Psychopharmacologic Therapy in Pregnancy: Effects on Newborns

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By Emilio J. Sanz, MD, PhD [4] and Carlos De Las Cuevas, MD, PhD [5]

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Although there is a tendency to avoid psychiatric medications during pregnancy, the high prevalence of psychiatric disorders in pregnant women—15% to 25%, according to recent epidemiologic studies [1][2][3]—means that women and their physicians often face impromptu decisions regarding the initiation or continuation of drug therapy during pregnancy. [4]

The management of psychiatric problems and pharmacologic treatment in pregnancy is complex and burdened with many biologic and personal factors. [5] Psychiatrists need to consider the impact of untreated illness on the mother and the fetus, as well as the possibility of increased risk for obstetric complications and congenital malformations associated with pharmacologic treatment. It should be stressed that untreated psychiatric illnesses pose a tremendous threat to the fetus because of maternal behavior and that discontinuing effective psychotropic treatments may exacerbate maternal mental illness and cause secondary effects on the fetus. All currently available psychopharmacologic agents and their metabolites cross the placenta, [6] and in some cases, intrauterine exposure to psychiatric drugs may lead to neonatal withdrawal syndrome (NWS), also called neonatal abstinence syndrome.

NWS occurs in newborns going through withdrawal symptoms as a result of the mother's use of psychoactive drugs during pregnancy. It is characterized by signs and symptoms of CNS hyper-irritability, GI dysfunction, and respiratory distress; and by vague autonomic signs and symptoms that include yawning, sneezing, mottling, and fever. This syndrome usually begins within 72 hours but may appear up to 2 weeks after birth. [6][7] The clinical presentation of neonatal drug withdrawal varies depending on the drug(s), timing, and amount of the last maternal use, maternal and infant metabolism and excretion, and other unidentified factors. [6]

Psychotropic medications given to the mother cause pharmacologic effects on the fetus. These effects are related to the mechanism of action and therapeutic objectives of the treatment (for the mother) and can produce symptoms and signs in the newborn that are distinct from those of NWS. In many cases, the clinical picture is very similar and, thus, difficult to differentiate.

Antipsychotics

This is probably the case with the effects of antipsychotics, which have been associated with tachycardia, GI dysfunction, sedation, and hypotension. In addition, extrapyramidal symptoms may include hyperactivity, hyperactive deep tendon reflexes, motor restlessness, and abnormal movements, which can persist for several weeks, [9] as well as tremors, posturing and flapping of the hands, increased muscle tone, vigorous rooting and suckling, arching of the back, and shrill crying. [10] NWS seems to be related to the pharmacologic effects of the drug, and once the drug is excreted, the symptoms resolve. Nevertheless, it is difficult to conclude that there is no withdrawal effect associated with the use of antipsychotics, because the clinical presentations are not exclusive. Despite this controversy, antipsychotics have not usually been associated with withdrawal symptoms but with pharmacologic effects in the newborn. For that reason, they have been excluded from further analysis in this review.

Antidepressants

The adverse effects of prenatal antidepressant exposure in the newborn may be secondary both to the effects of the drug and to its withdrawal. Both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are known to cause neonatal withdrawal symptoms when used
during the third trimester of pregnancy and especially when nearing time of delivery. Symptoms associated with antidepressant withdrawal are collectively called NWS or neonatal discontinuation.\textsuperscript{11,12} Withdrawal effects of TCAs have been characterized since at least 1979.\textsuperscript{13-16} The most common withdrawal symptoms include irritability, tremulousness, diarrhea, poor feeding, respiratory distress, and seizures (convulsions). These symptoms can occur in newborns whose mothers were taking either therapeutic or larger doses. Withdrawal can begin within 72 hours postpartum and last for several days.\textsuperscript{11}

