CASE REPORT

Antenatal Escitalopram Use and Necrotizing Enterocolitis in a Newborn: A Case Report

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The increased use of antidepressants during pregnancy has been associated with adverse effects in the newborn. We report a case of antenatal escitalopram use associated with necrotizing enterocolitis in a healthy term baby. We further discuss possible mechanisms that may explain this association. With increasing evidence of association of necrotizing enterocolitis with maternal exposure to antidepressants, more studies to find out causality and methods to predict babies at risk and their prudent management are needed.

INDEX TERMS: escitalopram, necrotizing enterocolitis, prenatal antidepressant-exposure syndrome, selective serotonin reuptake inhibitors, SSRIs, pregnancy, term neonate

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INTRODUCTION

The prevalence of depressive and anxiety disorders during pregnancy ranges between 10% and 20%. These untreated psychiatric illnesses during pregnancy have been shown to have detrimental effects on the mother as well as the fetus.^{1,2} Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants are frequently used as first-line drugs to treat depression during pregnancy, with a high response rate and efficacy. However, these have not only been associated with adverse pregnancy outcomes but also adversely affect the newborn, who may present with prenatal antidepressant-exposure syndrome (PAES),^{3,4} a withdrawal reaction to the chronic exposure to antidepressants. Babies born to mothers on antidepressive treatment also tend to have a higher incidence of respiratory problems (odds ratio, 1.40), lower 5-minute Apgar scores of less than 7 (odds ratio, 1.68), and need for neonatal intensive care unit monitoring (odds ratio, 1.24) compared with women with psychiatric disorder without medication use during pregnancy.⁵ One of the more serious adverse outcomes that have been described as single case reports is necrotizing enterocolitis (NEC) after exposure to maternal use of SSRIs during pregnancy. Exposure to escitalopram,⁶ paroxetine,⁷ and venlafaxine⁸ has

been associated with NEC in term neonates. The pathogenesis for this association is not exactly known but appears to be multifactorial. Here, we have described a neonate with NEC following antenatal exposure to the new SSRI escitalopram.

CASE

A 2.6-kg (22nd percentile) male infant was delivered by cesarean delivery at 36 weeks to a 20-year-old primigravida with a history of preeclampsia and schizophrenia. The mother had been treated with escitalopram (30 mg daily), which was started prior to and continued throughout the pregnancy. Bupropion was added at 20 weeks of gestation (100 mg twice daily) and was also continued throughout the pregnancy. There was no history of nicotine or alcohol use during the pregnancy. At birth, the baby had Apgar scores of 6 and 7 at 1 and 5 minutes, respectively. He required positive pressure ventilation with 100% oxygen and was transferred to the neonatal intensive care unit for sepsis evaluation, and management of hypoglycemia and hypothermia. He was empirically started on ampicillin (100 mg/kg/dose every 12 hours) and gentamicin (4 mg/kg/dose every 24 hours), which were administered for 2 days. On further evaluation, the infant had negative

blood cultures, normal complete blood counts, and normal serum glucose concentrations.

Formula feeding of 15 to 30 mL every 3 hours (Similac, Abbot Laboratories, Chicago, IL) were tolerated for first 2 days; however, on day 3 of life he had a non-bilious emesis that was followed by bilious vomiting episodes with a tender, distended abdomen with bloody stools. Abdomen X-ray was read as pneumatosis without free abdominal or portal vein air. Laboratory studies showed polycythemia, leukopenia, thrombocytopenia, hyponatremia, hypocalcemia, and elevated C-reactive protein concentration. Conservative therapy was started with ampicillin (100 mg/kg/dose every 12 hours intravenously for 10 days) and gentamicin (4 mg/kg/dose every 24 hours intravenously for 10 days). Enteral feedings were discontinued and total parental nutrition was started. No probiotics were given. A repeat abdominal X-ray on the same day showed mild bowel wall thickening without pneumatosis, and an upper gastrointestinal series ruled out malrotation. After completion of 10 days of antibiotics the follow-up abdominal X-ray was normal and he was started on 20 to 30 mL of every 3 hours (Nutricia North America, Gaithersburg, MD).

The baby also had associated tremors, irritability, and hypertonia in both limbs since the third day of life. Although the tremors and irritability improved early on, the tone was generally increased. Magnetic resonance imaging of brain was normal. Echocardiography, renal and sacral ultrasound, eye exam, karyotype, and single-nucleotide polymorphism tests were performed, and all results were normal.

At 3 weeks of life, he developed abdominal distention and tenderness, with redness of the abdominal wall that was associated with bilious vomiting and aspirates, and bloody stools. At this time the baby was on Neocate, which reached full feeds (i.e., 140 mL/kg/day) in 3 days of starting. An abdominal X-ray showed diffuse distension with pneumatosis. Conservative treatment for NEC was again started along with antibiotics for 14 days. This included nothing by mouth, orogastric tube for intermittent suction, respiratory support, and abdominal X-ray as needed. Vancomycin 10 mg/kg/dose every 8 hours and gentamicin 4 mg/kg/dose every 24 hours were started.

During the next 24 hours, the redness on the abdomen spread to a larger area. Laparotomy,

performed about 24 hours after the diagnosis, revealed poorly perfused intestine, and 100 cm of small intestine was resected and an ostomy was created. Intravenous metronidazole (15 mg/kg/dose every 12 hours) was added to the antibiotics regimen and was continued for 14 days. The baby became progressively more edematous, with increasing abdominal distension. The baby was operated on within 24 hours of diagnosis of the second episode of NEC. He was transferred to another hospital about 2 weeks after the second episode of NEC for continuing acute care as per parental request. Abdominal surgery was performed again. Complete necrosis of the bowel was noted. This resulted in short gut syndrome requiring total parental nutrition.

