OBSTETRICS

A review of sleep-promoting medications used in pregnancy

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Approximately 4% of adults who have symptoms of insomnia resort to various hypnotic or sedating medications for acute symptom relief. Although typically a common practice for nonpregnant adults, this is not the case for the thousands of pregnant women who also report substantial sleep issues. Unfortunately, a paucity of randomized controlled trials in this population, scant empiric evidence regarding the appropriateness of prescribing options, and the concern of subsequent teratogenicity restricts the ability of clinicians to make informed decisions. We synthesized the current research regarding hypnotics and sedating medications used (both on- and off-label) during pregnancy and their association with adverse outcomes. Medications that we investigated included benzodiazepines, hypnotic benzodiazepine receptor agonists, antidepressants, and antihistamines. Overall, the examined studies showed no correlation of increased risk of congenital malformations. However, benzodiazepines and hypnotic benzodiazepine receptor agonists may increase rates of preterm birth, low birthweight, and/or small-for-gestational-age infants. The small number of studies and the small number of subjects prohibit any definitive interpretation regarding the consequences of the use of hypnotic or sedating medications in pregnancy. Additional case reports, randomized clinical trials, and epidemiologic studies are needed urgently.

Key words: benzodiazepine, hypnotics, medication, pregnancy, sleep

Symptoms of insomnia are prevalent in adults. Approximately 50% of adults report difficulty initiating or maintaining sleep or having unrefreshing sleep (ie, symptoms of insomnia), whereas upwards of 20% of adults meet diagnostic criteria for insomnia.[1] Given these numbers, it is not surprising that a significant number of adults (4%) report frequent use of hypnotic or sedating medications to combat the symptoms of insomnia.[2,3] A variety of medications are prescribed commonly (on and off label for their sleep promoting effects), which includes benzodiazepines, hypnotic benzodiazepine receptor agonists, antidepressants, and antihistamines.

Many of the adults who take hypnotic or sedating medications are likely pregnant women, because pregnant women have symptoms of insomnia more often than their nonpregnant counterparts.[4,5] Further, because one-half of the annual 6 million pregnancies in the United States are unplanned, many women unintentionally may have exposed their fetus to a hypnotic/sedative medication.[6] As a result, hypnotic or sedating medication use during pregnancy is quite common.[7] Despite their frequent use, clinicians are often reluctant to prescribe medications to pregnant women for fear of teratogenic effects.[8,9]

This is exemplified in a recent article that noted that the Centers for Disease Control and Prevention deemed it critical to understand the existing evidence about medication use as it relates to associated pregnancy risks. The Centers for Disease Control and Prevention solicited experts in the field to draft a prototype to inform clinical decision-making for the management of health conditions in pregnancy.[10] This was a commendable effort and will likely address all classes of medications that may be used by pregnant women, not just hypnotic/sedatives alone. This prototype likely will retrieve most of its information from the seminal book by Briggs et al.[11] This compilation reviews every medication ever reported to be used in pregnancy. The downside to this book is that it is >2000 pages and is designed for clinical practice. As the dissemination of the incidence of sleep disturbances expands, an appreciation of the health risks associated with disturbed sleep also grows. Based on this, we proffer that the literature currently lacks a concise, easily obtainable review regarding the usage and possible teratogenic effects of sedative/hypnotic medications during pregnancy. Although pregnancy risk categories denoted by the regulatory authorities such as the US Food and Drug Administration (FDA) and the Australia Therapeutic Goods Administration (TGA) pregnancy risk categories can be used, a concise and up-to-date reference on sedative/hypnotic use during pregnancy does not exist. Previous reviews on medication safety during the perinatal period are not specific to sedative/hypnotic medications.[10,12] They often do not refer to newly developed drugs nor cover all drug categories, specifically medications that fall into the sedative/hypnotic class. Given the wide prevalence of sleep disorders and medication use in pregnancy, the aim of this review was to describe comprehensively the existing body of research to understand the use and impact of hypnotic/sedating drugs (both on-and off-label) during pregnancy and their possible consequences for maternal and fetal outcomes.

Methods

Search strategy

We exhaustively searched PubMed and found articles based on key search terms:

