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Review Article

Considerations in Treating Insomnia During Pregnancy: A Literature Review

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Background: *The prevalence of pregnancy-associated insomnia is high. Although insomnia may flow from normal physiologic features of pregnancy, it may also be an early warning sign of a relapse, or a trigger for a relapse, of a psychiatric illness. Those at risk for psychiatric illnesses may require medications as well as behavioral and psychotherapeutic interventions, to prevent relapse in the perinatal period. Unfortunately, few reviews of psychotropics used to treat pregnancy-related sleep disorders exist.*

Objective: *We discuss issues related to sleep and sleep disorders in pregnancy in the context of co-morbid psychiatric illness, and review the literature on the commonly-used medications (e.g., benzodiazepines, sedative-hypnotics, antihistamines, trazodone, and melatonin) for insomnia during pregnancy.*

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Key words: insomnia, pregnancy, women's mental health, medication safety, sleep medications

INTRODUCTION

Disrupted sleep affects up to 97% of women during their pregnancy.[1] The fetal effects of sleep medications have not been well studied. There are few reviews of medications used for sleep disorders in pregnancy, and they have limited risk-benefit analyses of their use for insomnia in the context of active psychiatric illness. We discuss pertinent issues related to sleep in pregnancy in the setting of psychiatric illness, and review the literature on the most commonly used medications for insomnia.

Sleep and Perinatal Mental Health

Sleep impairments in pregnancy are correlated with increased inflammation, gestational diabetes, and preeclampsia.[1] Poor sleep is a risk factor for relapse in women with mood disorders, and mood disorders in turn can cause changes in sleep.[1] Disrupted sleep in early pregnancy is associated with depression during pregnancy and postpartum.[1] Treating insomnia in the third trimester of pregnancy may decrease postpartum depressive symptoms.[2]

Addressing Sleep—Basic Principles

Normal physiologic changes during pregnancy can alter sleep; however, it is prudent to rule out psychiatric conditions that may lead to impairment in sleep and to recognize that women with underlying psychiatric illness may be vulnerable to the impact of these physiologic sleep changes.[3]

In women who have sleep disruption resulting from normal physiologic changes, nonpharmacologic

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interventions can be effective and should be considered as primary interventions.[3] Stimulus control techniques (bed restriction to sleep only) can be effective. Sleep hygiene practices, such as decreasing caffeine and regulating sleep-wake cycles, are also important. Fluid intake restriction in the late evening may reduce frequency of nocturnal urination. In the postpartum period, maximizing consecutive hours of sleep in the mother can be facilitated by using a breast pump or formula to allow others to assist with feeds.[3]

With women who experience insomnia from a psychiatric disorder, treatment should additionally focus on the underlying psychiatric disorder through psychotherapy and use of medications, if necessary.

MEDICATIONS

Benzodiazepines—Diazepam, Lorazepam, Alprazolam, Clonazepam, Chlordiazepoxide

Benzodiazepines are used for their sedative and relaxant properties[4]; they cross the placenta to varying degrees.[5,6] Diazepam crosses the placenta and accumulates in fetal tissue.[5] Lorazepam crosses the placenta less readily, and newborns can clear lorazepam.[6]

Congenital Malformations

Although some studies have found an association between benzodiazepines and congenital malformations, many studies do not support benzodiazepines being teratogens. A case-control study by Kjaer et al.[7] found an association between diazepam and neural tube defects, cleft lip, limb deficiencies, and intestinal atresia/stenosis. An indication for diazepam use was threatened abortion, and the authors did not control for this. Other studies that found associations between benzodiazepines and malformations did not control for some variables, like indication, concomitant medications, or substance use disorders.[8–10]

A large, prospective study examining the effect of exposure to benzodiazepines or hypnotic benzodiazepine receptor agonists (HBRAs) on congenital malformations did not find an association with congenital malformations after excluding pregnancies with concomitant antiepileptic exposure.[11] There was a marginally statistically significant association between gastrointestinal atresia and benzodiazepine or HBRA exposure (relative risk = 2.63, CI: 1.01–5.42), and between pylorostenosis and benzodiazepine or HBRA exposure (relative risk = 3.80, CI: 1.53–7.84); these associations included concomitant drug exposures.[11] An indication for benzodiazepines was threatened abortion, and the authors did not control for this.

Multiple well-designed studies have not supported teratogenicity of benzodiazepines when used alone.[12,13] An association between benzodiazepine monotherapy and congenital anomalies or congenital heart disease was not found after controlling for confounding variables like recent maternal illness, and maternal age.[12] Another large cohort study did not find an association between first trimester exposure to benzodiazepines, including diazepam and temazepam, and congenital malformations.[13] The study's strength is that it excluded women with severe psychiatric illness and with antiepileptic drug exposure, and accounted for body mass index and smoking, as these variables have been independently associated with congenital malformations.[13,14]

There are fewer studies assessing risks of individual benzodiazepines. A case-control study did not find an association between specific benzodiazepines, including alprazolam and clonazepam, in early pregnancy and congenital malformations.[4] A study by Czeizel et al.[15] did not find an association between chlordiazepoxide and congenital malformations. Similarly, other studies, did not find associations between alprazolam in the first trimester and congenital malformations.[16] Czeizel et al.[17] investigated the effects of short-term diazepam exposure in early pregnancy and malformations, and initially found an association between early diazepam exposure and malformations based on maternal report; the association was no longer seen when medical records were used to determine diazepam exposure, suggesting that the initial association may have been due to recall bias. A case-control study showed an association between lorazepam and anal atresia (OR = 6.19, CI: 2.44–15.74).[8] The study has methodological limitations including data analysis for only 40% of the sample, inadequate control of confounding variables, and the basis of the finding on only five cases.[8]

Obstetric and neonatal outcomes

Neonatal symptoms after exposure to benzodiazepines have been reported. There are case reports of