

# Venlafaxine-induced encephalopathy in term newborn

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## Abstract

The use of venlafaxine, a selective serotonin and norepinephrine reuptake inhibitor, for the management of depression in women of childbearing age has been on the rise, and there have been multiple case reports in the literature tying venlafaxine in-utero exposure to a form of neonatal encephalopathy presenting as neonatal abstinence syndrome. We present the case of a 5-day-old term infant whose mother was on venlafaxine throughout her pregnancy and presented with hypothermia, poor feeding, and decreased activity level. She subsequently had a negative sepsis workup and required nasogastric tube feedings for 2 weeks with spontaneous recovery and no clinical sequelae post-discharge. This case highlights the non-trivial potential risk of venlafaxine withdrawal in exposed newborns and the need for close observation. We propose a management framework for such situations in affected infants.

## Keywords

Venlafaxine, encephalopathy, newborn

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## Introduction

Depression impacts up to 23% of pregnant women, and the use of antidepressants during pregnancy has doubled since 2002 given the consequences of untreated depression and the associated negative neonatal outcomes.<sup>1</sup> Venlafaxine, a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), is closely related to the popular selective serotonin reuptake inhibitors (SSRIs) and is used in up to 6% of women with live births experiencing depression during pregnancy.<sup>2</sup> It has been repeatedly associated with a discontinuation syndrome which may present as encephalopathy characterized by tachypnea, poor feeding, and myoclonic seizure-like activity,<sup>3</sup> although no adequate studies exist formally evaluating this issue nor any guidelines regarding the management of newborns with in-utero venlafaxine exposure.

## Case presentation

A female infant was born via Cesarean section secondary to placenta previa at 37 weeks gestation without complications to a mother who had been on 112.5 mg of venlafaxine daily for depression throughout most of her pregnancy and then increased to 150 mg approximately 2 months prior to delivery. Apgar scores were 7 at both 1 and 5 min post-delivery and the birth weight was 2930 g. Mother was negative for

HIV, hepatitis B, syphilis, gonorrhea, and chlamydia. Group B streptococcus colonization testing during pregnancy was negative. She was rubella immune.

The baby had an uneventful nursery course, breastfed well, maintained stable vital signs, and was discharged home on day 3 of life with a 6.3% weight loss. She was brought back to the emergency department (ED) at 5 days of age with concerns of feeling cold to touch, a home-taken rectal temperature of 34.7°C, and decreased activity and feeding even though the maternal breast milk had fully come-in the day before.

In the ED, the rectal temperature was confirmed to be 34.7°C but otherwise the baby appeared clinically well with normal vital signs. A full sepsis workup was performed which revealed a modestly elevated C-reactive protein (CRP) level of 27 mg/L (normal range: 0–16 mg/L) and absolute bands of  $2 \times 10^9 \text{ L}^{-1}$  (normal range:  $0\text{--}1.4 \times 10^9 \text{ L}^{-1}$ ) with otherwise a normal complete blood count and

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comprehensive metabolic panel. The urinalysis showed an increased concentration but was otherwise normal. A lumbar puncture was attempted twice but failed. Blood and urine cultures were obtained, and the baby was empirically started on ampicillin and gentamicin intravenously following a normal saline fluid bolus.

The hypothermia resolved within 12 h, and the baby remained stable with no evidence of sepsis, including negative cultures at 48 h and a down-trending CRP. However, she continued to display poor oral feeding and excessive sleepiness, poor suck, and ineffective latching. Feeding evaluation did not reveal any anatomical or neuromuscular abnormalities. Given the ongoing weight loss and lack of progress, the decision was made to initiate nasogastric tube (NGT) feedings 24 h after admission with a 24 kcal/oz fortified formula and expressed breast milk at a total daily volume of 150 mL/kg/day which resulted in adequate weight gain.

Little progress was subsequently made from an activity and feeding standpoint until day 11 of admission. At this time, the infant seemed to have rapidly normalizing activity levels and was much more interested in oral feedings. She was transitioned to full oral feeds by day 13 of admission after being able to meet her feeding goals without NGT supplementation. She was eventually discharged home on day 15 of admission in good clinical condition and sustained weight gain with full oral feedings. Her discharge weight was 3025 g.

Subsequent follow-up in clinic at 2 months of age did not reveal any clinical or developmental abnormalities.

## Discussion

Up to 30% of infants exposed to SSRIs, with venlafaxine sharing their properties, appear to have symptoms of neonatal abstinence syndrome (NAS).<sup>4</sup> Unlike in-utero narcotic exposure-induced NAS where well-defined management guidelines exist, there is currently little to guide the clinician when faced with an SSRI-induced NAS-like constellation of symptomatology in term infants. Transplacental transfer of SSRIs and SSNRIs is substantial and NAS scores were noted to be significantly higher in exposed infants after 24 h of life.<sup>5</sup> Furthermore, it has been clearly demonstrated that the NAS symptoms were the result of venlafaxine withdrawal rather than toxicity given that the serum concentration of venlafaxine in exposed infants was undetectable at 18 h of life<sup>6</sup> with an elimination half-life between 12 and 15 h and clinical signs emerging with decreasing concentrations.<sup>7</sup> However, emerging literature suggests that there may be some venlafaxine-specific increases in cord blood and amniotic fluid compared with other medications in the same class.<sup>8</sup> In our case, there were no infectious, fetal or perinatal risk factors which could have explained our infant's described symptoms, and once the initial workup proved to be negative, the most likely remaining etiology was a venlafaxine withdrawal

encephalopathy, particularly since symptoms did not appear until day 3 of life. It should be pointed out that no head imaging was performed during the hospitalization and in retrospect should probably have been obtained to rule out an acute intracranial event such as non-accidental trauma.

The duration of symptomatology in our case (12 days) is well within what has been previously reported in the literature.<sup>3</sup> Given that there is some evidence that venlafaxine in breast milk could potentially attenuate SSRI-induced withdrawal symptoms<sup>9</sup> and the fact that the concentration of venlafaxine in human breast milk is not negligible with measurable concentrations present in the infants' plasma,<sup>10</sup> it is quite possible that the duration of symptomatology in our case could have been longer had the mother discontinued her venlafaxine intake after delivery while expressing breast milk. In the eventuality that maternal venlafaxine intake was discontinued after delivery, the option of supplementing the infant with oral venlafaxine has been demonstrated in one Dutch case report<sup>11</sup> which noted a subsequent reduction in withdrawal symptoms. This report, however, was limited to a single empirically determined dose and will require rigorous evaluation to determine true safety and efficacy in this situation.

Considering the above, our likely approach to future symptomatic term newborns with in-utero venlafaxine exposure will start with a full sepsis workup and brain imaging either via head ultrasound or magnetic resonance imaging (MRI) if dictated by the clinical situation or if the infant presents post-discharge. If the initial workup is negative, allow the mother to continue either breastfeeding or providing expressed breast milk while remaining on her pre-delivery venlafaxine dose. Standard care via the eat-sleep-console methodology will provide the adjunct therapeutic support aimed at minimizing withdrawal symptoms.

## Conclusion

Despite the current consensus that venlafaxine intake during pregnancy is generally safe to the newborn, it behooves the medical provider to closely monitor all term newborns with in-utero venlafaxine exposure for signs of withdrawal. This is particularly true after the first 24 h of life and for up to several days subsequently. Providers should also consider recommending ongoing maternal venlafaxine intake while breastfeeding in order to minimize or shorten withdrawal symptoms.

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## Ethics approval

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## Informed consent

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