted rate ratio was 1.46 (95% CI, 1.17 to 1.81).
- Yet another study about SSRIs and autism came out on April 14, 2014 in *Pediatrics*. Rebecca Harrington et al. evaluated a total of 966 mother-child pairs: 492 with autism spectrum disorder (ASD), 154 with developmental delay (DD) and 320 with typical development (TD). Overall, prevalence of prenatal SSRI exposure was lowest in TD children (3.4%) but did not differ significantly from ASD (5.9%) or DD (5.2%)

children. Among boys, prenatal SSRI exposure was nearly 3 times as likely in children with ASD relative to TD, and the strongest association occurred with first trimester exposure. However, the evidence does not prove that infants exposed to SSRIs that develop autism do so because of that prenatal exposure. Dr. Andrew W. Zimmerman of Massachusetts General Hospital, one of the lead authors of the study, says it is quite possible that the elevated likelihood of autism in children of mothers who take SSRIs could be masking for an association between maternal depression and autism. Association does not mean causation. It is also important to contextualize how many cases of autism could be accounted for if a causal link to SSRI proved true. Based on the cases in this study, SSRI exposure would account for *less than a percentage fraction* of kids with autism.

- Another study about the link between prenatal antidepressant exposure and autism came out in December 2015 by Boukhris et al. Data from a total of 145,456 infants was analyzed. 1054 children (0.7%) were diagnosed with autism spectrum disorder (ASD). The use of any antidepressant during the second and third trimester was associated with an increased risk of ASD (31 exposed infants; adjusted hazard ratio, 1.87). Use of SSRIs during the second and/or third trimester was associated with an increased risk of ASD (22 exposed infants; adjusted hazard ratio, 2.17). However, this study has been found to be flawed. Roy Perlis, a psychiatric geneticist at Harvard University, says that “the **critical flaw** in the new research is that it doesn’t fully account for the fact that women suffering from psychiatric illnesses already have a greater risk of having children with ASD.” There’s no way to tell whether the children were at higher risk because their mothers were taking more drugs or because the women had more severe depression. **Several papers, including two from Perlis’s group, have looked at large numbers of women and children and found no increased risk for ASD after adjusting for the severity of maternal depression, he says. “The risk travels with the disease, not the treatment,” he says.** Even if antidepressants did raise the risk, they would do so very modestly (from 1% to 1.87% per this study).
- According to a study published online in the British Journal Of Clinical Pharmacology in April 2012, taking antidepressants during pregnancy may raise the risk of high blood pressure in expectant mothers. Researchers examined data on 1,216 women with a diagnosis of pregnancy-induced hypertension with no history of hypertension before pregnancy. Among cases, 45 (3.7%) had used antidepressants during pregnancy compared with 300 (2.5%) in the control group. The use of antidepressants during pregnancy was significantly associated with increased risk of pregnancy-induced hypertension (OR 1.53). In stratified analyses, the use of SSRIs (OR 1.60), and more specifically, paroxetine (OR 1.81) were associated with risk of pregnancy-induced hypertension. It’s important to note that the absolute risk from taking these drugs remained low. Taking antidepressants of any kind raised an expectant mother’s absolute risk of hypertension from 2 percent to roughly 3.1 percent. Taking SSRI’s raised the absolute risk from 2 percent to 3.2 percent, and using Paxil specifically raised it from 2 percent to 3.6 percent.
- In June 2012, Jimenez-Solem and his group published a study in the *British Medical Journal* studying 848,786 pregnancies. They compared an exposed cohort (women taking SSRIs during pregnancy) with a control cohort comprised of women who had discontinued SSRI treatment during pregnancy. They found no increased risk of congenital heart malformations in women who took SSRIs during pregnancy. There was no pattern noted with regard to type of SSRI or dosage.
- There were three other studies in 2012 which found no significant increase in the risk of either major malformations or cardiac malformations after first trimester exposure to an antidepressant drug. Furthermore, the relative risks (RRs) and odds ratios (ORs) for these neonatal outcomes are closely similar across these types of studies,

indicating that the outcomes are relatively unaffected by the strengths and weaknesses associated with different types of observational study design. The three studies were done by Byatt et al., Koren et al., and Einarson et al. Einarson's study was a large meta-analysis of 23 observational studies; the mean number of exposed cases was 16,824 in the cohort studies and 1818 in the case-control studies.

