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Over-the-counter medications: Risk and safety in pregnancy

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ABSTRACT

Over-the-counter (OTC) medications are among the most commonly used products in pregnancy. Similar to prescription medications, for many products there is a lack of adequate data on safety of use in pregnancy. Assumptions of safety for these products based on long experience and OTC status, in the absence of data, may be ill founded. Examples of four OTC products used to treat common conditions in pregnancy are described. Potential links to adverse short- and long-term infant outcomes for these products are reviewed, and the strengths and limitations of data to support these. Research to detect or rule out these risks is essential.

Introduction

As has been recognized for decades, the majority of prescription medications and vaccines have not been evaluated systematically or adequately for safe use in human pregnancy.[1] This is in part because preclinical developmental toxicity studies are typically required and performed only in non-human animal species and may not be entirely predictive of the risk or safety of use of the same product at clinically relevant doses in humans. In addition, in most cases pregnant women have been excluded from clinical trials that have been conducted to establish the safety and efficacy of new medications. Once a drug is marketed, post-marketing studies for human pregnancy safety have not been routinely conducted. Even when human data are available, frequently sample sizes are too small, study designs inadequate, and detailed information on pregnancy exposures and outcomes is lacking. All of this presents a dilemma for health care providers and their patients in terms of reassurance regarding safe use of needed medications, as well as good information regarding counseling patients about risks or safety of exposures that have already occurred in pregnancy.

The same concerns apply to over-the-counter (OTC) medications and products. Despite the common misperception that an OTC designation indicates that the product is known to be safe for use in pregnancy, limited pregnancy safety data exist for the majority of these products as well.

From a public health perspective, the impact of OTC medications may be of even more importance than some prescription medications, due to the prevalence of use in the population. In a 2005 analysis using combined data from the Slone Epidemiology Center's Birth Defects Study and the National Birth Defects Prevention Study, Werler et al.[2] indicated that more than half of 10,533 women interviewed reported using an OTC analgesic such as acetaminophen or ibuprofen in the first trimester of pregnancy; 8.1% reported using pseudoephedrine, 5.3% an antihistamine, and 3.5% used a cough medication in the first trimester.

Given the frequency of use, OTCs are of high interest for study. In contrast to prescription medications, especially newly marketed products that may be infrequently used by

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pregnant women, the more common occurrence of OTC medication exposure in pregnancy overcomes some of the barriers to conducting research on these agents. However, there are still several challenges in conducting research focused on determining which medications are safe during pregnancy, including OTC products. These challenges include the following: the outcomes of interest, such as specific major birth defects, are rare, requiring larger sample sizes; critical windows of exposure in gestation may produce different outcomes and any given product may be taken only sporadically; and longer-term outcomes such as cognitive and behavioral performance in prenatally exposed children are difficult and costly to ascertain. An additional major methodological challenge in studying the safety of OTC medications taken in pregnancy is the fact that, unlike prescription medications, there may be no record that the drug was dispensed or taken. In recent years, database studies have made efficient use of pharmacy records, claims data, and other electronic health data collected for another purpose to link exposures to pregnancy outcomes. However, OTC medication use may never be recorded in these databases, making the mother herself likely the only valid source of exposure data, assuming she is able to accurately recall when a specific product was taken.

To illustrate these issues, four examples of commonly used OTC products will be described in this review, along with a summary of the available evidence regarding human pregnancy safety data, current interpretation for clinical practice, and gaps in knowledge.

Retinoids: Preformed vitamin A supplements

The risk of retinoic acid embryopathy following prenatal exposure to isotretinoin has been recognized since the 1980s.[3] The embryopathy in both animal models and humans appears to affect tissues derived from the cranial neural crest.[4] These data have been extrapolated to prenatal exposure to retinoids in any form, including dietary supplements containing vitamin A.

Rothman et al.[5] examined the risk of high vitamin A intake in pregnancy in a cohort of 22,748 obstetric patients recruited between 1984 and 1987 in over 100 participating practices in the Boston area. Women were interviewed in mid-trimester about their diet and the medications they had taken, including vitamin supplements, and outcomes were collected at the end of pregnancy. Of the 339 pregnancies that involved an infant with a major birth defect, 121 were considered to be neural crest in origin. For vitamin A from supplements alone, the prevalence ratio for neural crest cell-derived defects in babies born to women who consumed $>10{,}000$ IU/day compared to babies whose mothers consumed ≤ 5000 IU/day was 4.8 [95% confidence interval (CI): 2.2–10.5]. The increased frequency of defects was concentrated among babies born to women who had consumed high levels of preformed vitamin A before the 7th week of gestation.

This study exemplifies the need to obtain information on exposure and timing in gestation directly from the mother. The study findings were biologically plausible with respect to the specific types of defects associated with exposure as well as the gestational timing of exposure. Importantly, this study identified an agent that was available OTC and often found in doses at or near 10,000 IU/day in prenatal vitamin formulations available at the time. Ultimately, Tolerable Upper Intake Levels for preformed vitamin A were revised to 10,000 IUs preformed vitamin A for pregnant women 19 years of age or older. Preformed vitamin A in prenatal formulations was largely replaced by the vitamin A precursor, beta carotene.[6]

Decongestants: Pseudoephedrine

Pseudoephedrine is a sympathomimetic used to treat symptoms of allergy or upper respiratory infection. It has been one of the most commonly used OTC medications in pregnancy, with 8–12% of pregnant women reporting use in the first trimester.[2] It is an alpha-adrenergic receptor agonist, which causes blood vessel constriction and reduces airflow resistance in the nasal cavity. Pseudoephedrine is often part of a combination product, making it more challenging to study for its direct effects on pregnancy outcome, and to separate possible drug effects from the indication for which it is being used.

Several cohort and case–control studies have been conducted to examine the association of this vasoactive drug with birth defects overall as well as with specific birth defects. The specific defects that have been of interest include gastroschisis, small intestinal atresia, and hemifacial microsomia due to the biological plausibility that a vasoactive drug could produce defects that are thought to be vascular disruptive in origin. In a review by Werler, two cohort studies showed no association with birth defects overall, while five case–control studies showed elevated risks ranging from 1.8 to 3.2 for the specific defects mentioned above.[7] These data combined with another case–control study from the same group published later continue to suggest an association with defects, particularly gastroschisis. However, data are conflicting on the single ingredient vs. multiple component formulation, leaving open the question regarding the contribution of the mother's underlying condition.[8]

Strengths of the case–control studies were the sample size and statistical power for detecting associations with specific birth defects, and the fact that maternal interviews were used to ascertain whether the mother took this OTC product in pregnancy. However, mothers were typically asked to recall their first-trimester pseudoephedrine use months after delivery, so accuracy of recall about the specific product and gestational timing was a potential limitation.

If the risks for specific defects following early pregnancy exposure to pseudoephedrine are real, it is important to make two observations. The first is that the absolute risks for this OTC product are estimated to be very low for relatively rare defects. However, the second observation is that this is a product that has been widely used in pregnancy and has been considered "safe," so the public health impact of its frequent use in early pregnancy should also be considered.

Analgesics: Acetaminophen

Similar to pseudoephedrine, acetaminophen has been considered the drug of choice as an analgesic and an antipyretic