

Evidence in Action:

Acetaminophen Use During Pregnancy

By Robert Vining, DC, and Julie Hartman, DC



WE RECENTLY CONSIDERED THE QUESTION, “Is it safe to take acetaminophen during pregnancy?” To accurately answer this relatively simple question, we searched the literature for evidence.

Using the search terms “pregnancy,” “safety,” and “acetaminophen” in a popular search engine, we first examined an article published in the journal, *American Family Physician*, which states that over-the-counter pain medications are categorized by the Food and Drug Administration (FDA).¹ Acetaminophen is classified as category B, meaning that although no adverse effects were reported in animal reproduction studies, risks have not been fully quantified in humans. Because the article is 11 years old and not based on primary research, however, we decided to confirm the current classification and find more recent research-based information.

In doing so, we discovered that the FDA no longer categorizes medications as it did in 2003. The categories were removed due to the limitations in accurately conveying risk and benefit and because the category system had the potential to mislead providers and women.² We had to look further to answer the original question of whether or not it is safe to take acetaminophen during pregnancy.

An evidence-based consideration

To better understand what risks are associated with acetaminophen use during pregnancy, we placed the following words into the PubMed search area: “Safety, Acetaminophen, and Pregnancy.” The subsequent search resulted in approximately 30 articles. One article that caught our attention was published in the April 2014 issue of *JAMA Pediatrics* and entitled, “Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders,” by Zeyan Liew, MPH; Beate Ritz, MD, PhD; Cristina Rebordosa, MD, PhD et al.³

Study description

Liew, et al. analyzed findings from the Danish National Birth Cohort (DNBC), which is a Danish nationwide research program focusing in part on pregnancy, infants, and childhood disease. Investigators designed the study to determine if an association existed between acetaminophen use during pregnancy and an increased risk for developing attention-deficit/hyperactivity disorder (ADHD)-like behaviors or hyperkinetic disorders (HKDs) in children. ADHD is generally considered to be a broad diagnosis, characterized by impulsiveness, hyperactivity, and/or inattention behaviors. HKD, however, is diagnosed when a child exhibits all three of the previously mentioned behaviors, which makes HKD a narrower diagnostic subcategory of ADHD.⁴

Study team members conducted phone interviews with expectant mothers from 1996 to 2002. More than 64,000 study participants were recruited through general practitioners when these women were between 6 and 12 weeks of gestation. Phone interviews included many lifestyle questions including over-the-counter pain medication use.

HKD was defined by investigators as those children who received an HKD diagnosis after age 5. ADHD behaviors were defined by the following two criteria: 1) the Danish Prescription Registry documented two or more filled ADHD prescriptions; and 2) Strengths and Difficulties Questionnaire (SDQ) scores indicated the condition. The SDQ is an assessment tool for children ages 4 to 16 years composed of 25 questions in the categories of hyperactivity, peer relationships, prosocial behavior, conduct and emotional symptoms.⁵

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Mothers or main caregivers completed the SDQ when children reached age 7.

Factors that could potentially confuse or confound interpretation were mitigated through a statistical process called adjusting. Multiple confounders were adjusted for in this study including items, such as socioeconomic status, smoking and alcohol consumption during pregnancy.

Limitations

In this study, recall bias is a potential limitation. Some mothers were not able to remember their medication use and some may have remembered incorrectly. When a mother was unable to remember when she took the medication, investigators based the analysis on the trimester of pregnancy in which the interview occurred rather than a gestational week. Dose and frequency information were not analyzed because of the difficulty in accurate recall. Though several potential confounding factors were accounted for, there is no way to know if all factors that can influence results were recognized (such as genetic factors or the reason for taking acetaminophen).

Study findings

We can glean from the study by Liew, et al. that there is an increased risk for ADHD-like behaviors and HKD when acetaminophen is taken during pregnancy for relatively long periods and throughout multiple trimesters. Additional research is needed to determine whether acetaminophen plays a direct or indirect role in causing these disorders.

Synthesizing the evidence

When we review the results of the study by Liew, et al. we find that there is no straightforward answer to the question, “Is it safe to take acetaminophen during pregnancy?” The article informed us that prolonged regular acetaminophen use by a mother during pregnancy resulted in an increased risk for the child to develop HKD or ADHD-like behavioral problems. The risks, however, are difficult to quantify, especially with results from a single study. The highest risks occur when acetaminophen is taken during the 2nd and 3rd trimesters and when it is taken for more than 20 weeks. Short duration use (less than one week) did not show an increased risk.

The authors cite studies suggesting mechanisms by which acetaminophen can potentially influence fetal development. Some literature suggest that with the capacity to cross the placenta, acetaminophen has the potential to increase the risk for cryptorchidism, asthma, and some

congenital malformations.⁶⁻⁸ However, potential mechanisms don't necessarily equate with increased risk. Therefore, an observational study like the one conducted by Liew, et al. is needed.

So how will we answer the question? Current research shows some increased risk for ADHD-like disorders in the presence of prolonged acetaminophen use during pregnancy. Short-term use does not show an increase in risk for the same disorders. There is some evidence to suggest that acetaminophen can cause other health problems in children but little is yet known about whether it actually does. Given the many scenarios from which this question could arise, we may also recommend a discussion with a family practice or obstetric physician to explore alternatives. Research in this area is ongoing and it is likely that we will know more in the coming months or years, at which point we should be able to provide more definitive risk information. However, that will mean we need to again review current literature.

Clinicians are aware, of course, that evidence-based practice is comprised of 3 parts: 1) clinician judgment; 2) patient preference/values; and 3) best available scientific evidence. Anyone who works with the literature has come up against the fact that evidence is often inconclusive or sparse. In such cases, it is good practice to ask patients for their thoughts on the topic before arriving at a treatment decision. ■

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