- Another reassuring study was published in the New England Journal of Medicine on June 14, 2014 by Huybrechts et al. No increased risk was found between first-trimester use of antidepressants and cardiac abnormalities. Researchers analyzed Medicaid data on roughly 950,000 females (aged 12-55) and their live-born infants. During the first trimester, 6.8% used an antidepressant, more than two thirds of whom used SSRIs. No association was found between overall antidepressant use and cardiac malformations. In addition, there was no association between Paxil and right ventricular outflow tract obstruction or between Zoloft and ventricular septal defects. This very large study, which adjusted for important confounders (such as depression severity, sociodemographics and multiple gestation), is reassuring in suggesting a lack of association between first-trimester antidepressant exposure and risk for cardiac defects.
- A large study published April 17, 2015 by Furu and colleagues was able to analyze malformation risk in children exposed to SSRIs or Venlafaxine in utero using data from the health registries of five Nordic countries (a total of 2.3 million live births). Data was analyzed from 36,772 infants exposed to any SSRI in early pregnancy and compared to unexposed infants and sibling controls. This study found no substantial increase in the overall prevalence of birth defects among infants exposed to SSRIs or Venlafaxine in utero.
- A study published July 8, 2015 by Reefhuis and colleagues looked at 660 cases of birth defects in babies of mothers who had used SSRIs in the month before or first 3 months of pregnancy. They found: (1) Zoloft was not associated with any birth defects. (2) Neither Celexa nor Lexapro was associated with any birth defects, except for a "marginal link" between Celexa and neural tube defects. (3) Prozac was associated with cardiac (ventricular) defects and craniosynostosis (premature closure of joints of the baby's skull). (4) Paxil was associated with anencephaly, atrial septal defects, right ventricular outflow tract obstruction cardiac defects, gastroschisis, and omphalocele. The authors note that if the associations observed are causal, the absolute risks are small. For example, for babies exposed to Paxil, the absolute risk for anencephaly would increase from 2 to 7 per 10,000. Also, any risk cannot be fully separated from the underlying condition.
- In a Dec 2016 study, Cantarutti and colleagues looked at 384,673 births from 2005 to 2010. Maternal use of antidepressants before and during pregnancy was investigated. Women who received an antidepressant drug during pregnancy were more likely to deliver prematurely and have an infant with low birth weight. However, these risks were statistically significant only when compared with women who did not receive antidepressants during or before pregnancy. The risks were not significant when compared with women who received an antidepressant during the 9 months before pregnancy but not during pregnancy. **These findings suggest that depression in itself, rather than antidepressant medication, might be implicated in the causal pathway of preterm birth and low birth weight.**
- In a study published Jan 2017, Bérard and colleagues included 18,487 pregnant women from the Quebec Pregnancy Cohort. All pregnancies with a diagnosis of depression or anxiety and exposed to antidepressants in the 12 months before and during pregnancy were included. Of the women studied, 3,640 – about 20 per cent – took antidepressants in the first three months. They found that SSRI use increased the risk of some organ-specific malformations in a cohort of pregnant

women with depression. When looking at the specific types of antidepressants used during the first trimester, only citalopram was statistically significantly increasing the risk of major congenital malformation overall (aOR 1.36; 88 exposed cases), although there was a trend towards increased risk for the most frequently used antidepressants. Further analyses on organ system defects showed that antidepressants with serotonin reuptake inhibition effect (SSRI, SNRI, amitriptyline (the most used TCA)) were increasing the risk of certain organ-specific defects: paroxetine increased the risk of cardiac defects (aOR 1.45), and ventricular/atrial septal defects (aOR 1.39); citalopram increased the risk of musculoskeletal defects (aOR 1.92), and craniosynostosis (aOR 3.95); TCA was associated with eye, ear, face and neck defects (aOR 2.45), and digestive defects (aOR 2.55); and venlafaxine was associated with respiratory defects (aOR 2.17). Limitations of this study include missing information on potentially important confounders such as smoking, folic acid intake and alcohol intake.

