Journal of Family and Reproductive Health Summer2007;1(1):1-5

New generation of antidepressants in pregnant women

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Received June 2007; Revised and accepted August 2007.

Abstract

Although pregnancy was once thought to protect against psychiatric disorders, gravid and non gravid women have similar risks for major depression, at 10% to 15%. Both depression and antidepressant treatment during pregnancy have been associated with risks. Few medications have been proved unequivocally safe during pregnancy. Although certain antidepressants have not been linked with an increased risk of birth defects or impaired development including bupropion, citalopram, escitalopram and venlafaxine, the latest studies aren't necessarily reassuring. As researchers continue to learn more about antidepressants, the risks and benefits of taking the drugs during pregnancy must be weighed carefully on a case-by-case basis. This review discusses about the use of new generation of antidepressants in pregnancy

Key words: *Antidepressants, Bupropion, Citalopram, Escitalopram, Pregnancy, Venlafaxine*

Introduction

The prevalence of clinical depression during pregnancy has been estimated to be 7-12% by a recent meta-analysis (1-3). Additionally, in over 3000 obstetric patients screened, 20% had high scores on Center for Epidemiological Studies Depression Scale (4). The decision of whether or not to keep a woman on medication during pregnancy is complex. Many possible adverse effects of untreated depression must be considered. There is a growing body of literature on an association of obstetrical complications with untreated maternal depression. Women with untreated depression are also more likely to use alcohol, tobacco, and illicit drugs (5).

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They may be less able to motivate themselves to attend prenatal appointments or follow medical advice and have poor nutrition (4). The risk of self injury and suicide is a real concern (6). Thus, it is essential to consider each case individually prior to making medicine changes.

Lexapro (escitalopram)

Escitalopram is a SSRI (selective serotonin reuptake inhibitor) used in the treatment of depression. Escitalopram, marketed as Lexapro, is the active isomer of citalopram, thus the two compounds are chemically similar.

Congenital anomalies

Unpublished animal studies examining the effects of prenatal exposure to escitalopram have been conducted by the manufacturer (7). No increase in congenital anomalies was seen at doses 75X the maximum recommended human dose (MRHD) in rats. Decreased fetal body weights,

delays in ossification, slightly increased offspring mortality, and signs of maternal toxicity were observed at the higher doses. To date there have been no human studies examining the effects of prenatal exposure to escitalopram. There is human data, however, about citalopram use in pregnancy, the results of which should have some application to escitalopram.

Celexa (citalopram)

Citalopram, marketed as Celexa, is the SSRI used to treat depression. Due to the relatively recent marketing of this medication (approved by the FDA in 1998), data examining the effects of prenatal exposure, particularly long term development, is limited.

Congenital anomalies

Unpublished experimental animal studies examining the effects of prenatal exposure to citalopram have been conducted by the manufacturer (7). Teratogenic effects (cardiovascular and skeletal defects) were only observed at the highest doses when maternal toxicity symptoms were present. Lowered birth weights and increased offspring mortality were also present at the higher doses. No adverse effects were seen with rabbit studies with doses 5X MRHD.

Two small prospective human studies have been performed examining birth outcomes following prenatal exposure to citalopram. One study prospectively followed a group of 10 women taking citalopram 20-40mg/day throughout pregnancy and one woman taking citalopram starting in the second trimester (8). These women were being treated for either depression or panic disorders. There were no major malformations present and no differences in the Apgar scores or birth weight compared to a control group. Additionally, a larger prospective study from a drug recording program of the Swedish Medical Birth Registry reported the pregnancy outcomes of 531 infants prenatally exposed to SSRIs, 365 of which were exposed to citalopram (9). This registry identifies early pregnancy exposures, but timing and dosing were poorly specified. Of those infants exposed to citalopram, there was no increase in major malformations and no pattern to any of the birth defects. The authors also noted that due to two reports to the FDA, they specifically checked but did not find any cases of optic nerve hypoplasia, although the infants were evaluated only in the perinatal period. They did find a small but significant increase in prematurity (OR =1.6) in women taking any SSRIs. It is not clear what role the medicine, maternal condition, or life style factors associated with the maternal condition played.

Neonatal withdrawal

Nordeng et al. (10) described 5 possible cases of neonatal withdrawal with various SSRIs, including one case of an infant whose mother took 20mg/day of citalopram from months 5-7 and an increased dose of 30mg/day from months 7-9. The infant was born at term and had light abstinence symptoms with increased tonus in his extremities and neck, and was jittery. All symptoms, with the exception of tonus, resolved within seven days of birth (10). No medical treatment was needed. Laine et al. (11) prospectively followed 20 infants exposed to citalopram (N=10) and Prozac (N=10) compared to control group of healthy women not receiving psychotropic medication. While they found a 4-fold increase in serotonergic symptoms (tremor, restlessness and rigidity) in SSRI exposed infants aged 1-4 days, there were no significant differences in symptom scores when only the citalopram group was compared to the controls. No differences were found in blood pressure, heart rate and body temperature between the two groups, with the exception of a statistically significant increase in heart rate in the SSRI group at 2 weeks of age. No specific medical treatment was needed.

Long term development

Psychotropic medications alter neurotransmitter levels in the maternal brain, thus there is a theoretical risk that they can also alter the developing fetal brain. These brain alterations

could potentially lead to behavioral or learning deficiencies.
In the study by Heikkinen et al. (8), 11 infants who were exposed to citalopram in utero were followed until the first year of life. The body weights of all infants were normal at first year, as was the neurological development. One child could not walk at the age of 1 year, but the neurological status of this child was evaluated as normal 6 months later (8). Due to the limitation of the small sample size and limited follow up time, further investigation in this area is necessary.

