

FPIN's Clinical Inquiries

Prenatal Acetaminophen Use and Attention-Deficit/Hyperactivity Disorder

Stephanie Matosich, DO, and Gary Kelsberg, MD, Providence Spokane Family Medicine Residency, Spokane, Washington
Sarah Safranek, MLIS, University of Washington, Seattle, Washington

Clinical Question

Is maternal prenatal acetaminophen use associated with increased rates of attention-deficit/hyperactivity disorder (ADHD) in offspring?

Evidence-Based Answer

Pregnant patients should discuss acetaminophen use with their maternal health care professional because it is associated with an increased risk of ADHD in offspring. (Strength of Recommendation [SOR]: B, systematic review and meta-analysis of prospective cohort studies.) ADHD is most strongly related to prolonged antepartum use of acetaminophen (28 days or greater) and use during the third trimester. Fever and infections in the first trimester may also be associated with an increased risk of ADHD and may be a reason for increased acetaminophen use. (SOR: C, large prospective cohort studies with conflicting results.)

Evidence Summary

A systematic review and meta-analysis of eight prospective cohort studies ($n = 244,940$) evaluating a possible connection between maternal prenatal acetaminophen use and the development of ADHD in offspring found an increased risk

overall (relative risk [RR] = 1.25; 95% CI, 1.17 to 1.34), with use of 28 or more days (RR = 1.63; 95% CI, 1.23 to 2.16), and with any use during the third trimester (RR = 1.26; 95% CI, 1.08 to 1.47).¹ The authors included studies from Europe (five), the United States (two), and Oceania. Six studies were rated high quality, and two were moderate quality. Seven studies used self-reported questionnaires during pregnancy, mainly during the second and third trimesters, to assess days of maternal acetaminophen use (one study used serum biomarkers; no study measured the dose or frequency). The eight studies used six standardized measures to diagnose ADHD in offspring. Study participants were followed for an average of 6.3 years (follow-up = 1.2 to 16 years).

Among the offspring of patients who did not take acetaminophen, the average prevalence of ADHD was 4%.¹ Most studies evaluated and eliminated potential confounders (i.e., education level; socioeconomic status; and prepregnancy health, including maternal mental health, age, parity, smoking, and alcohol use). Six of the eight studies evaluated maternal febrile illness during pregnancy and found no correlation with ADHD in their offspring. Three studies ($n = 191,836$) found no association between second-trimester acetaminophen use and ADHD (RR = 1.06; 95% CI, 0.95 to 1.17), and three studies ($n = 225,926$) found no association with ADHD when acetaminophen was used for fewer than 28 days during pregnancy. The authors described three potential weaknesses in the meta-analysis. The self-reported use of acetaminophen potentially limits the accuracy of dosing and timing data. Six different diagnostic methods and the range of follow-up times, including very young ages at which ADHD is not usually diagnosed, could introduce variation in the assessment for the disorder.

Three of the four subsequent large, prospective, cohort studies found a similar association between maternal acetaminophen use in pregnancy and ADHD in offspring.²⁻⁴

The most recent study reported an increase in attention problems at three years of age ($n = 2,423$; adjusted odds ratio [aOR] = 1.21; 95% CI, 1.01 to 1.45) among the first babies of predominantly educated women with private insurance.² The authors used the Child Behavior Checklist to determine attention problems (not a formal diagnosis of ADHD) and an interview in the third trimester to assess acetaminophen use (not characterized for dose, length, or pregnancy-specific

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This series is coordinated by John E. Delzell Jr., MD, MSPH, associate medical editor.

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Author disclosure: No relevant financial relationships.

months of use). The study accounted for potential maternal confounders (i.e., education; self-reported race and ethnicity; marital status; and prepregnancy health, including mental health, smoking, and alcohol use). The second study found that acetaminophen use during pregnancy, but not before or after pregnancy, was associated with an increased risk of ADHD in offspring (n = 8,856; aOR = 1.34; 95% CI, 1.05 to 1.72).³ The authors used maternal self-reporting to assess acetaminophen use and whether offspring had a formal diagnosis of ADHD.

The third study found that maternal antepartum acetaminophen use was associated with hyperactivity/inattention in boys six years of age (n = 4,231; aOR = 1.42; 95% CI, 1.06 to 1.92) but not at 11 years of age, and not in girls at either age.⁴ The authors assessed acetaminophen use by maternal self-report during a postpartum interview. Psychologists scored the children for hyperactivity/inattention with the Strengths and Difficulties Questionnaire.