- In April 2017, two important studies came out in JAMA: (1) Brown and colleagues studied 35,906 singleton births and found no statistically significant association between exposure to serotonergic antidepressants and autism spectrum disorders. Although a causal relationship cannot be ruled out, the previously observed association may be explained by other factors. (2) Sujan and colleagues studied 1.58 million offspring in Sweden. After accounting for confounding factors, first-trimester antidepressant exposure, compared with no exposure, was associated with a small increased risk of preterm birth but no increased risk of small for gestational age, autism spectrum disorder (ASD), or attention-deficit/hyperactivity disorder (ADHD).
- In May 2017, a study in BMJ by Rai and colleagues found that autism rates were highest among 3,300 Swedish children exposed to antidepressants during pregnancy (4%), compared with 12,000 children of mothers with a psychiatric disorder but no prenatal antidepressant exposure (3%), and 240,000 with no maternal psychiatric disorder or antidepressant exposure in utero (2%). Paternal antidepressant use didn't significantly change the results. The authors caution that there still could be some unmeasured genetic confounding since the results were only significant for autism without intellectual disability, which may be a more heritable condition. However, even if the association between antidepressant use and autism is causal, only 2% of cases would be prevented if no women with psychiatric disorders used antidepressants during pregnancy, which must be carefully weighed against the substantial health consequences associated with untreated depression.
- According to a case-control study published in BMJ Open on October 2019, Dandjinou and colleagues found that the use of some antidepressants was associated with a small increased risk of gestational diabetes (GDM). Among 20,905 cases and 209,050 matched controls, 9,741 (4.2%) women were exposed to antidepressants (ADs). When adjusting for potential confounders, AD use was associated with an increased risk of GDM (aOR 1.19, 95% CI 1.08 to 1.30); venlafaxine (aOR 1.27, 95% CI 1.09 to 1.49) and amitriptyline (aOR 1.52, 95% CI 1.25 to 1.84) were also associated with an increased risk of GDM. Moreover, the risk of GDM was increased with longer duration of AD use, specifically for serotonin norepinephrine reuptake inhibitors, tricyclic ADs and combined use of two AD classes. No statistically significant association was observed for selective serotonin reuptake inhibitors (SSRIs). The findings suggest that ADs—and specifically venlafaxine and amitriptyline—were associated with an increased risk of GDM.

During Delivery:

- **Neonatal Abstinence Syndrome (NAS):** Some babies born to mothers who are taking SSRIs 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 SSRIs. 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. Many studies have been done about this, but most conclude that these symptoms are self-limiting and minimal if they occur at all. For example, a study from 2008 (by Jordan et al.) found that in comparing 2 groups of women (those taking and not taking an SSRI) NAS was seen in 28% of SSRI exposed infants – *but* these infants were not more likely than unexposed infants to be born prematurely, have fetal growth restriction, be admitted to a higher nursery, experience respiratory abnormalities, or have prolonged hospitalization (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 SSRIs and PPHN. Shortly after, seven more studies came out 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 (OR) 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 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.” 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. A more recent study was a meta-analysis published in *BMJ* by Sophie Grigoriadis et al. in 2014. She reported an even lower risk of PPHN of 1.32-4.73 per 1000 after exposure to SSRIs in late pregnancy (OR about 1-2). Another recent study by Huybrechts et al. published in *JAMA* in June 2015 echoes this low risk. This study looked at 3.7 million women enrolled in Medicaid. Adjusted odds ratios were 1.10 for SSRI use and 1.02 for non-SSRI use. There were other variables that were more strongly associated with PPHN: maternal diabetes (OR 2.93), obesity (OR 2.02), cesarean delivery (OR 3.20), and black race (OR 1.30). These findings are consistent with previous studies of risk factors for PPHN. Thus, the risk of PPHN associated with late pregnancy exposure to SSRIs—if present—is very small (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).
- 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).
- In a study published March 26th, 2014, Krista Huybrechts et al. looked at 41 studies on preterm birth rates in women taking antidepressants during pregnancy. Preterm birth was defined as less than 37 weeks. Pooled adjusted odds ratios were 1.53 for antidepressant use at any time and 1.96 for 3rd trimester use. There was no increased risk with 1st trimester exposure. In this study, controlling for the diagnosis of depression did not eliminate this effect. However, the possibility of confounding cannot be ruled out. For example, a past diagnosis of depression doesn't mean the control women were depressed during their pregnancy.
- Olof Stephansson and his group published a study in *JAMA (The Journal of the American Medical Association)* in January 2013 where they looked at 1.6 million births from 1996 to 2007. Using national registries in five Nordic countries, they identified women who filled a prescription for an SSRI from 3 months before they became pregnant through birth (1.8% of the mothers). They found that SSRI use during pregnancy is not associated with stillbirth or infant mortality.
- A study published on March 5, 2012 by Hanan El Marroun et al. in the *Archives of General Psychiatry* found that untreated maternal depression was associated with slower rates of fetal body and head growth. In contrast, pregnant mothers treated with SSRIs had fewer depressive symptoms and their fetuses had no delay in body growth. However, they did have delayed head growth and were at increased risk for preterm birth. These investigators studied 7,696 pregnant women, which included 570 women with depression who were not on medication and 99 women with depression who were being treated with SSRIs. The authors point out that untreated depression during pregnancy has also been linked to adverse pregnancy outcomes and neonatal complications.
- One study published in July 2012 by Hayes, et al. in the *American Journal of Obstetrics and Gynecology* looked at 2,490 women who used an antidepressant throughout pregnancy (SSRIs and non-SSRIs). Filling 1, 2, and ≥ 3 antidepressant prescriptions during the second trimester was associated with shortened gestational age by 1.7, 3.7 and 4.9 days, respectively. However, they mention that this is not thought to be clinically significant. Third-trimester SSRI use (but not non-SSRI use) was associated with infant convulsions; adjusted odds ratios were 1.4, 2.8 and 4.9

