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Neonatal Withdrawal Syndrome: A Diagnosis to Keep in Mind

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Case Report
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Abstract

During pregnancy, women are put through many challenges, sometimes facilitating the appearance of depression and anxiety symptoms, leading to the use of psychotropic drugs like benzodiazepines.

We present the case of a male new born who presented breathing distress signs during the first hour of life, needing supplemental oxygen. His mother was diagnosed with depressive syndrome and anxiety and was medicated with escitalopram until six months of pregnancy and diazepam as needed until the end of gestation. He was admitted to the Neonatal Intensive Care Unit. In the first 12 hours of admission, he started with irritability, difficulty calming, and exaggerated Moro reflex. Blood tests, lumbar puncture, and cultures were performed, and antibiotics were started. During the first five days of admission, while on antibiotics, he also presented poor sucking reflexes, altered stools, hyper alert look, hyperreflexia, and jitteriness episodes, with low blood inflammatory markers. Withdrawal syndrome was considered after blood and cerebrospinal fluid cultures were negative, and no improvement of the neurological status with antibiotics. He was monitored with Finnegan's score and improved with containment and comfort measures. This case pretends to emphasize the importance of adequate psychiatric follow-up during pregnancy and of awareness among neonatologists and pediatricians regarding the medicines that can be related to withdrawal syndrome.

Keywords: Benzodiazepine; Neonatal Withdrawal Syndrome; Neonatal Respiratory Distress Syndrome; Neonatology

Abbreviations: NICU: Neonatal Intensive Care Unit; SSRIs: Selective Serotonin Reuptake Inhibitors

Introduction

Antenatal depression is the most common psychiatric disorder during pregnancy, with rates of 2,3-3,3% in Europe [1]. Anxiety disorder is another important co-morbidity during pregnancy, with rates up to 15%, sometimes needing medical therapy [2,3]. Benzodiazepines are an important pharmacological class used to treat anxiety and panic disorders, and Portugal is one of the countries with the highest consumption of anxiolytics, where benzodiazepines are included [2-4]. Neonatal withdrawal signs are acknowledged causes of neonatal morbidity [5] although the presentation signs and symptoms, like irritability, poor feeding, and

respiratory difficulties, require an extensive assessment to rule out other conditions, such as infections, neurologic, metabolic, and circulatory ones [6]. This work aims to present a case of neonatal withdrawal syndrome, where the first signs and symptoms resemble a septic condition.

Case Report

We present the case of a male new-born who was the first child of a non-consanguineous couple. Twenty-seven-year-old Primigravida was previously diagnosed with depressive syndrome and anxiety, followed in Psychiatric appointments without Psychology follow-up, and was medicated with escitalopram 20 mg until six months of pregnancy and diazepam 5 mg as needed until the end of gestation. The pregnancy was unremarkable, with a negative screening for *Streptococcus agalactae*. Membrane rupture occurred seven hours before delivery, and maternal fever was registered during childbirth. One dose of cefazoline was administered 30 minutes before delivery. Lower segment cesarean section delivery was done due to cephalopelvic disproportion at 41 weeks of gestation, with an Apgar score at the 1st and 5th minutes of 9/10. The post-delivery clinical examination was uneventful. According to the Fenton Growth Charts, birth weight was appropriate for gestational age (3140 g). He then presented polypnea, nasal flare, and grunting during the first hour of life. Supplemental oxygen was provided to keep peripheral oxygen saturation (SpO2) above 94%. He was admitted to the Neonatal Intensive Care Unit (NICU) with a fraction of inspired oxygen of 25%, without signs of difficulty breathing. Shortly after the first hour of admission, he was tolerating room air with adequate SpO2. However, during the first 12 hours of admission, he started with irritability, difficulty calming, and exaggerated Moro reflex. Blood tests showed a leucocyte count of 23400/uL with 17400/uL neutrophils and 3880/uL lymphocytes, and C reactive protein (CRP) of 3,53 mg/dL. Hemoculture was drawn. A lumbar puncture was also performed, but no biochemical exam was done because of a small sample volume; only a cultural exam was done. Cerebral ultrasound performed at this time was normal. Intravenous ampicillin and gentamicin were initiated, considering the possibility of central nervous system infection.

Twenty-four hours after antibiotics were started, CRP dropped to 1,57 mg/dL, but he maintained periods of irritability that were hard to calm. A nasogastric tube had to be placed due to poor sucking reflexes, which subsisted up to day four. On D5, day four of antibiotics, he presented hyperalert look, hyperreflexia, and jitteriness episodes. No clonus, unstable temperature, or hypoglycemia were registered. Serial cerebral ultrasounds were unremarkable. Blood tests showed no alterations, including thyroid function. Blood and liquor cultures were negative at this point, and a Neuropediatric appointment was requested. The neurologic exam showed some tremors at manipulation but otherwise unremarkable. Withdrawal syndrome was considered once he maintained periods of irritability, intense crying, and altered stools. Maximum Finnegan score was 16 at D9. The mother was always cooperative and accepted the urine drug test, which was positive for benzodiazepines. Social service was also contacted, and they approved the discharge. During hospitalization, containment and comfort measures were used. He was discharged at D14 of life, only maintaining some periods of irritability but easier to calm than previously reported. He had a maximum Finnegan score of six in the previous 24 hours. At the outpatient clinic, no signs or symptoms of withdrawal syndrome were described at two months of age.