NWS associated with the use of SSRIs has been under discussion for several years and the concept is now well established, although it is still underresearched; its incidence is estimated to be around 30% of exposed neonates.\textsuperscript{17} NWS seems to be a class-related problem because it has been described with almost every SSRI; however, there is speculation that some agents in this class are more prone to induce this problem than others. When administered in the third trimester, fluoxetine increased the risk of premature delivery, the need for special-care nurseries, and the incidence of lower birth weight and length.\textsuperscript{18} The most common symptoms associated with SSRI deprivation in neonates were respiratory difficulties, cyanosis on feeding, and jitteriness.\textsuperscript{19,20} Other common neonatal withdrawal symptoms included low Apgar scores, irritability, constant crying, shivering, increased tonus, eating and sleeping difficulties, and convulsions.\textsuperscript{21} This syndrome is usually self-limited and resolves quickly; in most cases, Apgar scores reach 8 to 9 after 1 minute.

In the World Health Organization case series,\textsuperscript{20} paroxetine was more frequently associated with NWS than were other SSRIs, but the methodology used can neither confirm nor deny this difference. Because of its pharmacokinetic and pharmacodynamic properties, there may be a higher risk of NWS with paroxetine. Costei and associates\textsuperscript{22} followed up 55 neonates exposed to paroxetine in the third trimester and found a significant increase in respiratory distress, hypoglycemia, and jaundice when compared with neonates exposed to paroxetine in the first 2 trimesters or those who were not exposed.

The symptoms of NWS seem to be associated with a serotonergic imbalance. Laine and associates\textsuperscript{23} used a prospective controlled study of 20 mothers taking either fluoxetine or citalopram during the third trimester to measure neonatal withdrawal symptoms and levels of monoamines in the umbilical cord. Children exposed to an SSRI had lower Apgar scores during the first 15 minutes and presented a 4-fold increase in serotonin-related symptoms (myoclonus, restlessness, tremors, shivering, hyperreflexia, uncoordination, and rigidity) during the first 4 days of life compared with controls. Levels of monoamines (serotonin, its metabolite 5-hydroxyindole acetic acid, the dopamine metabolite homovanillic acid, and noradrenalin) in the umbilical cord were reduced in newborns exposed to SSRIs.

**Anxiolytics**

The effects of anxiolytics, especially benzodiazepines (BZDs), in the newborn are a mixture of the pharmacologic effects of the substance and possible withdrawal symptomatology. Even if some investigators have described lower birth weights, shorter birth length, and significantly more perinatal complications than in their unexposed control groups,\textsuperscript{24} there are 2 different neurologic consequences in the newborn: the floppy infant syndrome and NWS. When diazepam and other BZDs were administered close to delivery, the neonates frequently presented with floppy infant syndrome, which is characterized by muscular hypotonia, hyperthermia, lethargy, respiratory problems, and feeding difficulties. Although some investigators claim that infants recover without long-lasting effects, it is speculated that these effects cause some types of neurocognitive developmental delays. Although it is difficult to ascribe these effects to BZD action on the brain or to sudden deprivation, NWS symptoms after exposure have been well documented for a variety of BZDs.\textsuperscript{25,26} NWS symptoms included low Apgar scores, hypertonia, irritability, abnormal sleep patterns, constant crying, tremors, myoclonus, bradycardia, cyanosis, sucking difficulties, apnea, feeding aspirations, diarrhea, vomiting, and growth retardation.

Both pharmacologic effects and NWS can be present at the same time, making the clinical picture more bizarre. The frequency and severity of NWS can be related to the pharmacokinetic profile of the particular BZD. Diazepam is long-acting and has a long half-life\textsuperscript{27}; a longer half-life can be associated with a prolonged effect of the drug in the newborn, whereas a shorter half-life can, more frequently, be associated with deprivation syndrome. It has been hypothesized that there is a relationship between long-term effects of BZD and brain development involving neurocognitive function. The topic is highly controversial, but studies have
only been conducted in animal models, which showed that BZD exposure produced immediate and long-lasting effects. Rats prenatally exposed to diazepam had significant deficits in acquisition and retention of spatial discrimination tasks.\textsuperscript{28} Another investigated substance, alprazolam, given prenatally to mice\textsuperscript{29} and rats\textsuperscript{30} produced significant increases in anxiety in offspring that were tested as either juveniles or adults. These long-lasting effects may be related to the desensitization of the $\gamma$-aminobutyric acid (GABA) receptor. A recent study showed that male rats exposed to BZD had behavioral deficits and were hypersensitive to pentylenetetrazol, a GABA antagonist.\textsuperscript{31} This effect seemed to be less pronounced in female rats, but the gender differences have to be more thoroughly explored.