for filling 1, 2, and ≥ 3 prescriptions, respectively. However, this data contradicts 2 other papers (two case reports in 2006 by Pakalapati et al. and one case report in 2010 by Hoppenbrouwers et al.) of seizures in newborns linked to Effexor exposure (a non-SSRI).

- A meta-analysis by Lori Ross et al. published in *JAMA Psychiatry* in March 2013 analyzed 23 studies looking at risks of antidepressant exposure during pregnancy. There was no significant association between antidepressant exposure and spontaneous abortion. Antidepressant exposure was associated with the following: slightly shorter gestation, slightly lower birth weight and slightly lower Apgar scores. However, it is reassuring that the observed effects were small: about 3 days shorter gestational age, 75 g lower birth weight, and less than half a point on the 1- and 5-minute Apgar scores. Furthermore, these values typically fall within the normal range. The clinical significance of these findings is unclear. For example, the mean Apgar score of the exposed infants at 1 minute was 7.52 and at 5 minutes was 8.65. While these scores are lower than in the unexposed infants, Apgar scores of 7 or higher indicate that a neonate's condition is normal to excellent.
- Another study published in March 2013 in *The American Journal of Psychiatry* showed even more reassuring results – that neither SSRI exposure nor depression itself affects infant growth. In this study, Wisner et al. studied 3 groups of women: women with no SSRI exposure and no depression (N=97), women with SSRI exposure (N=46) and women with major depression without SSRI treatment (N=31). Both adjusted and unadjusted analyses revealed neither antenatal major depression nor SSRI exposure was significantly associated with any changes in infant weight, length, or head circumference relative to no exposure. *So why have other studies suggested that antidepressants may affect infant growth?* This study highlights the importance of carefully collecting and analyzing high quality data and making an effort to minimize the contribution of various confounding factors (e.g., other untreated maternal illness, other medications, and substance use).
- Deborah Cowley et al. published a paper in the *British Medical Journal* in August 2013 about a possible small association between depression and postpartum hemorrhage. Postpartum hemorrhage occurs in 3% of US deliveries at baseline – sometimes necessitating maternal blood transfusions. Because serotonin reuptake inhibitors (SRIs) can increase bleeding risk, investigators examined a Medicaid database to determine rates of prenatal SRI monotherapy and postpartum hemorrhage in 106,000 low-income women with live births and diagnoses of depressive and anxiety disorders. Among those with current prescriptions, hemorrhage rates were highest with serotonin-norepinephrine reuptake inhibitors (5.0%) and lowest with bupropion (3.6%); rate was 3.8% with selective SRIs. This is comparable to one additional case of postpartum hemorrhage per 80 to 100 current antidepressant users. This study has several limitations: the authors could not control for alcohol use, smoking, illicit drug use, or severity of psychiatric illness; could not confirm that women were taking their antidepressants; and could not determine which cases of postpartum hemorrhage were associated with worse outcomes.
- In one study published in *Neonatology* in 2014, Engelstad et al. looked at 3,695 women with depression who delivered between 2009-2011. They found that tobacco use, obesity, and diagnosis of depression, **but not SSRI use**, were independently associated with NICU admission.
- Heli Malm et al. published a study Aug 4, 2015 in the *American Journal of Psychiatry* which showed that women who take SSRIs during pregnancy appear to have fewer delivery complications. Offspring of mothers who received SSRI prescriptions during pregnancy had a lower risk for late preterm birth (OR=0.84), for very preterm birth

