Pharmacologic Treatment of Sleep Disorders in Pregnancy

Laura P. McLafferty, MD[a,*], Meredith Spada, MD[b], Priya Gopalan, MD[b]

KEYWORDS

• Pregnancy • Sleep disorders • Sleep aids • Insomnia • Restless legs syndrome • Narcolepsy

KEY POINTS

- Sleep disorders during pregnancy have adverse effects on both mother and fetus that may necessitate pharmacologic treatment.
- In addition to general side effects, sleep medications in pregnancy may affect fetal development, timing and duration of delivery, and postnatal outcomes.
- Pharmacologic treatment of sleep disorders in pregnancy must include an individualized assessment of benefit and risk for both the patient and her unborn child.

INTRODUCTION

Pregnancy is a unique physiologic state whose characteristics often predispose women to new-onset sleep disturbances or exacerbations of pre-existing sleep disorders. Pregnancy-related factors that can disrupt sleep include heartburn, nocturnal oxytocin secretion, nocturia, and fetal movement. Sleep disorders in pregnancy include insomnia (primary and secondary), restless legs syndrome (RLS), and narcolepsy.[1]

Primary and Secondary Insomnia

Sleep duration decreases during the later phases of pregnancy.[2] Factors associated with shorter sleep duration include nulliparity, younger maternal age, advanced gestational age, and elevated blood pressure.[3] Excessive sleep disruption places pregnant and postpartum women at risk of new-onset and recurrent mood disturbance,[4] and is associated with increased risk of longer labor duration and need for caesarean delivery in nulliparous women,[5] as well as risk of preterm birth.[6] For primary insomnia, treatment strategies include cognitive behavioral and pharmacologic therapies.[1] For secondary insomnia, therapeutic management should include treatment of the underlying psychiatric and/or medical disorder.

Restless Legs Syndrome

Patients with RLS describe an unpleasant sensation that causes an overwhelming urge to move their legs. This sensation tends to worsen at night and during periods of rest. RLS is found in more than one-fourth of pregnant women[7,8] and almost two-thirds have no symptoms before pregnancy.[9] For most women, symptoms resolve

Disclosure Statement: None of the authors have any relationship with a commercial company that has a direct financial interest in subject matter or materials discussed in the article or with a company making a competing product.

[a] Department of Psychiatry and Human Behavior, Thomas Jefferson University, Thompson Building, Suite 1652, 1020 Sansom Street, Philadelphia, PA 19107, USA; [b] Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, 3811 O'Hara St., Pittsburgh, PA 15213, USA
* Corresponding author.
E-mail address: laura.mclafferty@jefferson.edu

Sleep Med Clin 13 (2018) 243–250
https://doi.org/10.1016/j.jsmc.2018.02.004

postdelivery.[10] RLS is linked to dopamine metabolism dysfunction in the central nervous system,[1] which, in pregnancy, may be linked to serum iron deficiency due to increased iron requirements,[8] folate deficiency,[11] and hormones such as estradiol.[12] Management strategies include pharmacologic therapy and reducing exposure to known triggers such as caffeine, smoking, and certain drugs.[1]

Narcolepsy

It is a clinical syndrome of daytime sleepiness caused by dysfunctional transition between sleep stages and is often accompanied by cataplexy, hypnagogic hallucinations, and sleep paralysis.[13] Given the peak incidence of narcolepsy from adolescence to early in the third decade of life, afflicted women are likely to have a pregnancy affected by the condition, and 40% report worsening symptoms in pregnancy.[1,14] Pregnant women with narcolepsy have higher rates of anemia and glucose intolerance, although there is no significant difference in mean weight and gestational age at birth.[14] Labor may be a trigger for cataplexy.[1]

SLEEP MEDICATIONS IN PREGNANCY

The goals of treating sleep disorders in pregnancy include the promotion of restorative sleep and the benefits it brings to both mother and fetus. Pregnancy is unique, however, in the presence of a fetus, who is also affected by any medication the patient takes. The prescribing of any sleep aid in pregnancy must include consideration of the risks and benefits of that medication for both mother and fetus.[15] The following pharmacologic agents and their perinatal effects are organized according to the sleep disorders they are intended to treat.

Primary and Secondary Insomnia

Benzodiazepines

Benzodiazepines function at the limbic, thalamic, and hypothalamic levels of the central nervous system to enhance neurotransmission of gamma-aminobutyric acid (GABA). They work via a modulatory site on the $GABA_A$ receptor complex to produce their sedative, anxiolytic, and antiepileptic effects are, used for the treatment of insomnia, anxiety, and seizures.[16,17] Although better suited for the short-term treatment of insomnia and anxiety, long-term use for these purposes is common and is associated with significant morbidity, including dependence and withdrawal, drowsiness and cognitive dulling, falls, and fractures.[18,19] They are commonly prescribed for the treatment of perinatal insomnia[16] and, because half of pregnancies are unplanned, there is the potential for accidental early fetal exposure.[20]

Benzodiazepines readily cross the placenta. However, despite access to fetal tissues as a result of placental transfer, studies indicate that benzodiazepines are not teratogenic.[21,22] Although early case-control investigations reported increased incidence of cleft lip or palate with benzodiazepines,[23,24] these findings have not been replicated in subsequent research.[21,25–27] Evidence does suggest, however, that benzodiazepines may contribute to increased rates of preterm birth and low birthweight.[28]

Hypnotic benzodiazepine receptor agonists

Medications in the hypnotic benzodiazepine receptor agonist (HBRA) class, also known as Z-drugs, include the imidazopyridine zolpidem; the pyrazolopyrimidine zaleplon; and the cyclopyrrolone, zopiclone (not commercially available on the market in the United States); and eszopiclone (the active enantiomer of zopiclone). HBRAs are now the most commonly prescribed hypnotics worldwide, including among pregnant women. Although not chemically related to benzodiazepines, they are agonists at the $GABA_A$ receptor, reducing sleep latency and improving sleep quality,[29,30] and they are thought to have minimal disruption of sleep architecture. Many potential adverse reactions have been noted, including memory loss, daytime fatigue, hallucinations, and tolerance or physiologic dependence.[31,32] HBRAs, like benzodiazepines, cross the human placenta and rapidly clear the fetal circulation.[33,34] HBRAs do not seem to increase risk for congenital malformations at usual clinical doses.[28,34–37] There is a case report, however, of neural tube defects occurring with high-dose exposure to zolpidem in the first trimester of pregnancy.[38] HBRAs may increase rates of preterm birth, low birthweight, and/or small-for-gestational-age infants[34,39]; however, studies were small and results showed statistical but likely no clinical significance.

Antidepressants

Regardless of class, all currently available antidepressants are thought to work through the modulation of the monoamine neurotransmitters, serotonin, norepinephrine, and dopamine, for the treatment of depression and anxiety. Given the sedating nature of some antidepressants, including tricyclic antidepressants (TCAs); the piperazinoazepine agent mirtazapine; and the serotonin-2 receptor antagonist and serotonin