A fourth cohort study evaluated a subset of 996 mother-baby dyads for which cord plasma samples were available and found that an increased risk of ADHD was associated with offspring having the highest blood levels of acetaminophen metabolites.⁵ The authors recruited mother-baby dyads for whom cord plasma samples were available from 3,163 pairs in the Boston Birth Cohort and followed the offspring for 10 years. They compared the lowest vs. highest tertiles for acetaminophen metabolites and correlated them with physician-diagnosed ADHD (OR = 2.86; 95% CI, 1.77 to 4.67), controlling for confounders previously noted.

Two other studies evaluated the association between maternal antepartum acetaminophen use and ADHD in offspring and found conflicting correlations with gestational infections and maternal fever.^{6,7} A prospective cohort study (n = 114,000) evaluated the diagnosis of ADHD by standardized testing of offspring at eight years of age in mothers who had antepartum fever.⁶ The study found that ADHD was more common when maternal fever was noted during the first or second trimester vs. no fever (aOR = 1.30; 95% CI, 1.15 to 1.47), but there was no difference in ADHD risk between mothers who took acetaminophen (standardized mean difference = 0.08; 95% CI, -0.02 to 0.18) and those who did not (standardized mean difference = 0.10; 95% CI, 0.02 to 0.18). The second study followed children for 15 years and found an association between ADHD and maternal acetaminophen use in any trimester (n = 4,750; aOR = 1.20; 95% CI, 1.01 to 1.42); however, this was independent of gestational infections.⁷

Recommendations From Others

The Society for Maternal-Fetal Medicine Publications Committee recommends that physicians communicate the risks vs. benefits of acetaminophen use during pregnancy and consider it a reasonable and appropriate medication for pain or fever during pregnancy.⁸

The American College of Obstetricians and Gynecologists states that acetaminophen is one of the only safe pain relievers for pregnant patients, that no clear evidence proves a direct relationship between the use of acetaminophen during any trimester and fetal developmental issues, and that any medication taken during pregnancy should be used only as needed, in moderation, and after the pregnant patient has consulted with their health care professional.⁹

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Address correspondence to Stephenie Matosich, DO, at stephenie.matosich@providence.org. Reprints are not available from the authors.

References

- Gou X, Wang Y, Tang Y, et al. Association of maternal prenatal acetaminophen use with the risk of attention deficit/hyperactivity disorder in offspring: a meta-analysis. *Aust N Z J Psychiatry*. 2019;53(3):195-206.
- Sznajder KK, Teti DM, Kjerulff KH, et al. Maternal use of acetaminophen during pregnancy and neurobehavioral problems in offspring at 3 years: a prospective cohort study. *PLoS One*. 2022;17(9):e0272593.
- Liew Z, Kioumourtzoglou MA, Roberts AL, et al. Use of negative control exposure analysis to evaluate confounding: an example of acetaminophen exposure and attention-deficit/hyperactivity disorder in Nurse's Health Study II. *Am J Epidemiol*. 2019;188(4):768-775.
- Tovo-Rodrigues L, Schneider BC, Martins-Silva T, et al. Is intrauterine exposure to acetaminophen associated with emotional and hyperactivity problems during childhood? Findings from the 2004 Pelotas birth cohort. *BMC Psychiatry*. 2018;18(1):368.
- Ji Y, Azuine RE, Zhang Y, et al. Association of cord plasma biomarkers of in utero acetaminophen exposure with risk of attention-deficit/hyperactivity disorder and autism spectrum disorder in childhood. *JAMA Psychiatry*. 2020;77(2):180-189.
- Gustavson K, Ask H, Ystrom E, et al. Maternal fever during pregnancy and offspring attention deficit hyperactivity disorder. *Sci Rep*. 2019;9(1):9519.
- Chen MH, Pan TL, Wang PW, et al. Prenatal exposure to acetaminophen and the risk of attention-deficit/hyperactivity disorder: a nationwide study in Taiwan. *J Clin Psychiatry*. 2019;80(5):18m12612.
- Society for Maternal-Fetal Medicine (SMFM) Publications Committee. Prenatal acetaminophen use and outcomes in children. *Am J Obstet Gynecol*. 2017;216(3):B14-B15.
- American College of Obstetricians and Gynecologists. ACOG response to consensus statement on paracetamol use during pregnancy. September 29, 2021. Accessed July 3, 2023. <https://www.acog.org/news/news-articles/2021/09/response-to-consensus-statement-on-paracetamol-use-during-pregnancy> ■