DISCUSSION

We describe a term neonate who developed NEC during his hospitalization, which may be associated with maternal escitalopram use, given the absence of any other risk factors. It was also associated with PAES, as suggested by the presence of tremors, irritability, and hypertonia. Necrotizing enterocolitis is a rare occurrence in term neonates; only 1 case has been reported in term neonates where it was associated with SSRI.⁶ Unlike the case associated with exposure during lactation and milder disease, our patient had a recurrent NEC that was more extensive, involving all of the small and large intestine. The association of NEC with maternal SSRI use could be related to transplacental transference of escitalopram and its metabolite demethylescitalopram to the developing fetus.

This association of NEC and antenatal SSRIs could be related to SSRIs' effects on ischemia-reperfusion or sustained low perfusion, and to platelet inhibition. SSRIs are known to inhibit the vasodilator nitric oxide and prostacyclin, which cause increased concentrations of and sensitivity to local vasoconstrictors like endothelin 1. This leads to increased vascular resistance and ischemia of the area supplied by intramural intestinal arteries and submucosal arteriolar plexus. Further, SSRIs increase serotonin, which has inherent vasoconstrictive properties that add to this effect. This mechanism is similar to the better-described mechanism by which SSRIs are associated with persistent pulmonary hypertension of the newborn.^{9,10} A second potential mechanism by which

SSRIs may be related to NEC is by reducing stored serotonin inside platelets, by inhibiting reuptake that ultimately prevents platelet aggregation, thereby predisposing one to bleeding in the gastrointestinal tract. However, a withdrawal phenomenon has been described with the sudden withdrawal of SSRIs after birth; increase in platelet activation and aggregation occur, causing a hypercoagulable state that predisposes one to NEC. This mechanism forms the basis for the potential use of platelet-activating factor to control NEC.^{7,11} In keeping with these mechanisms, the histologic appearance of NEC in term babies with antenatal use of SSRIs shows congestion, hemorrhage, inflammation, and transmural necrosis, and thus supports this pathogenesis.

PAES related to the SSRI is associated with high concentrations of extracellular serotonin in the central nervous system, which can affect neurotransmission and is said to cause neurobehavioral effects in children exposed to late-trimester SSRIs.¹² A self-limiting neonatal withdrawal syndrome consisting of jitteriness and central nervous disturbances, feeding, and respiratory disturbances often occurs in 20% to 30% of newborns with maternal intake of SSRI use, especially in the third trimester,³ and the prognosis is good with conservative management. As observed in our baby, there was respiratory distress and cerebral irritability, as evidenced by jitteriness, irritability, and increased general tone. These along with occurrence of NEC might be related to the increased circulating serotonin, which can be the cause for both of these clinical presentations.

Despite increasing use of SSRIs during pregnancy, the relative rarity of all serious side effects, including NEC, could be associated with differences in receptor reuptake efficiency.¹² A 44-base pair polymorphism in the promoter sequence of the SLC6A4 gene that codes for the receptor, termed the 5HTT-linked polymorphic region or 5HTTLPR, causes differential receptor reuptake and efficiency of the drug. The short (s) variant is associated with reduced transcription of SLC6A4 and an approximately 50% reduction in serotonin reuptake compared with the long (l) variant. The ss genotype thus has maximum inhibition of reuptake of serotonin and is associated with increased side effects, especially respiratory problems; and conversely, the ll variant is associated with increased uptake and decreased side effects.¹² This may account for the rarity of

adverse outcomes in newborns and may be potentially explored to identify neonates at higher risk for side effects of maternal SSRIs. In addition, defective maternal and fetal CYP2D6 alleles that result in inactive or reduced concentrations of CYP2D6 enzymes or MAO-A and COMT genotypes that regulate the activity of enzymes that metabolize SSRIs can also affect the quantity of drug that the baby is exposed to and cause an increased incidence of adverse events.¹³⁻¹⁵ These tests, although described in a research setting, are not generally available for routine clinical use at this time.

One limitation of our case report is the concomitant use of bupropion. Although there is no reported association of NEC with maternal use of bupropion, it inhibits CYP2D6,¹⁶ which may elevate serum concentrations of escitalopram and hence increase side effects related to escitalopram. However, unlike escitalopram, bupropion was not used through the duration of pregnancy; therefore, it is less likely that it was associated with NEC.

With the high prevalence of psychiatric conditions that require treatment with SSRIs and the new report⁶ of adverse effects on pregnancy and fetal well-being, there is an increasing need to have more evidence-based studies and protocols to individualize maternal treatment. We have to consider the dual risks of not treating the disorders in the mother, with the adverse effects due to treatment with SSRIs on the fetus. Pharmacogenetic may be used to identify individuals who are rapid metabolizers of drugs, or those at a high risk of drug adverse events due to their genotype profile. This would help identify those individuals who would benefit from measurement of serum drug concentrations during pregnancy and adjustment of doses based on blood or amniotic fluid drug concentrations. This would also enable the practitioner to anticipate the use of platelet-activating factor to control NEC, establishing feeding protocols for babies who are at higher risk are some of the areas where more research would have high clinical impact. Furthermore, neonatologists and pediatricians have to be aware of the possibility of such adverse side effects and need to closely monitor newborns exposed to SSRIs during pregnancy.

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Abbreviations NEC, necrotizing enterocolitis; SSRIs, selective serotonin reuptake inhibitors; PAES, prenatal antidepressant-exposure syndrome

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