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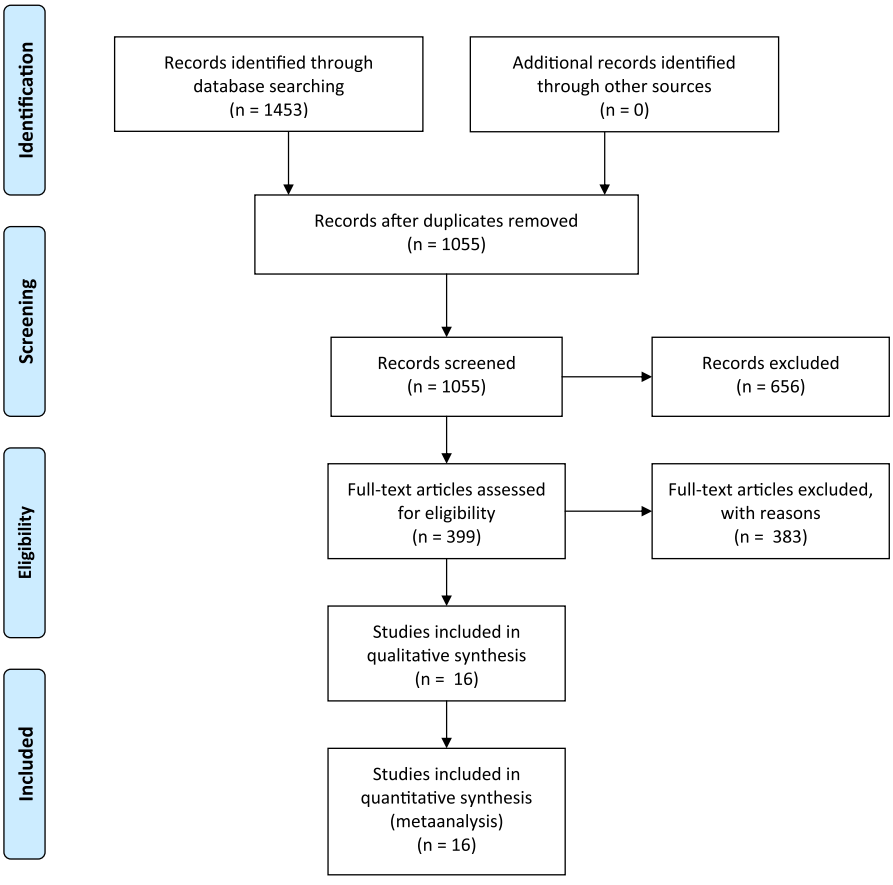
pregnancy and sleep with various medications or drug classes (*hypnotics*, *sedatives*, *benzodiazepine*, *nonbenzodiazepine*, *melatonin*, *antidepressants*, *antihistamines*, *ramelteon*, *zolpidem*, *zopiclone*, *zaleplon*, *alprazolam*, *clonazepam lorazepam*, *medazepam*, *nitrazepam*, *temazepam*, *tofisopam.*, *mirtazapine*, *trazodone*, *diphenhydramine*, *doxylamine*, *hydroxyzine*, *pheniramines*). These search terms, which allowed for 30 different searches, resulted in 1452 articles.

Our primary focus was to summarize comprehensively the current literature on medications that are used for sedative or hypnotic purposes by pregnant women. Thus, we excluded results that were animal studies, neonatal studies, reviews, inaccessible full texts, non-English publications, or for-medication doses that fell outside of the FDA-specified hypnotic/sedative doses. These exclusions removed a substantial number from our potential article pool and resulted in 1055 articles. After removing duplicate articles from the multiple searches, we had 399 articles to review. Of these 399 articles, we scanned the titles and abstracts and narrowed inclusion further by excluding articles in which prescription reason or dose was specified outside of the sedative realm. This resulted in a total of 16 articles to use. The Preferred Reporting Items for Systematic Reviews and Metaanalyses format for the literature search process is diagrammed in the Figure.

FIGURE
PRISMA diagram shows the selection of articles



Adapted from Moher et al.[82]

Okun. Sleep drugs in pregnancy. Am J Obstet Gynecol 2015.

Data abstraction

In our review, we categorized the articles by drug class. We examined 6 articles on benzodiazepines, 5 articles on hypnotic benzodiazepine receptor agonist (HBRA) drugs, 2 articles on both benzodiazepines and HBRA drugs, 2 articles on antidepressants, and 1 article on antihistamines. We extracted the key data through the research findings that were presented in the articles with the use of a tabulation method. The summary table for all articles describes extracted data under the fields: author, date of publication, location(s) of study, type of study, population size, drug(s) studied, outcomes/results, and key findings. Based on this information, we compared and collected the results to focus in on general conclusions of the safety of each drug and/or drug class during pregnancy.

Drug categories

After the notable cases of thalidomide-caused fetal malformations in the 1960s, most countries require all drugs to be classified into 'pregnancy categories' that denote risk of unwanted effects. Three of the most widely accepted international pregnancy classifications include the FASS (Swedish Catalogue of Approved Drugs), the US FDA, and the Australian systems, which vary slightly because of differences in safety data interpretation.[13] The categorization of drugs into risk classes for use in pregnancy categories by the FDA and the TGA are outlined in Tables 1 and 2.

Results

All studies included here reported on pregnant women. Most of the studies were retrospective cohort studies. Most of the data emanated from Sweden, the United States, and the United Kingdom, with a few studies from Taiwan, Hungary, and Canada. Prospective comparative and prospective cohort (matched pairs) studies were the second most common study design.

Because most data came from registries, in some cases it is not clear whether a drug was used off-label for sleep and/or insomnia, particularly for antidepressant drugs. Further, in cases of self-report, the