

Neonatal Abstinence Syndrome Due To In-Utero Exposure To SSRI: A Case Report

A Brzenski, M Greenberg

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Abstract

A 4.4-kilogram neonate developed symptoms of Neonatal Abstinence Syndrome (NAS) after in-utero exposure to the selective serotonin reuptake inhibitor (SSRI) sertraline. The neonate developed severe symptoms of irritability, tremulousness, difficulty eating and difficulty sleeping two days after delivery. While conservative management is often undertaken following in-utero SSRI exposure, this neonate required treatment with phenobarbital to control his symptoms. We present this case with a discussion of medication treatments for persistent or severe symptoms following SSRI-exposure in-utero.

INTRODUCTION

Neonatal abstinence syndrome (NAS) is an increasing problem that can occur after delivery in newborn babies who are exposed to maternal medications and substances in-utero (1). In-utero exposure to pain medications, such as methadone, for chronic pain or prior addiction is the most common reason for NAS (2), but the etiology of NAS has changed in the past 40 years. Maternal use of psychotropic medications has increased over the past 15 years (3,4) with increased in-utero exposure to selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and benzodiazepines. Fetal exposure to SSRIs/SNRIs in the 3rd trimester is associated with increased adverse events following delivery (5, 6), but the etiology of these events is controversial as these events can be secondary to either withdrawal of the antidepressant, toxicity of the agent causing serotonin excess syndrome, or a direct action of the drug on the infant. Conservative management of newborns suffering from NAS from SSRI withdrawal is common and the symptoms are usually self-limiting. However, some infants are severely affected, requiring gavage feedings and intravenous nutrition to maintain normoglycemia and adequate hydration. We present the case of a neonate with severe symptoms of NAS from sertraline withdrawal necessitating medical treatment with phenobarbital.

PRESENTATION OF CASE

A 4.4-kilogram male infant was born to a 40-year-old female with asthma, morbid obesity, attention deficit hyperactivity disorder (ADHD), anxiety and depression, at 41 weeks and 1 day post-conceptual age. The mother took amphetamine and dextroamphetamine for her ADHD and escitalopram for her depression prior to her pregnancy but was advised to discontinue both medications when she became pregnant. The mother reported good control of her symptoms throughout her pregnancy until 25-weeks gestation at which point her depression symptoms became sufficiently severe that the benefit was greater to re-start her on the selective serotonin reuptake inhibitor (SSRI) sertraline than the risk. Initiation of sertraline combined with mental health therapy adequately controlled her symptoms.

At 41 weeks and 1 day post-conception, the neonate was born by cesarean section for protracted active phase labor with arrest of descent. In addition, mom had developed chorioamnionitis. On delivery it was noted that the neonate was covered with thick meconium, requiring suctioning and eventual intubation. The neonate was extubated on day of life 1. By day of life 2 the neonate was noted to be irritable with signs of withdrawal, including severe irritability, tremulousness, difficulty feeding with emesis after each feed, and difficulty sleeping. The severity of symptoms required staff to continuously hold the infant. Finnegan abstinence scores were as high as 14. The neonatal pain

service was consulted and determined that the infant was most likely withdrawing from an intra-uterine exposure to sertraline. Mom denied any opioid intake, urine drug test was negative and withdrawal symptoms were atypical for opioids. A trial of phenobarbital was initiated with a 10-mg/kg oral load followed by 3-mg/kg/day oral dose divided every 12 hours. Within 24 hours of initiating the treatment with phenobarbital the infant's tremor stopped and his irritability improved. Finnegan abstinence scores fell to zero and his appetite improved. The neonate remained on phenobarbital for 5 days at which point the medication was discontinued. The baby remained symptom free and was discharged home without any further problems. At follow-up he continued to be symptom free.

DISCUSSION

Neonatal abstinence syndrome is an increasingly costly (7) problem that is inundating NICUs throughout the United States. NAS can present from prenatal exposure to maternal medications throughout the pregnancy, specifically near the time of delivery, or from postnatal exposure to prolonged infusions of sedative/analgesic medications following delivery. Historically, exposure to maternal pain medications in-utero was the most common etiology of neonatal abstinence syndrome. With the increasing opioid epidemic, pain medications remain the most common etiology of NAS. However, the presentation of NAS is shifting and the offending agent is increasingly something other than opioids, such as antidepressants, anxiolytics and/or other illicit substances (8).

