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Hypothermia as a Presenting Sign of Venlafaxine-Induced Neonatal Abstinence Syndrome in 2 Neonates

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Maternal antidepressant use has increased during the past 2 decades, with venlafaxine emerging as a common agent during pregnancy. Both venlafaxine and its active metabolite possess prolonged half-lives in adults; however, abrupt discontinuation may lead to withdrawal including irritability, jitteriness, lethargy, restlessness, and insomnia. The drug and its metabolite readily cross the placenta, posing additional considerations during pregnancy. Two neonates were admitted to our hospital on 5 and 6 days of life with hypothermia and lethargy among other symptoms of neonatal abstinence syndrome (NAS) requiring an extensive medical workup. Both neonates were exposed to venlafaxine *in utero* and exclusively fed infant formula since birth. Given that venlafaxine crosses the placenta and into breastmilk, NAS was suspected as a result of the abrupt discontinuation of venlafaxine upon delivery, and the decision was made to introduce mothers' breast milk. Symptoms of NAS, including hypothermia, resolved in both patients. The reported incidence of NAS with venlafaxine alone is limited, likely due to variation in breastfeeding practices among new mothers. Diagnosis of NAS due to venlafaxine requires a high index of suspicion because symptoms are nonspecific and the presentation may be delayed after birth. The effective treatment of NAS using mothers' breast milk illustrates the importance of counseling mothers to provide breast milk as a preventative strategy for withdrawal in their newborns. The cases involving the 2 neonates described in this article emphasize the importance of assessing *in utero* exposure to medications beyond the immediate newborn period and their possible role in causing unusual symptoms in newborns.

ABBREVIATIONS CMP, comprehensive metabolic panel; ED, emergency department; FDA, US Food and Drug Administration; IV, intravenous; NAS, neonatal abstinence syndrome; ODV, O-desmethylvenlafaxine; PCR, polymerase chain reaction; PICU, pediatric intensive care unit

KEYWORDS neonatal abstinence syndrome; neonatal adaptation syndrome; neonate; pharmacology; venlafaxine

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Introduction

Depression is one of the most common disorders during pregnancy and the postpartum period, with a prevalence ranging from 6.5% to 12.9%.[1] The use of antidepressant medications during pregnancy has increased significantly in the United States from 1976 to 2008.[2] Currently, the most common antidepressants used during pregnancy include selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors. These agents cross the placenta, raising concern for their effects on the fetus, though there has been no association with structural congenital anomalies.[3] However, neonatal abstinence syndrome (NAS), otherwise known as neonatal adaptation syndrome, has been reported in 20% to 77% of newborns exposed to antidepressants.[4–7]

A common antidepressant used in pregnancy is venlafaxine, a bicyclic ethylamine compound that is approved by the US Food and Drug Administration (FDA) to manage symptoms of depression.[8] Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), increase serotonin, norepinephrine, and dopamine concentrations in the brain by blocking transport proteins and inhibiting their reuptake at the presynaptic terminal. This results in more neurotransmitters at the synapse, and therefore, increased stimulation of postsynaptic receptors.

Serotonin norepinephrine reuptake inhibitors act predominantly on the serotonergic and noradrenergic neurons while metabolism is facilitated via CYP2D6.[8] In adults, venlafaxine has a half-life of 5 ± 2 hours and its metabolite's half-life is 11 ± 2 hours.[9] Therapeutic plasma concentrations of venlafaxine usually range from 30 to 300 ng/mL and for the active metabolite, ODV, concentrations range from 50 to 500 ng/mL.[10] Venlafaxine is usually well tolerated; however, it may cause adverse effects that include insomnia, somnolence, anorexia, abnormal dreams, anxiety, and tremors.[8] Venlafaxine is typically prescribed as a long-term treatment and

should not be abruptly discontinued. If abrupt discontinuation occurs in adults, it can lead to withdrawal symptoms that include irritability, jitteriness, tiredness, restlessness, anxiety, and insomnia.[8,9]

With limited published literature, newborns who were exposed *in utero* to venlafaxine but whose exposure abruptly ceased upon delivery, developed symptoms of NAS that included temperature instability, chills, feeding difficulties, hypertonia, irritability, jaundice, restlessness, seizures, sleep disturbances, tachypnea, tremors, and vomiting.[4,11] Typically, the onset of NAS occurs within 24 to 72 hours after birth and disappears within a few weeks. Although temperature instability as a broad term has been reported with NAS, the only report of hypothermia was in an FDA surveillance report without specific details.

