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Neonatal Complications Associated with Late Pregnancy Use of Selective Serotonin Reuptake Inhibitors

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The prevalence of depression among women peaks during the childbearing years (Burke *et al.*, 1991). With up to 14% of pregnant women displaying symptoms of depression, treatment of major depression during pregnancy is quickly becoming a major public concern (Evans *et al.*, 2001).

In addition to concerns that women with untreated depression are less likely to follow through with prenatal care and more likely to develop unhealthy behaviors or consider suicide, some studies have suggested that maternal depression is associated with pregnancy complications such as pre-term birth and low birth weight, as well as adverse cognitive/emotional effects in the child (reviewed in Bonari *et al.*, 2004; Mian 2005). Further, for pregnant women with a history of major depression, relapse occurred during pregnancy in 68% of those who discontinued their medications, as compared to 26% of those that continued taking medication for their depression (Cohen *et al.*, 2006). The potential for relapse and the possible adverse effects of depression itself on the pregnancy need to be considered when discussing whether or not a specific patient should remain on antidepressants throughout pregnancy.

Selective serotonin reuptake inhibitors (SSRIs), a class of antidepressants that increase the levels of circulating serotonin in the body, are just as effective as older tricyclic antidepressants and have fewer side effects (nausea, insomnia, sexual dysfunction, etc.) and higher tolerability in general (reviewed in Zohar and Westenberg, 2000). As a result, the prevalence of those taking SSRIs to treat their depression has increased dramatically in the past decade (Meijer *et al.*, 2004).

A number of studies have found no association with congenital anomalies and SSRIs with use during the first trimester of pregnancy (reviewed in Nonacs and Cohen, 2003; Wen and Walker 2004). In contrast to this reassuring data, a retrospective and unpublished investigation by GlaxoSmithKline, the makers of paroxetine (Paxil), suggests an increased risk for cardiovascular defects (most commonly ventricular septal defects) of 2% compared to 1% in the general population (reviewed in Williams and Woolerton 2005; GlaxoSmithKline study EPIP083 2005). Additional studies are still needed for confirmation since controlled prospective studies have not seen an increase in congenital anomalies with paroxetine.

There is also accumulating reports regarding concerns of SSRI use after the first trimester. Therefore, this newsletter will focus on the neonatal effects that have been associated with use of SSRIs during the second half of pregnancy, such as poor neonatal adaptation, and the recent reported association with persistent pulmonary hypertension of the newborn (PPHN).

Poor Neonatal Adaptation

Goldstein (1995) reviewed 112 prospective pregnancy outcomes on the use of fluoxetine (Prozac) that were voluntarily reported to the manufacturer, Eli Lilly. He found that 15/115 (13%) of infants experienced different postnatal complications, such as irritability, hyperbilirubinemia, or sleepiness, which he noted was similar to the National Hospital Discharge Survey. There was also no pattern of complications and no dose relationship to further a cause and effect relationship between fluoxetine and the complications. However, absence of a specific control group and a high rate of unknown outcomes limited his conclusions.

Subsequently, Chambers et al. (1996) prospectively followed 73 pregnant women taking fluoxetine during the third trimester. The authors reported poor neonatal adaptation among 31.5% of infants exposed to fluoxetine in the third trimester, compared to 8.9% among infants exposed early in pregnancy (Chambers et al. 1996). With exclusion of the premature infants, 23% of late exposed infants were admitted to the special care nursery compared to 9.5% of early exposed infants or 6.3% of infants never exposed to fluoxetine. Health care workers, however, were not blinded to maternal medication use when examining the infants, a possible study bias.

Similar results were noted in a study of 55 infants exposed to paroxetine during the third trimester. In this study, 22% of infants experienced neonatal complications (including 3 premature infants), as compared to 6% of unexposed infants or infants exposed only in the first and second trimester (Costei et al., 2002). Of the 12 infants that had complications, respiratory distress was noted in nine, hypoglycemia in two, and jaundice in one. Symptoms disappeared in one to two weeks.

Oberland et al. (2004) performed a prospective cohort on three small groups of infants. Twenty-eight infants were exposed to SSRIs alone (paroxetine, fluoxetine, and sertraline), 18 infants had exposure to an SSRI and the benzodiazepine clonazepam, and 23 control infants had no medication or depression exposure. Twenty-five percent of the SSRI group alone, 39% of the SSRI group plus clonazepam, and 9% of control infants had symptoms of poor neonatal adaptation.

Symptoms included mild respiratory distress, transient tachypnea of the newborn, and hypotonia. All symptoms resolved in 48 hours and no significant differences in development were noted at follow-up at 2 and 8 months of age using the Bayley Scales of Infant Development.

Based on their findings, the authors recommended avoiding polypharmacy when possible and specifically monitoring mothers and infants when paroxetine was used in combination with clonazepam. They also noted that their data should not preclude the urgency to treat maternal depression or anxiety when warranted.

Sivojelezova et al. (2005) prospectively followed 132 women taking citalopram (Celexa) in whom 54% of the total group took citalopram throughout pregnancy. Following third trimester exposure, 16% of infants were admitted to the special care nursery versus 4% of infants not exposed to citalopram during the third trimester. Additionally, Malm et al. (2005) used Finnish population based registries to identify 597 women who purchased SSRIs in the third trimester. Citalopram (N=228) and fluoxetine (N=239) were most commonly purchased while paroxetine (N=64), sertraline (N=41), and fluvoxamine (N=27) were also purchased. There was a small but significant difference in that 15.4% were treated in the special care nursery versus 11.2% with only first trimester purchase. An obvious criticism of this study is that purchasing the medicine does not necessarily mean the medicine was taken during pregnancy.