Depression, in the form of major depressive disorder, or as a component of bipolar disorder, is a major health issue. 10-20% of pregnant women have been diagnosed with major depressive disorder. Neonates born to mothers with depression during their pregnancy are associated with worse outcomes. Poor maternal health behaviors such as increased tobacco, alcohol and drug use, as well as, decrease use of prenatal care are found (9). Once born, neonates born to mothers with depression have an increased risk of low birth weight and preterm delivery (10-13). Due to the significant risk that depression poses during pregnancy, identification and treatment is essential to prevent postnatal problems. The National Birth Defects Prevention Study in the United States (14) demonstrated that antidepressant use during pregnancy has increased over 300% from 1998-2005 with the largest class of medication increase from the SSRI antidepressants. Currently, the United States Federal Drug Agency (FDA) lists all SSRI medications, with the exception of paroxetine,

as class C ("risk can not be ruled out") during pregnancy. Paroxetine, is known to have an increase in cardiovascular malformations, leading to a class D designation. Due to the limited number of high quality studies examining the effect of SSRI medications during the entire peripartum period, the American College of Obstetric and Gynecology Practice Guidelines on Psychiatric Medication Use During Pregnancy and Lactation (3) states, "treatment with SSRIs or SNRIs during pregnancy should be individualized."

Neonates exposed to SSRI medications in-utero late in the third trimester have an increased incidence of neurobehavioral and systemic symptoms within the first days following delivery. Tremor, sleep disturbance, inconsolable high-pitched cry, and gastrointestinal disturbances are the most frequent seen symptoms (15-17). Studies suggest that at least 30% of SSRI exposed neonates will develop some symptoms following delivery (6, 15, 18). Debate exists as to if these symptoms are due to withdrawal in the form of NAS, serotonin excess, or as a direct effect of the drug (19) as many of these symptoms are shared between these etiologies. Management is further complicated given the treatments are conflicting. In adults, abrupt discontinuation of antidepressants, including SSRIs, are associated with antidepressant discontinuation syndrome in 9-60% of patients depending on the antidepressant (20, 21). In most cases, symptoms will resolve with reintroduction of the antidepressant. Symptoms of serotonin excess in adults include mental status changes, agitation, hyperreflexia, shivering, tremor, nausea, diarrhea and fever. Treatment includes supportive care and removal of the offending agent in mild cases, and the addition of benzodiazepines or cyproheptadine in moderate to severe cases. In some cases of NAS in exposed infants, the poor feeding and lethargy may be associated with the direct effect of the drug, which improves as the drug is cleared from the infant's circulation.

There is currently little in the literature regarding treatment of neonatal symptoms following in-utero SSRI exposure. Unclear etiology of the neonatal symptoms, combined with lack of SSRI dosing in neonates, leads to difficulty recommending a pharmacologic treatment. Nordeng H, et al (22) in a small cohort, treated these symptoms with chlorpromazine. We chose not to use chlorpromazine due to limited use within our NICU as well as the significant potential adverse effects. Given our familiarity with phenobarbital and its use to suppress the neurologic symptoms in NAS from other etiologies, we treated the newborn with phenobarbital. Phenobarbital is effective in

decreasing the irritable nervous system, as with its use in treating seizures. Interestingly even though the drug decreases irritability it also improves the feeding disorder, which cannot be explained by inhibition of the central nervous system. In this infant, all the symptoms resolved, including feeding, and Finnegan Abstinence Scores dropped to zero within a day of initiating treatment. We chose to complete a 5 day course of phenobarbital given most neonates have resolution of their symptoms within one week of life.

Non-pharmacologic measures are a significant part of treatment in NAS of all etiologies. Given the neuro-irritability of newborns with NAS, these non-pharmacologic measures are aimed at decreasing environmental stimuli. Some of these measures include maintaining a quiet environment, swaddling, holding and rocking the baby. The incorporation of breastfeeding in these infants is controversial. In opioid induced NAS breastfeeding is encouraged as the small amount of opioid transferred in breast milk can aid in withdrawal symptoms. However, the etiology of NAS from SSRI exposure is not known, making the decision regarding breastfeeding less clear. If serotonin excess is the etiology of symptoms in these newborns, transfer of the SSRI via breast milk would further lengthen the time of symptoms. Thus breastfeeding should only be encouraged when the transfer of medications from mom to infant is small. The exact acceptable amount of SSRI transferred that is acceptable is unknown. Typically an infant plasma concentration less than 10% of therapeutic maternal plasma concentration is acceptable. Paroxetine is the only SSRI that in multiple studies has been shown to have an infant to maternal ratio less than .10 consistently. Sertraline has been found to have an infant to maternal ratio of less than .1 in some studies (23), however the Wiesman study(24) showed over 6% of infants had an infant to maternal ratio of greater than .1. With this information, the decision to proceed with breastfeeding should be individualized. We did not encourage breastfeeding while the infant was being treated with phenobarbital, but once the symptoms had resolved the mother began to breastfeed.

Infants exposed to SSRIs in-utero develop symptoms of neuroexcitability and gastrointestinal distress for the first weeks following birth. Although symptoms are typically treated conservatively since the symptoms resolve in most infants, we would recommend pharmacologic treatment with phenobarbital in persistent or difficult to control NAS symptoms from in-utero SSRI exposure.

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Author Information

Alyssa Brzenski, MD

Associate Clinical Professor of Anesthesiology, University of California, San Diego, Department of Anesthesiology
San Diego, CA

Mark Greenberg, MD

Professor of Anesthesiology and Pediatric, University of California, San Diego, Department of Anesthesiology
San Diego, CA