**Antiepileptic drugs (AEDs)**

A mother's use of AEDs is linked to the immediate withdrawal effects of the newborn and to long-term neurologic dysfunctions. Valproate was shown to be associated with immediate NWS symptoms, such as hyperexcitability, causing neurologic deficits, seizures, and jitteriness.\textsuperscript{32,33} Furthermore, in a retrospective study based on hospital records, Dean and associates\textsuperscript{34} found significant NWS symptoms, including jitteriness, hypotonia, seizures, apneic episodes, hypoglycemia, and feeding disorder, after exposure in utero to valproate, phenytoin, or combination therapy. Long-term effects of AEDs have also been demonstrated. In the study by Koch and associates,\textsuperscript{32} when children were examined 6 years later, they continued to have long-term neurologic dysfunctions, which are more congruent with drug toxicity than withdrawal effects. Similar results are reported in the study by Moore and associates\textsuperscript{33} of 57 children prenatally exposed to AEDs: 77% had learning difficulties, 81% had speech delay, 60% had gross motor delay, and 42% had fine motor delay. Eighty percent of these children had prenatal exposure to valproate alone or in combination with another AED. Seventy-four percent of school-aged children were enrolled in special education classes or were receiving learning support, and 81% had some type of behavioral dysfunction; of these, 60% had some autistic features and 39% had hyperactivity, but autism or Asperger syndrome had actually been diagnosed in only a few. The developmental effects seem to be associated not only with valproate but also with carbamazepine, phenytoin, and polypharmacy.\textsuperscript{34} Although these investigators did not find a link between NWS and cognitive dysfunction, this is a topic in which further research is badly needed.

**Conclusions**

Pregnant women with psychiatric conditions must be adequately treated. Pharmacologic treatment should be initiated or maintained when the disorder is severe and the efficacy of the psychopharmacologic approach has been demonstrated, giving attention to nonpharmacologic alternatives in order to prevent the relapse of the disease in the mother. Psychiatric clinical practice shows that most pregnant women with psychiatric conditions are treated with polypharmacy,\textsuperscript{35} making it even more complex to identify the effects of these drugs on the newborn. Psychopharmacologic agents can induce direct effects on the newborn, as well as withdrawal symptoms associated with their suppression. The clinical picture of both cases is often similar and confounding. Nevertheless, NWS has clearly been associated with TCAs, SSRIs, and AEDs. However, with the exception of AEDs, the clinical picture for most of these drugs appears to be self-limited and moderate, most frequently needing only supportive therapy.

*Dr Sanz is associate professor in clinical pharmacology at the University of La Laguna in Tenerife, Canary Islands, Spain, and a member of the Review Panel of Experts of the WHO Collaborating Centre for International Drug Monitoring. He reports that he has no conflicts of interest concerning the subject matter of this article.*

*Dr De las Cuevas is associate professor of psychiatry at the University of La Laguna in Tenerife, Canary Islands, Spain, a specialist in psychiatry with clinical responsibilities, and a senior member of the Educational Liaisons Network of the World Psychiatric Association. He reports that he has no conflicts of interest concerning the subject matter of this article.*

**References:**

1. Altshuler LL, Hendrick V, Cohen LS. An update on mood and anxiety disorders during pregnancy
29. Christensen HD, Gonzalez CL, Rayburn WF. Effects from prenatal exposure to alprazolam on the


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