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. 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. 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...
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. The embryopathy in both animal models and humans appears to affect tissues derived from the cranial neural crest. These data have been extrapolated to prenatal exposure to retinoids in any form, including dietary supplements containing vitamin A.

Rothman et al. 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 formulas available at the time. Ultimately, Tolerable Upper Intake Levels for preformed vitamin A were revised to 10,000 IU.

### 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. 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 gastrochisis, 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.

These data combined with another case–control study from the same group published later continue to suggest an association with defects, particularly gastrochisis. 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.

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
in pregnancy. However, there is a potential for fetal liver toxicity after maternal overdose in pregnancy. Two series of 113 and 300 overdoses (treated with N-acetylcysteine, ipecac, or methionine) in pregnant women have been reported in the literature, and neither series suggested strong associations with adverse fetal outcomes. Relative to use of acetaminophen in the therapeutic range, recent concerns have been raised regarding respiratory outcomes and long-term neurodevelopmental effects. With respect to the former, two studies have suggested that prenatal exposure to acetaminophen predicted wheezing. In one study, use of acetaminophen in midpregnancy to late pregnancy but not early pregnancy was associated with wheeze in the first year of infant life. In the second study, prenatal exposure to acetaminophen predicted wheeze at 5 years of age in the offspring. A subsequent meta-analysis of six studies of children ranging from 30 to 84 months estimated the risk of any exposure to paracetamol in pregnancy was 1.21 (95% CI: 1.02–1.44). However, another study did not find any association between prenatal exposure to acetaminophen and childhood asthma.

Three studies published within the last 2 years have raised the question of a possible effect of prenatal exposure to acetaminophen and behavioral problems in children. The first was a Norwegian cohort study conducted between 1999 and 2008 involving 48,631 mothers interviewed at 17 and 30 weeks’ gestation and again at 6 months postpartum who subsequently completed a set of questionnaires when the child was 3 years of age. The questionnaires consisted of the Ages and Stages Screening tool, the Child Behavior Checklist and a measure of temperament. From this pool, a sample of 2919 same sex sibling pairs was selected. The authors found that longer-term use (>28 days) of paracetamol in pregnancy was associated with poorer gross motor development, communication, externalizing and internalizing behavior, and higher activity levels in the children. In contrast, ibuprofen exposure was not associated with any neurodevelopmental outcomes. In the second study derived from the Danish National Birth Cohort, Liew et al. studied 64,322 mother–child pairs enrolled between 1996 and 2002. Mothers were interviewed about their pregnancy exposures three times in pregnancy and one time 6 months postpartum. Children were assessed at 7 years of age using the Strengths and Difficulties Questionnaire, diagnosis for hyperkinetic disorders obtained from national registries, and prescriptions were identified for medications used to treat attention deficit hyperactivity disorders (ADHD). Children whose mothers reported acetaminophen use while pregnant were at higher risk of receiving a hospital diagnosis of hyperkinetic disorder [hazard ratio (HR) = 1.37, 95% CI: 1.19–1.59], use of ADHD medications (HR = 1.29, 95% CI: 1.15–1.44), or having ADHD-like behaviors at 7 years of age (risk ratio = 1.13, 95% CI: 1.01–1.27). Stronger associations were found with the use of acetaminophen in more than one trimester and with increasing frequency of use. The last study was conducted in New Zealand between 1995 and 1997 using children selected at birth and evaluated at 3, 5, and 11 years of age.

Data on prenatal exposures was obtained at birth by maternal interview and review of obstetric records. The parent completed the Connors Behavioral Rating Scale and the Strengths and Difficulties Questionnaire when the child was 7 and 11 years of age, and the child format of the Strengths and Difficulties Questionnaire was completed by children at 11 years. Significantly higher total difficulty scores were observed by parent report at 7 years of age and by child report at 11 years of age among children born to mothers who reported any acetaminophen use. No such associations were found for other medications including anti-inflammatories, aspirin-based analgesics, or antacids.

Although findings from these three studies are consistent, cautious interpretation is necessary. These studies exemplify the difficulty of conducting long-term neurodevelopmental follow-up, including poor and/or perhaps biased retention of study subjects and the difficulty of accounting for postnatal environmental influences and genetics. However, in all three studies published to date, the prevalence of use of acetaminophen in pregnancy approximated 50%. Given the widespread use of this OTC product, it is essential to pursue this important set of associations with further research.

**Antiemetics: Doxylamine**

Doxylamine succinate is a first-generation antihistamine that is effective as a short-term sedative and is an ingredient in some OTC sleep aids. Between 1958 and 1983, doxylamine was an ingredient in the product Bendectin, an anti-nauseant that was commonly used for the treatment of nausea and vomiting of pregnancy. Bendectin was withdrawn from the market by the manufacturer on the basis of reports of birth defects attributed to prenatal exposure to the drug. However, numerous subsequent epidemiological studies consistently did not support increased risks for this product. Meta-analyses of 17 and 27 studies found no increased risks for all birth defects combined or for specific defects, respectively.

OTC sleep aids containing doxylamine have been used “off-label” in combination with OTC vitamin B6 to treat nausea and vomiting of pregnancy on the basis of the volume of data showing null findings for Bendectin.

**Conclusion**

Assumptions of safety for OTC products can be based on long experience with their use and the fact that no prescription is required. However, in the absence of data, these assumptions may be incorrect. Challenges in studying the safety of OTC products in pregnancy are great, including validation of exposure timing and dose. However, the public health impact of even small elevations in risk for these products could be large given the high prevalence of use of many OTC medications such as acetaminophen. Research to detect or rule out these risks is essential.

**References**