Wellbutrin/Zyban (bupropion)

Bupropion is an aminoketone used both as an antidepressant (Wellbutrin) and as an aid in smoking cessation (Zyban).

Congenital anomalies

One study in rabbits only saw an increase in skeletal anomalies and delayed ossification at the highest dose when maternal toxicity was present (12). This same study reported that high doses given to pregnant rats produced maternal toxicity, but that no congenital anomalies were found in the offspring. The majority of human data on pregnancy exposure is available through a bupropion pregnancy registry maintained by the manufacturer, Glaxo Smith Kline (13). The registry prospectively collected pregnancy exposure information and outcomes since September 1997. Controls were not used. The current update of this registry (February 2004) indicated that 534 pregnancy outcomes have been prospectively analyzed with 354 live births following first trimester exposure. Of these first trimester exposures, there were 12 pregnancy outcomes resulting in birth defects (3.4%), which is not higher than the general population. However, of the 12 birth defects, 7 were isolated heart defects. Therefore there is continued study to assess an association specifically with cardiac defects. Additionally, a prospective controlled study found no increase in the rate of malformations in 136 women taking bupropion in the first trimester (14). Forty-five women took bupropion throughout pregnancy. There were 72 live births and no major malformations reported. Due to the small sample size this study had a 80% power to identify a 5 fold increased risk for malformations. There were also no differences in birth weight, gestational age at birth, or stillbirth compared to the controls. There was a significant increase risk for miscarriage among women taking any antidepressant or taking bupropion (12.3-15.4%) compared to a control group without depression (6.7%). In addition to the medicines, this latter finding could reflect factors with the maternal depressive condition or simply reflect an unusually low miscarriage rate in control women.

Neonatal withdrawal

No reports of neonatal withdrawal have been published.

Long term development

There are at present no published studies examining the long term effects on development in children prenatally exposed to bupropion.

Effexor (venlafaxine)

Venlafaxine is a bicyclic antidepressant marketed as Effexor.

Congenital anomalies

Unpublished animal data available from the manufacturer (Wyeth) reported no increase in malformations in the offspring of rats given 11 times and rabbits given 12X MHRD. Decreased weight and viability were noted in offspring at 10X MHRD in rats. Another study by da-Silva et al. produced similar results in rats prenatally exposed to venlafaxine (15). They found no increased risk for congenital malformations, but did find a slight decrease in birth weight of litters exposed to venlafaxine. Data obtained from the U.K. Drug Safety Research Unit included pregnancy outcomes for 26 live births in women who took venlafaxine during pregnancy, no major malformations were reported .A larger study by

Einarson et al. (16) prospectively collected information about birth outcomes of 150 women exposed to venlafaxine during pregnancy, 126 of which used the medication during the first trimester and 34 throughout the pregnancy. Seventy percent of the woman took 75mg venlafaxine (range: 37.5-300mg). The authors compared pregnancy outcomes of this group to two control groups, women who used SSRI's during pregnancy and women who did not take antidepressants. Pregnancy outcomes such as the number of live births, spontaneous abortions, preterm delivery, birth weight and major malformations were examined. The pregnancy outcomes were not statistically different between the three groups for any of these factors. The results from this study are promising, but are limited by the small sample size which provides only an 80% power to detect a 4-fold increase in malformations.

Neonatal withdrawal

The WHO Collaborating Centre for International Drug Monitoring in Sweden described 17 reports of neonatal withdrawal syndrome, of which only 6 were regarded as potentially related (17). An individual case report in a German journal described an infant with restlessness, hypertonia, jitteriness, irritability and poor feeding (18). The diagnosis of neonatal withdrawal was further suspected when there was a temporary improvement after administration of low dose (1 mg) venlafaxine. After 8 days, with no further treatment, the infant's symptoms resolved. The long term effects on development in children prenatally exposed to venlafaxine have not been studied.

Conclusion

Reproductive studies do not suggest an increase in congenital anomalies for any of the four medications discussed, although the studies are still limited by their small sample sizes. Studies with sample sizes less than 150 women allow at most a 4 fold detection of increased risk. Further evaluation of a possible association with bupropion and cardiac defects is still needed. Exposure to antidepressants which inhibit serotonin reuptake during the third trimester of pregnancy carries the risk of a neonatal withdrawal/serotonergic syndrome. Reported symptoms are non specific and typically self limiting. Symptoms most commonly reported include agitation, irritability, hypotonia, hypertonia, hyperreflexia, drowsiness, persistent crying, and sucking problems (19). Small non blinded case series suggest such findings occur in 20-30% of infants with third trimester exposure to the older SSRIs (Prozac, Paxil, and Zoloft) compared to 6- 9% of control infants (18). Individual case reports of withdrawal-like symptoms also exist for Celexa and Effexor. However, discontinuing antidepressants near delivery is controversial due to maternal and infant adverse effects with postpartum depression. Long term studies about any effects on neurobehavioral outcomes are absent. Currently there are only studies on early childhood development for Prozac and the tricyclic antidepressants. It should be noted that stopping medication is not a "no risk" option since there are concerns to a pregnancy with untreated maternal depression. The severity of maternal symptoms should dictate medicine use during pregnancy.

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