Discussion

After being admitted for transient tachypnea of the newborn, the neurological exam of the presented infant prompted the hypothesis of clinical sepsis with meningitis. As in this case, other diagnoses must be considered and investigated when clinical evolution is not as expected. Clinical history was revised because antibiotics did not improve neurological behaviour, and microbiological results were negative. The mother's medical history brought the hypothesis of neonatal withdrawal syndrome. Prescription medications (such as opioids, selective serotonin reuptake inhibitors (SSRIs), and benzodiazepines) and illicit drugs (stimulants, cannabis) can be responsible for the appearance of abstinence symptoms in the newborn [7,8]. Neonatal withdrawal signs and symptoms are due to the cessation of exposure to the said substance, and their severity depends on gestational age, substance or substances used during pregnancy, and the last time that substance was ingested [7,8]. When women stop taking their antidepressants during pregnancy, like in the presented case, this poses the risk of depression relapse during pregnancy or post-partum [1]. Untreated maternal depression is an independent risk factor for operative delivery, preterm birth, and low birth weight [6-8]. Of the possible consequences, cesarean delivery was the only present in the clinical case. On the other side there is evidence that any antidepressant class can be associated with new born withdrawal symptoms, diminished 1' and 5' Apgar scores, and NICU admission [1]. Neonatal withdrawal syndrome is associated with prolonged hospitalization, admission to the NICU, higher healthcare costs, and an increased risk of infant mortality [9]. So, it is essential to balance the need for pharmacological treatment and the least harmful medicine to the fetus. Mother's mental health should be assessed during pregnancy and post-partum, and Psychology follow-up should be suggested as an adjuvant tool in these cases. Other non-pharmacological methods that should be considered in anxiety disorders are relaxation and behavioural techniques [10]. In the presented

case, two drugs could be theoretically responsible for the symptoms: escitalopram and diazepam. Escitalopram is an SSRI and is considered safe during pregnancy and breastfeeding [10-12]. Case reports of withdrawal syndrome regarding this drug are associated with its use during the third trimester [10-12]. Tharp et al. published a retrospective cohort study of women taking antidepressants before and during pregnancy [10]. This work found that women who did not take escitalopram during the third trimester, compared with those who took it throughout the pregnancy, had lower rates of new borns needing NICU admission and adaptation syndrome Koren, et al. [10] commented on six studies where neonatal SSRI withdrawal or serotonin toxicity syndrome is described and refer that 6% to 9% of unexposed infants and those exposed early in pregnancy have similar symptoms [13]. With this literature, escitalopram is unlikely to be responsible for the withdrawal syndrome symptoms of our case once it was stopped before the third trimester.

Diazepam is a long-acting benzodiazepine indicated for short-term relief of anxiety symptoms [14]. It crosses the placenta since early pregnancy, and this passage is facilitated after six months of pregnancy [14]. So, after this period, more substance gets to the fetus. It is also essential that the half-life of diazepam is longer in new-borns than in children (31h vs. 18h) [14,15]. In our case, the first withdrawal symptoms were present a few hours after birth, but some authors describe the beginning of symptoms weeks after birth [8]. There is a spectrum of clinical presentation, and because of this, the diagnosis suspicion may not be immediate [9-14]. In our case, the new born presented with irritability, hyperreflexia, inconsolable crying, tremors and jerking of the extremities, and suckling difficulties. The improvement was significant in the second week of life, and no symptoms were described at one-month-old. Other neonatal withdrawal symptoms are hypertonia, restlessness, abnormal sleep patterns, apnea/bradycardia, cyanosis, gastrointestinal symptoms like diarrhea and vomiting, and growth retardation [14]. Modified Finnegan Score is one of the tools available to monitor withdrawal signs and symptoms, which we use to monitor our new born [7,8]. This score consists of punctuating 19 signs and symptoms and recording the presence or absence of nine unscored items. It should be accessed every 3 hours [8]

It is also important that healthcare professionals know the interventions that are useful for newborns undergoing drug withdrawal symptoms. The first line of treatment is non-pharmacological measures used for withdrawal symptoms despite the substance responsible for it. These measures include environmental control (room lighting, positioning), feeding methods, and social integration (including mother-newborn skin-to-skin contact), and some authors also defend the use of acupuncture [6,7]. Severe benzodiazepine withdrawal symptoms can be treated with phenobarbital, especially if failure to thrive is present [8]. The initial dose is 3-5 mg/kg/day in divided doses, which can be increased to 10 mg/kg/day [8]. The authors want to emphasize that pregnant women must get adequate treatment for psychiatric disorders once they affect pregnant women's health and infants. This case is intended to remind that diazepam, a commonly used drug, may be associated with neonatal abstinence syndrome. Obstetricians and Pediatricians should be aware of this possibility and make a cautious clinical history.

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