(OR=0.52), and for cesarean section (OR=0.70) compared with offspring of mothers unexposed to medications but with psychiatric disorders. However, offspring of SSRI-treated mothers and mothers unexposed to medications but with psychiatric disorders were both at increased risk of many adverse pregnancy outcomes, including cesarean section and need for monitoring in a neonatal care unit.

- In Oct 2016, Nörby and colleagues looked at neonatal morbidity in children exposed to SSRIs. Data from a total of 741,040 singletons, born between 2006 and 2012 were included in the analysis. The study observed that in the group of infants exposed to SSRIs, 13.7% were admitted to the NICU compared to 8.2% in the unexposed group (adjusted odds ratio: 1.5). When they looked at the children with late pregnancy exposure to SSRIs, the NICU admission was 16.5% compared to 10.8% with only early pregnancy only (adjusted odds ratio: 1.6). The SSRI-exposed children were admitted to the NICU for a variety of reasons. The most common reasons for admission were for respiratory disorders (5.7%), most commonly transient tachypnea (4.6%). Other common reasons for admission included hyperbilirubinemia (5.2%), hypoglycemia (4.0%), and feeding difficulties (1.3%). These were also the most common reasons for admission in non-exposed infants; however, for some, but not all causes, SSRI-exposed children were more likely than unexposed children to be admitted. PPHN was more common when comparing SSRI exposure versus nonexposure (OR: 1.3) and when comparing treatment during late versus early in pregnancy (OR: 2.1). This study has certain limitations. The biggest hurdle remains how to best assess the impact of untreated psychiatric illness in the mother on neonatal outcomes. Here, the researchers compared outcomes in infants with early versus late exposure to antidepressants. While we can safely assume that most, if not all, women taking SSRIs have a history of depression and/or anxiety, we cannot assume that the women who take antidepressants only early in the pregnancy are the same as those with late exposure. It is likely that the women with late exposure have more severe or recurrent illness; they elected to remain on medication during pregnancy or they experienced symptoms during the course of pregnancy that prompted them to resume treatment with medication. It is important to emphasize that even if we assume a modest increase in the risk of neonatal morbidity in infants exposed to SSRIs, the absolute risk is small and it may not justify avoiding or discontinuing antidepressants during pregnancy.
- A study published March 24, 2020 in *Pediatric Perinatal Epidemiology* by Palsten and colleagues looked at the risk of preeclampsia and postpartum hemorrhage in women taking antidepressants during pregnancy. Women with sustained antidepressant exposure during pregnancy, especially at higher doses, were at increased risk for preeclampsia and postpartum hemorrhage. However, we cannot rule out the possibility that underlying depression and anxiety may contribute to the increased risk. While the women in the control group have histories of depression and/or anxiety, it is likely that women who elect to discontinue medication may have milder illness than women who decide to maintain treatment.

After Delivery:

- Some researchers have studied children whose mothers took antidepressants. They have found no link to serious problems with language, behavior or intelligence.
- In a study published in November 2012, Nulman and colleagues found no effect of antidepressant medication on children's intellectual or behavioral outcomes. Women on Effexor and SSRIs were studied. However, it did demonstrate that exposure to untreated maternal depression *in utero* and during early childhood – not antidepressants – is associated with worse cognitive and behavioral outcomes.