In this article, we present the case of 2 infants who developed hypothermia as part of NAS that was suspected to be due to withdrawal from venlafaxine, as well as a review of the literature using PubMed.[12] The following MESH terms were used: venlafaxine, trazodone, neonate, pediatrics, children, neonatal abstinence syndrome, neonatal adaptation syndrome, breastmilk, fetus, pharmacology, and pregnancy. This search was conducted between September 1, 2021, and October 31, 2022.

Case Presentation 1. The patient was born at 38 1/7 weeks' gestational age, with a birth weight of 2.88 kg, via a repeated cesarean delivery at a neighboring hospital. The pregnancy was complicated by poorly controlled gestational diabetes mellitus requiring insulin. The mother had a history of depression, anxiety, and sleep disturbances and was prescribed venlafaxine and trazodone during pregnancy (venlafaxine 225 mg orally daily and trazodone 200 mg orally daily). The mother denied consuming any additional medications including illicit drug use, over-the-counter medications, or herbal products. At birth, the patient APGAR scores were 7, 8, and 9, at 1, 5, and 10 minutes, respectively. Shortly after birth, the patient had an episode of hypothermia to 37.4°C rectally that resolved with swaddling, an episode of hypoglycemia that resolved with oral feeds, and jitteriness that resolved without intervention. She was admitted to the neonatal intensive care unit for presumed sepsis and was placed on continuous positive pressure therapy. The patient was discharged home on day 2 of life after sepsis was ruled out. She was exclusively fed Alimentum (Abbott Nutrition, Columbus, Ohio) owing to a history of milk protein allergy in an older sibling. At 4 days of life, while the mother was feeding the patient on the couch, the mother fell asleep and woke up to the patient crying on the floor.

At 6 days of life, weighing 2.99 kg, the patient presented to our emergency department (ED) with a chief complaint of lethargy and hypothermia with a home rectal temperature of 35.3°C according to the patient's mother. The mother also noted that 2 days prior to admission, the infant had difficultly waking up for feeds and was more difficult to arouse.

The patient had a rectal temperature of 35.7°C in the ED, prompting initiation of a sepsis protocol with intravenous (IV) antibiotics that included ampicillin and gentamicin. Blood culture, urinalysis, urine culture, complete blood count, comprehensive metabolic panel (CMP), venous blood gas, thyroid function tests, a COVID-19 polymerase chain reaction (PCR) test, electrocardiogram, chest radiography, computed tomography, and lumbar puncture were performed. Cerebral spinal fluid studies were within normal limits and thyroid function results were within normal range. The CMP was remarkable for an elevated aspartate aminotransferase at 122 international units/L. White blood cells, C-reactive protein, and lactate concentrations from a venous blood gas were within normal limits. Urinalysis was unremarkable and PCR test for COVID-19 was negative. Computed tomography of the brain without contrast was read as normal. It was conducted owing to the patient's previous history of falling. An electrocardiogram showed right ventricular hypertrophy, which was expected given the mother's gestational diabetes. A chest radiograph was determined to be noncontributory. The repeated rectal temperature 2 hours after admission to the ED was 34.1°C and the patient was placed on warming gel pads, swaddled, given warm IV fluids, placed in an isolette with a temperature set at 37°C, and placed on nothing-by-mouth protocol. The patient was then admitted to our pediatric intensive care unit (PICU) for further management.

Upon physical examination in the PICU, the patient appeared pink and well perfused. Although she was sleepy, she was aroused with stimulation, cried normally, and was readily calmed. Primitive and suck reflexes were present, but suck reflexes were poor.

At 10 hours from admission while in the 37°C isolette, the patient's temperature increased from 34.1°C to 36.5°C, rectally. The patient was placed in an open, nonwarmed crib with environmental modifications including a short-sleeved onesie, long-sleeve footed onesie, a hat, and swaddled with 2 blankets. Sixty minutes after these modifications, the patient's rectal temperature was reported at 36°C. Owing to the patient's inability to maintain normothermia, she was placed back in the isolette, set at 37°C.

