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PERINATAL/NEONATAL CASE PRESENTATION

Necrotizing enterocolitis associated with *in utero* and breast milk exposure to the selective serotonin reuptake inhibitor, escitalopram

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A term neonate presenting with necrotizing enterocolitis following *in utero* and breast milk exposure to the newest serotonin selective reuptake inhibitor, escitalopram, is described.
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Introduction

The use of selective serotonin reuptake inhibitors (SSRIs) has become more common for treatment of depression during pregnancy.[1] Although data suggest that most SSRIs are safe during pregnancy, limited information is available regarding their effects on the newborn. A neonatal behavioral syndrome, characterized by tremors or jitteriness, increased muscle tone, feeding and digestive disturbances, irritability and agitation, and respiratory distress has been described as a result of neonatal exposure to SSRIs late in pregnancy. Signs may be present at birth and last a few weeks.[2] Persistent pulmonary hypertension has been described also in infants exposed to SSRIs late in pregnancy.[3–4] Although the exact mechanism is unknown, vasoconstriction of smooth muscle in the pulmonary vasculature and inhibition of nitric oxide are two possible theories. Two reports have shown a correlation of the SSRI paroxetine and neonatal behavioral syndrome with necrotizing enterocolitis.[5] We report a term infant presenting with necrotizing enterocolitis following *in utero* and breast milk exposure to the newest SSRI, escitalopram. Approval for review of this case, and its publication, was obtained from the Vanderbilt University Medical Center Institutional Review Board.

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Case

A 3033 g term female infant was delivered by cesarean section at 38 weeks gestational age to a 37-year old gravida 4 woman, who reported having used escitalopram 20 mg daily throughout pregnancy. Apgar scores were 8 and 8 at 1 and 5 min, respectively. She reported no additional drug use during pregnancy with the exception of prenatal vitamins, and denied using prescribed or over-the-counter non-steroidal anti-inflammatory agents or tobacco. After birth, the infant was admitted briefly to the special care nursery for 2 days to manage respiratory distress thought to be related to retained fetal lung fluid. This management included assisted ventilation for a short duration (5 h) on the day of birth, followed by weaning nasal cannula oxygen to room air by the end of the first 24 h. She did not receive umbilical arterial catheterization. She was discharged home on the third postnatal day, breastfeeding and breathing comfortably on room air.

On the fifth postnatal day, the infant exhibited lethargy, had decreased oral intake and passed grossly bloody stools. Her mother brought her to the emergency department, where on examination the abdomen was noted to be soft and nondistended. However an abdominal radiograph revealed evidence of pneumatosis intestinalis (Figure 1), and no free intraperitoneal air. She was admitted to the neonatal intensive care unit and provided intravenous nutrition, ampicillin, gentamicin and metronidazole for 14 days, and nasogastric suction with bowel rest for 10 days. Blood and urine cultures remained negative. Laboratory data revealed an elevated C-reactive protein of 89 mg/l on admission (normal < 10 mg/l); there was no anemia, polycythemia, neutropenia or thrombocytopenia; coagulation studies were normal. Doppler ultrasonographic assessment of splanchnic blood flow was normal. Congenital heart disease was ruled out by echocardiography. Serial radiographs demonstrated resolution of the pneumatosis within 72 h. On the tenth hospital day, enteral feeding was started using a protein hydrolysate formula. No problems were encountered and the feedings were advanced to full volume over the next 5 days.

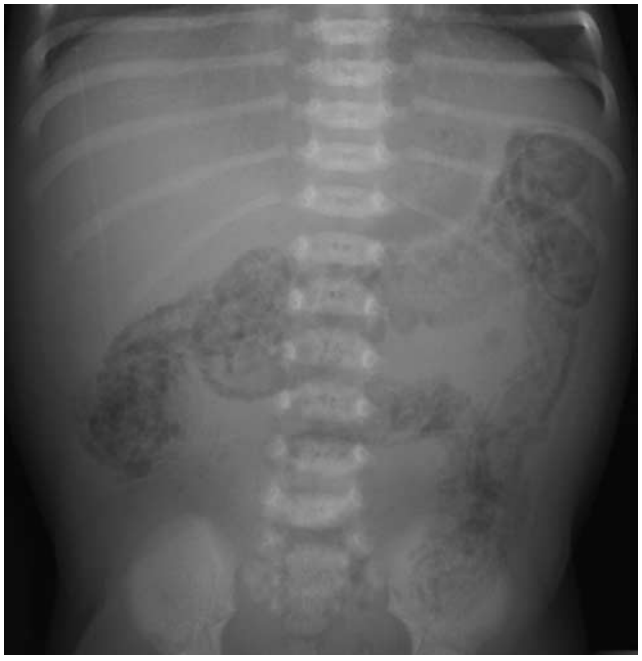

Figure 1 Necrotizing enterocolitis: pneumatosis intestinalis in the large bowel at presentation on day 5 after birth in a term newborn.

The likelihood of greater maternal benefit being derived from the control of her depression on escitalopram, and the risk of the infant's potential exposure to SSRI via breast milk, led to a mutual decision on the part of the neonatal intensive care unit team and the mother to discontinue breastfeeding.

Discussion

Published data suggest that all SSRIs cross the placenta and are readily secreted into breast milk.[6–7] Fluoxetine with its long half-life and active metabolite, norfluoxetine, have been associated with a concern for withdrawal or a toxicity syndrome, characterized by feeding intolerance and jitteriness in the newborn.[2,8–9] Additionally, paroxetine when studied with other SSRIs (fluoxetine, fluvoxamine and sertraline) is associated with a higher risk of withdrawal (or toxicity) in the neonate potentially owing to its short half-life.[9] There are no data on the effects of the newest SSRI on the market, escitalopram, the S-enantiomer of citalopram. Data suggest increased risk to the fetus exposed to citalopram late in pregnancy as described for other SSRIs. Sivojelezova *et al.,*[10] studied citalopram and its association with an increased incidence of adverse pregnancy outcomes. A total of 125 women took citalopram during the first trimester of pregnancy and 54% of those enrolled continued throughout their entire pregnancy. Fetal survival rates, mean birth weights and duration of pregnancy were not statistically different between the groups. There was a higher risk of admission to special care nurseries among those exposed to citalopram late in pregnancy, as compared with controls. They concluded that although citalopram use in early pregnancy does not pose a teratogenic risk, its use late in pregnancy is associated with a higher risk for neonatal behavioral syndrome.[10]

We report a breastfed term infant with minimal known risk for necrotizing enterocolitis, who presented with this clinical picture on day 5 after birth. As described in previous case studies, platelet activating factor in the intestine may play a major role in the pathogenesis of NEC owing to platelet aggregation. Chronic SSRI exposure inhibits platelet serotonin uptake, and therefore decreases platelet serotonin.[11–12] SSRIs are known to cause platelet dysfunction and bleeding, and when withdrawn could conceivably expose the neonate to a hypercoagulable state. Additionally, serotonin acts as a vasoconstrictor on smooth muscle and inhibits nitric oxide production. It is these mechanisms that are believed to be operative in the association of SSRIs with neonatal pulmonary hypertension. A similar effect of SSRIs on smooth muscle in the gut could potentially lead to vasoconstriction and poor perfusion in the gut mucosa predisposing infants to NEC. As clinicians become more familiar with the risks associated with maternal use of SSRI during pregnancy and lactation, and their effects on the newborn, it is still important to report all adverse effects seen with this class of agents until more controlled studies can be identified.

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