- In April 2014, Skurtveit and colleagues examined the association between maternal SSRI use and language competence in their children at age 3. Compared with children whose mothers took no SSRI, relative risk (RR) of having fairly complete sentences were 1.21 and 2.28 for short- and long-term SSRI use, respectively. The adjusted RR of language delay were 0.86 and 2.30. However, symptoms of anxiety and depression in pregnancy were also independently related to language delay, adjusted RR 1.25 and 1.83 for short- and long-term symptoms, respectively. The authors point out that very few children could be classified as having clinically impaired language even after long-term prenatal exposure to SSRI. Furthermore, maternal depression was independently associated with language delay. The authors also note that none of these findings should be used as an argument not to treat pregnant women for depression when such treatment is needed.
- Two studies published in April 2015 illustrate how there may be risks to both untreated depression and medication during pregnancy. In one study by Nemoda et al., they found that untreated maternal depression altered children's DNA methylation patterns of genes affecting immune function, inflammatory processes and stress reactivity. In another study by Brandlistuen et al., they found that prenatal exposure to antidepressants increased anxiety in 3-year-olds.
- In a study by Brown and colleagues published Oct 2016, children up to 14 years of age were studied, looking at any long-term consequences of SSRI use during pregnancy. The sample included 845,345 pregnant women and their singleton offspring. They compared 3 groups of children: (1) children with SSRI exposure and a mother with depression, (2) children with no SSRI exposure and a mother with depression and (3) children with no SSRI exposure and a mother without depression. The researchers observed that the offspring of mothers who purchased SSRIs at least twice during pregnancy had a 1.37-fold increase in risk for speech/language disorders compared to the offspring in the depressed but unmedicated group. Compared to both unexposed groups, there was a 1.63-fold increase in risk of speech/language disorders in the SSRI-exposed offspring. There were no significant differences in risk for any other disorders in the SSRI-exposed group and the unmedicated group. **Based on these findings, it appears that if the mother suffers from depression during pregnancy, the risk of having a child with a speech/language disorder is increased. The risk is elevated whether or not you take an antidepressant. One way to look at this result is to say that antidepressants confer some degree of risk, but also that the underlying psychiatric illness (or some other factors associated with the illness) contributes to this risk.** Even if we assume that prenatal SSRI exposure increases risk for speech/language disorders, the increase in risk demonstrated here — 1.37-fold — is very small. Furthermore, there was no observed association between SSRI exposure and risk for scholastic or motor disorder.
- In a Nov 2016 study, Handal and colleagues looked at motor development in children exposed to SSRIs. Motor development was assessed by maternal reports of fine and gross motor development at child age 3 years. 381 women reported use of SSRIs during pregnancy, and of these 159 reported prolonged use. Prolonged SSRI exposure was associated with a delay in fine motor development, odds ratio 1.42 compared with no SSRI exposure, after adjusting for symptoms of anxiety and depression before and during pregnancy. Prolonged prenatal exposure to SSRIs was weakly associated with a delayed motor development at age 3 years, but not to the extent that the delay was of clinical importance.
- A study published July 12, 2017 in JAMA by Viktorin and colleagues found there was no association between intellectual disability and prenatal antidepressant exposure. The study included 179,007 children. The mean age at the end of follow-up was 7.9 years; 51.5% of the children were male and 48.5% female. The cohort included 3,982 children (2.2%) born to mothers with at least 2 dispensations of

antidepressant medication during pregnancy. This study suggests that the association seen in unadjusted analyses may be attributable to factors other than antidepressant exposure, such as parental age and maternal psychiatric illness.

- A study published September 2019 in the American Journal Psychiatry by Zou and colleagues found that exposure to postpartum depression leads to changes in children's brain development. Neuroimaging with MRI was performed in children at age 10. The researchers observed that higher maternal depressive symptoms were associated with smaller total gray matter volume in the children. However, when they adjusted for potential confounding variables, only exposure to maternal depressive symptoms at two months postpartum was associated with smaller total gray matter volumes in the offspring at age 10. Furthermore, smaller gray matter volumes were associated with attention problems in the children. No association was found between maternal depressive symptoms at any time point and volumes of the thalamus, amygdala, or hippocampus.

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 some detailed summaries of these 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 cytogenetic 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 event 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.

New England Journal of Medicine. 2006 Feb 9; 354(6):579-87.

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 or other herbal products are 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.
<https://www.mothersbaby.org/otis-fact-sheets-s13037>
- 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
- <http://www.womensmentalhealth.emory.edu> - 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>