One of the authors suspected a possibility of neonatal drug withdrawal from venlafaxine exposure *in utero* because the patient had exclusively been formula-fed since birth. A literature search showed limited evidence to associate venlafaxine alone with NAS but given the drug and its metabolite's proclivity to cross the placenta and into breast milk, the suggestion was made to feed the patient the mother's breast milk to manage this withdrawal.

At 18 hours from admission, the infant was fed 60 mL of breast milk. After approximately 18 hours following this feed, the patient tolerated a wean in the isolette's temperature from 37°C to 32°C, as she was normothermic.

At 50 hours from admission, she was tolerating oral feeds with both 380-mL expressed breast milk and 100 mL of Alimentum per 24 hours (160 mL/kg/day). Upon physical examination she was lying comfortably in her isolette and had normal tone, and suck reflexes. All cultures were negative and antibiotics were discontinued.

At 54 hours from admission, 36 hours after starting breast milk, the infant's hypothermia completely resolved. She remained normothermic in a non-warmed open crib, was hemodynamically stable, and was more awake and interactive and tolerating oral feeds with both expressed breast milk and Alimentum. The mother was instructed to continue to breastfeed the patient for a minimum period of 2 weeks, to allow for a gradual discontinuation of venlafaxine. The infant was successfully discharged from the hospital at 64 hours from admission.

Case Presentation 2. The patient was born at 36 0/7 weeks' gestational age, with a birth weight of 2.8 kg at a neighboring hospital. His mother had a history of anxiety and depression and was prescribed venlafaxine during pregnancy. During the first 6 weeks of pregnancy, the dose was 150 mg orally daily, then 75 mg orally daily between the sixth and eighth weeks of pregnancy, followed by 37.5 mg orally daily after the eighth week of gestation until delivery. All prenatal testing and ultrasound scans of the fetus were normal, and she did not consume alcohol or use any additional medications including illicit drugs, over-the-counter medications, or herbal products during pregnancy. At birth, APGAR scores were 9 and 9 at 1 and 5 minutes, respectively. The infant was discharged at 2 days of life.

At 5 days of age, the patient presented to our ED via urgent care secondary to irritability and hypothermia, with a rectal temperature of 35.1°C. The patient weighed 2.675 kg. His mother stated that the child had been exclusively fed Similac (Abbott Nutrition, Columbus, Ohio) infant formula.

At presentation, the patient was evaluated for sepsis, which included a lumbar puncture and blood and urine cultures, and IV ampicillin and gentamicin were started. He was then transferred to our PICU. At 4 hours of hospital admission, the patient's rectal temperature was 35.1°C and he was placed in an isolette set to 37°C. At this point, he developed episodes of bradycardia, 80 beats/min, which improved upon stimulation, and was started on acyclovir empirically. The patient was placed on bilevel positive airway pressure to assist in ventilation, and warm IV fluids were administered with improvement in heart rate and activity. Respiratory viral panel and COVID-19 PCR tests were negative. Both complete blood count and a CMP were within normal limits and a chest radiograph was determined to be noncontributory. The pediatric cardiologist consulted determined that the patient's bradycardia was secondary to hypothermia. The patient's temperature remained stable at 35.2°C while in the isolette (37°C). The patient continued to be fed Similac infant formula every 3 hours. Intravenous fluids were weaned and bilevel positive airway pressure was discontinued. The mother was unable to express her breast milk consistently and the infant was too sleepy to successfully breastfeed.

At 28 hours from admission, a head ultrasound scan was reported as unremarkable. Given the previous admission of the patient in case 1 who developed NAS due to venlafaxine, the mother was encouraged to breastfeed. The mother was able to express 40 mL of breastmilk, which was combined with 160 mL Similac infant formula (75 mL/kg/day). Once breast milk was given, the infant was transferred to an open, non-warmed crib. Within 6 hours the patient's temperature increased to 37°C. The patient was able to feed by mouth and transitioned to an open crib at the same time breast milk was initiated.

At 60 hours from admission, the patient received 60 mL of breastmilk with 440 mL Similac infant formula (187 mL/kg/day). The patient's blood, urine, and cerebro spinal fluid cultures were negative and antimicrobials were discontinued.