Levinson-Castiel (2006) identified 60 infants with prolonged exposure to SSRI paroxetine (N=37), fluoxetine (N=12), citalopram (N=8), venlafaxine (n=2), and sertraline (N=1). Symptoms of neonatal abstinence syndrome were present in 30% of the exposed infants versus none of the control infants. Clinical assessment was not made blinded and medicine use was based on maternal report. The most common symptoms were tremors, gastrointestinal disturbances (poor feeding, vomiting, loose stools), and sleep disturbances. Maximum mean daily symptoms occurred within the first 48 hours. None of the

infants in this study required any treatment for the symptoms.

A dose relationship with increasing symptoms and increasing dose was seen for paroxetine (the only medicine that could be studied for dosing) but no cut-off point of an increased risk could be identified due to the small sample size. Based on their findings, the authors recommended that exposed infants should be closely monitored by using a standardized protocol for a minimum of 48 hours and should not be discharged early from the hospital.

The results of a meta-analysis of studies involving late gestational SSRI exposure, including many of the ones described previously, indicated an overall neonatal behavioral syndrome risk ratio of 3.0 (95% CI, 2.0-4.4) (Moses-Kolko E 2005). Paroxetine and fluoxetine were reported most often but may reflect their more common use. The authors noted that tapering and then discontinuing SSRIs a couple weeks prior to the due date and then resuming treatment right after delivery may be an option for some women. They did note that a late tapering has not been proven effective for avoidance of neonatal complications and that it puts patients at risk for postpartum depression.

It is unclear whether the symptoms noted in some infants born after in utero exposure to SSRIs is due to withdrawal from medication at delivery or to serotonergic overstimulation due to exposure late in pregnancy. The symptoms of these syndromes overlap in adults, and appear to overlap in infants as well (Jaiswal *et al.*, 2003).

Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension of the newborn (PPHN) is described as a failure of normal pulmonary vascular relaxation shortly after birth, which ultimately results in unoxygenated blood being shunted into the systemic circulation (via patent ductus arteriosus and/or foramen ovale) and profound hypoxemia (reviewed in Dakshinamurti 2005). This condition is associated with substantial morbidity and, despite treatment, can result in death.

A recent study published in the *New England Journal of Medicine* found that SSRI use after the 20th week of gestation is associated with PPHN (Chambers *et al.*, 2006). This study was prompted by the authors original cohort study that identified two infants with PPHN following third trimester fluoxetine use. For this case-control study of 377 infants with PPHN and 836 controls, mothers were interviewed within 6 months of delivery regarding their medical and obstetric histories, habits, occupations, and medication use during the period of 2 months before conception and the end of pregnancy. The mothers were explicitly asked whether they had taken medications for depression, and if they responded positively, they were provided a list of antidepressant medications from which to identify the one(s) they had taken. The specific SSRI medications that participants reported included citalopram, fluoxetine, paroxetine, and sertraline. Doses of medication and the number of women reporting use of each medicine was not listed.

Fourteen infants with PPHN had been exposed to SSRIs, as compared to only 6 control infants. This resulted in an odds ratio of 6.1. Given the general population rate of 1-2/1000 for PPHN, this translates into an absolute risk of 0.6-1.2%. 12/14 mothers with infants with PPHN continued the SSRI at least into the eighth months of pregnancy. Using 26 gestational weeks as a cutoff therefore yielded identical results.

The authors of this study point out that such an association cannot establish causality, but that there is biological plausibility to their finding. The lungs have been reported to act as a reservoir for SSRIs, the vasoconstrictive properties of SSRIs may increase pulmonary vascular resistance, and the mitosis-inducing properties of the drugs may result in the over-proliferation of the smooth muscle cells in the lung (Chambers *et al.*, 2006). Further, the authors also suggest the idea that SSRIs affect the synthesis of nitric oxide, which is known to play a role in regulation of vascular tone and reactivity as yet another

mechanism for the occurrence PPHN in SSRI-exposed infants (Chambers *et al.*, 2006). They propose that PPHN may represent the severe end of the neonatal complications (Chamber *et al.*, 2006).

Although the study design was the most appropriate in order to assess this rare outcome, its retrospective design makes it vulnerable to recall bias, especially with prompting women with medicine names. The authors point out that the same association was not found with tricyclic antidepressants even with medicine name prompting. It is still important to replicate these findings before definitive conclusions can be drawn.

Summary

Use of SSRIs late in pregnancy is associated with an approximate 20-30% chance for nonspecific and typically transient neonatal complications. Therefore, these infants should be carefully monitored in the newborn period. While an initial study on these affected infants did not find development impairment at eight months of age, longer term neurobehavioral evaluations in this subpopulation are still needed. It should be noted that the SSRI associated neonatal complications can also be seen with other types of antidepressants and in a smaller number of infants whose mothers do not take any antidepressants.

An approximate 1% link between PPHN and late pregnancy SSRI needs to be replicated for verification but may represent the severe end of these neonatal complications. These findings act as a reminder that a woman's individual clinical state should be considered when deciding to keep a patient on a psychotropic medicine throughout pregnancy. Due to concerns with untreated maternal depression, continuing treatment in women with clinical depression may still be the least risky option for many women.

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