At 68 hours from admission, the patient tolerated oral feeds and his mother was expressing her breast milk through a breast pump. The patient remained normothermic in an open crib for 48 hours and was successfully discharged from the hospital. Prior to discharge, the mother was instructed to continue to feed the patient breast milk for a minimum period of 2 weeks, to allow for a gradual discontinuation of venlafaxine.

Discussion

During the workup for both patients, infectious etiologies were ruled out. Consideration of whether these patients' presentations were consistent with serotonin syndrome was discounted owing to the divergent manifestations of NAS versus serotonin syndrome. Serotonin syndrome assumes a direct serotonin modulating effect that results in agitation, myoclonus, tachycardia, hyperreflexia, and diaphoresis.[13] One of our patients was exposed to trazodone during pregnancy. We did not suspect trazodone to cause NAS owing to the lack of data to support its role exclusively in causing NAS.

Manifestations of NAS due to venlafaxine include hypoglycemia, hypotonia and/or hypertonia, tachycardia and/or bradycardia, hypothermia, irritability, constant crying, shivering, eating and sleeping difficulties, and convulsions.[12–15] Consistent with the literature, our patients experienced hypotonia, hypoglycemia, bradycardia, irritability, and hypothermia. A literature search revealed support for the role of venlafaxine in NAS with symptoms occurring within 1 to 4 days after birth.[14,16–19]

With limited pharmacokinetic data of venlafaxine and its metabolite in the neonatal population, we postulated the half-lives of venlafaxine and its metabolite may be prolonged in this population. Metabolism of venlafaxine occurs via CYP2D6 to its active metabolite. During fetal development, CYP2D6 enzyme activity is relatively low, and the expression and activity gradually increase over the first months as the liver matures and develops.[20] This may explain the prolonged time from discontinuation of venlafaxine to the presentation of NAS in neonates.

The maternal dose concentration may be relevant in NAS. Holland and Brown[18] reviewed 14 cases, with gestational ages ranging from 29 to 42 weeks, of venlafaxine discontinuation phenomenon and found that onset of symptoms usually occurs at 12 hours to 4 days of life with symptoms of jittery movements and poor feeding/sucking.[18] They found that higher maternal dosing caused the most severe and longer-lasting symptoms of NAS. In the cases we describe both neonates developed symptoms within 4 days of life. The patient in case 1 was exposed to higher venlafaxine doses and for a longer period *in utero* and had a prolonged temperature instability as compared with the patient in case 2. Normothermia occurred after 18 hours in case 1 versus 6 hours in case 2.

Withdrawal symptoms may result from the abrupt discontinuation of venlafaxine post birth. This is expected because venlafaxine readily crosses the placenta, thus neonatal withdrawal would be expected to occur at approximately 4 to 5 half-lives of both venlafaxine and its active metabolite.[21–23] Venlafaxine's active metabolite's (ODV's) time to disappearance in adult patients is estimated to occur after 60 hours of discontinuation; however, this may be prolonged in neonates. This may explain the lag time between the expected disappearance of the drug and metabolite and the onset of NAS symptoms.

Both patients shared the unusual presentation of hypothermia as part of their NAS symptoms. The FDA adverse event reporting system is the only published reference that described hypothermia as a possible serotonin reuptake inhibitor–related neonatal withdrawal symptom in 5 infants.[12]

There are a few reports of breast milk being used to treat NAS.[18,19,24,25] In a case series by Boucher et al,[14] among 7 infants who developed NAS from venlafaxine withdrawal, breast milk was initiated at 7 days of life and symptoms improved. Consistent with the literature, there seems to be a time-dependent response to breast milk in reversing NAS in our patients.

Venlafaxine has been reported to have a very high fetal to maternal plasma concentration ratio, with umbilical cord to maternal serum concentration ranging from 80% to 170%.[14,16,17] The fetal to maternal ratios of the metabolite ODV have been reported to range from 56% to 335%.[14,16,17]

Venlafaxine crosses into breast milk readily. Three studies evaluating mothers who received venlafaxine 225 to 375 mg daily estimated that an exclusively breastfed infant would receive 3.2% to 7.6% of the maternal weight–adjusted dosage of venlafaxine with peak venlafaxine and ODV concentrations in breast milk observed at 8 hours after the administration of the maternal dose.[19,25,26] The milk to plasma ratio has been reported for venlafaxine as 4.14 (range, 3.26–5.18) and 3.06 (range, 2.93–3.19) for the metabolite.[27] Data on serum venlafaxine concentrations in breastfed infants are limited. In infants who were breastfeeding while their mothers were receiving venlafaxine, Newport et al[24] found that the correlated infant dose was estimated to be 0.07 mg/kg/day. None of the infants who were breastfed continuously showed signs of NAS or other symptoms of venlafaxine withdrawal, such as hypothermia or irritability.

There are currently limited data on the dosing of venlafaxine in a neonate to treat NAS when a mother is unable to produce breast milk.[28] de Moor et al[28] administered venlafaxine 1 mg orally as a 1-time dose to a newborn at 1 day of age, and symptoms improved over 8 days. The estimated dose to the child in this case was 0.3 mg/kg/dose.

Our patients experienced different manifestations of NAS due to venlafaxine with the unique presentation of hypothermia along with lethargy. The late presentations of these infants to the hospital following birth and discharge home made it challenging to suspect that medication exposure *in utero* was responsible for NAS. The longer half-lives of venlafaxine and its metabolite contributed to the prolonged time before NAS symptoms appeared. After introduction to breast milk, both patients were able to resolve the symptoms of NAS and were able to maintain normothermia.

Conclusion

The incidence of NAS due to venlafaxine is low, likely due to variation in breastfeeding practices. In our patients, there was suspicion that the abrupt discontinuation of venlafaxine exposure upon delivery may have contributed to the development of NAS. We postulate that because venlafaxine and its active metabolite cross into the placenta and breast milk, once breast milk was introduced, NAS resolved in both patients. In both cases, an extensive diagnostic workup was performed, including blood work, lumbar puncture, and imaging as well as intensive care unit admission. We hope these case reports emphasize the importance of suspecting NAS within the first week of life in infants exposed to venlafaxine *in utero*. Expectant mothers who are receiving venlafaxine should be counseled to provide any amount of breast milk to the child to avoid the potential development of NAS. When NAS is suspected in a neonate who is exclusively fed formula-milk, a trial of breast milk may be an effective management strategy.

Article Information

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References

1. Gavin NI, Gaynes BN, Lohr KN, et al. Perinatal depression: a systematic review of prevalence and incidence. *Obstet Gynecol*. 2005;106(5 pt 1):1071–1083.
2. Mitchell AA, Gilboa SM, Werler MM, et al. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. *Am J Obstet Gynecol*. 2011;205(1):51.e1–51.e8.
3. Bellantuono C, Vargas M, Mandarelli G, et al. The safety of serotonin-noradrenaline reuptake inhibitors (SNRIs) in pregnancy and breastfeeding: a comprehensive review. *Hum Psychopharmacol*. 2015;30(3):143–151.
4. Levinson-Castiel R, Merlob P, Linder N, et al. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. *Arch Pediatr Adolesc Med.* 2006;160(2):173–176.
5. Convertino I, Sansone AC, Marino A, et al. Neonatal adaptation issues after maternal exposure to prescription drugs: withdrawal syndromes and residual pharmacological effects. *Drug Saf*. 2016;39(10):903–924.
6. Einarson A, Bonari L, Voyer-Lavigne S, et al. A multicentre prospective controlled study to determine the safety of trazodone and nefazodone use during pregnancy. *Can J Psychiatry.* 2003;48(2):106–110.
7. Einarson A, Choi J, Einarson TR, Koren G. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. *Can J Psychiatry.* 2009;54(4):242–246.
8. Singh D, Saadabadi A. Venlafaxine. In: *StatPearls*. StatPearls Publishing; 2022. Accessed October 25, 2022. http://www.ncbi.nlm.nih.gov/books/NBK535363/
9. Effexor (venlafaxine hydrochloride) [package insert]. Wyeth Pharmaceuticals. US Food and Drug Administration website. Published 2006. Accessed September 17 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020151s044,020699s071lbl.pdf
10. Mandrioli R, Protti M, Mercolini L. New-generation, non-SSRI antidepressants: therapeutic drug monitoring and pharmacological interactions—Part 1: SNRIs, SMSs, SARIs. *Curr Med Chem*. 2018;25(7):772–792.
11. Mossabeb R, Sowti K. Neonatal abstinence syndrome: a call for mother-infant dyad treatment approach. *Am Fam Physician*. 2021;104(2):222–223.
12. Moses-Kolko EL, Bogen D, Perel J, et al. Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. *JAMA*. 2005;293(19):2372–2383.
13. Laine K, Heikkinen T, Ekblad U, Kero P. Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. *Arch Gen Psychiatry.* 2003;60(7):720–726.
14. Boucher N, Koren G, Beaulac-Baillargeon L. Maternal use of venlafaxine near term: correlation between neonatal effects and plasma concentrations. *Ther Drug Monit.* 2009;31(3):404–409.
15. Ferreira E, Carceller AM, Agogué C, et al. Effects of selective serotonin reuptake inhibitors and venlafaxine during pregnancy in term and preterm neonates. *Pediatrics*. 2007;119(1):52–59.
16. Matthys A, Ambat MT, Pooh R, Kupesic Plavsic S. Psychotropic medication use during pregnancy and lactation: role of ultrasound assessment. *Donald Sch J Ultrasound Obstet Gynecol*. 2014;8(1):109–121.
17. Larsen ER, Damkier P, Pedersen LH, et al. Use of psychotropic drugs during pregnancy and breast-feeding. *Acta Psychiatr Scand Suppl*. 2015;(445):1–28.
18. Holland J, Brown R. Neonatal venlafaxine discontinuation syndrome: a mini-review. *Eur J Paediatr Neurol*. 2017;21(2):264–268.
19. Ilett KF, Kristensen JH, Hackett LP, et al. Distribution of venlafaxine and its O-desmethyl metabolite in human milk and their effects in breastfed infants. *Br J Clin Pharmacol*. 2002;53(1):17–22.
20. Stevens JC, Marsh SA, Zaya MJ, et al. Developmental changes in human liver CYP2D6 expression. *Drug Metab Dispos Biol Fate Chem*. 2008;36(8):1587–1593.
21. Sit D, Perel JM, Wisniewski SR, et al. Mother-infant antidepressant concentrations, maternal depression, and perinatal events. *J Clin Psychiatry*. 2011;72(7):994–1001.
22. Rampono J, Proud S, Hackett LP, et al. A pilot study of newer antidepressant concentrations in cord and maternal serum and possible effects in the neonate. *Int J Neuropsychopharmacol.* 2004;7(3):329–334.
23. Hostetter A, Ritchie JC, Stowe ZN. Amniotic fluid and umbilical cord blood concentrations of antidepressants in three women. *Biol Psychiatry*. 2000;48(10):1032–1034.
24. Newport DJ, Ritchie JC, Knight BT, et al. Venlafaxine in human breast milk and nursing infant plasma: determination of exposure. *J Clin Psychiatry*. 2009;70(9):1304–1310.

25. Koren G, Moretti M, Kapur B. Can venlafaxine in breast milk attenuate the norepinephrine and serotonin reuptake neonatal withdrawal syndrome. *J Obstet Gynaecol Can*. 2006;28(4):299–301.
26. Hendrick V, Altshuler L, Wertheimer A, Dunn WA. Venlafaxine and breast-feeding. *Am J Psychiatry*. 2001;158(12):2089-a.
27. Briggs GG, Freeman RK, Towers CV, Forinash AB. *Briggs Drugs in Pregnancy and Lactation : A Reference Guide to Fetal and Neonatal Risk*. 12th ed. Wolters Kluwer Health; 2017 Accessed February 16, 2024. https://web.p.ebscohost.com/ehost/ebookviewer/ebook/ZTYwMHh3d19fMzMyMjg4M19fQU41?sid=f4ca4ad8-ab7e-4087-8e45-85b012ea9358@redis&vid=0&format=EK&lpid=navPoint-10&rid=0
28. de Moor RA, Mourad L, ter Haar J, Egberts AC. Withdrawal symptoms in a neonate following exposure to venlafaxine during pregnancy [in Dutch]. *Ned Tijdschr Geneeskd*. 2003;147(28):1370–1372.