

Acetaminophen in pregnancy and future risk of ADHD in offspring

Jill A. Blaser MSc MD CCFP G. Michael Allan MD CCFP

Clinical question

Does taking acetaminophen during pregnancy increase the future risk of attention deficit hyperactivity disorder (ADHD) in offspring?

Bottom line

Two high-quality cohort studies suggest an association between acetaminophen use in pregnancy and an increased risk of ADHD or similar behaviour in children. While cohort studies cannot prove causation, there might be a small risk with prolonged use of acetaminophen, especially in late pregnancy. Study limitations prevent specific conclusions.

Evidence

- In a Danish prospective cohort of 64 322 pregnancies,¹ acetaminophen use in pregnancy was associated with significantly higher scores for behavioural problems at 7 years (risk ratio 1.13, 95% CI 1.01 to 1.27).
 - In a central government registry (during about 11 years), there were significantly more
 - diagnoses of hyperkinetic disorder (hazard ratio 1.37, 95% CI 1.19 to 1.59); and
 - prescriptions for 2 or more ADHD medications (hazard ratio 1.29, 95% CI 1.15 to 1.44).
- In a Norwegian prospective cohort of 48 631 pregnancies with a focus on 2919 same-sex sibling pairs,² acetaminophen use for 28 or more days in pregnancy correlated significantly with maternally assessed (at 3 years) reduced gross motor skills, delay in walking, increased activity, reduced communication skills, and attention-seeking or aggressive behaviour.
 - Correlation β coefficients ranged from 0.2 to 0.26, an approximate 50% to 60% relative increase.
 - A study strength was studying sibling pairs (eliminating differences in mothers or families) and a weakness was the short duration and maternal assessment.
- Both studies (results inconsistent) suggest longer use and use later in pregnancy might have stronger associations.^{1,2}
- Older cohort of 355 children found no association between maternal use of acetaminophen in the first 5 months of pregnancy and attention testing at age 4.³

Context

- Cohort studies show association but not causation. They are subject to “confounding” risk.
 - Women who use acetaminophen might have more pain or headaches, which perhaps contribute to ADHD.

- Based on a 5.3% worldwide prevalence of ADHD⁴ and a possible 13% to 37% relative increase,¹ the absolute increase might be 0.7% to 2%, if real.
- Acetaminophen is used by 55% to 65% of pregnant women.^{1,5,6}
- Acetaminophen is believed to be safe in pregnancy⁷ and is first-line treatment for pain owing to safety^{8,9}; these statements precede the recent research.^{1,2}

Implementation

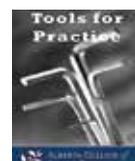
There are few options for analgesia that are safe in all 3 trimesters.¹⁰⁻¹² While acetaminophen has long been considered a safe treatment for headache, fever, and myalgia in pregnancy, the results from these 2 studies might cause us to reconsider the timing and amount of acetaminophen that we recommend. However, making definitive conclusions about acetaminophen causing ADHD in children would be interpreting the data inaccurately, as there might be confounding risks. Further evidence is needed to prove causation. 🌿

Dr Blaser is Assistant Professor in the Department of Academic Family Medicine at the University of Saskatchewan in Saskatoon. Dr Allan is Professor in the Department of Family Medicine at the University of Alberta in Edmonton.

The opinions expressed in Tools for Practice articles are those of the authors and do not necessarily mirror the perspective and policy of the Alberta College of Family Physicians.

References

1. Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. *JAMA Pediatr* 2014;168(4):313-20.
2. Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. *Int J Epidemiol* 2013;42(6):1702-13.
3. Streissguth AP, Treder RP, Barr HM, Shepard TH, Bleyer WA, Sampson PD, et al. Aspirin and acetaminophen use by pregnant women and subsequent child IQ and attention decrements. *Teratology* 1987;35(2):211-9.
4. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and meta-regression analysis. *Am J Psychiatry* 2007;164(6):942-8.
5. Thorpe PG, Gilboa SM, Hernandez-Diaz S, Lind J, Cragan JD, Briggs G, et al. Medications in the first trimester of pregnancy: most common exposures and critical gaps in understanding fetal risk. *Pharmacoepidemiol Drug Saf* 2013;22(9):1013-8.
6. Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. *Am J Obstet Gynecol* 2005;193(3 Pt 1):771-7.
7. Scialli AR, Ang R, Breitmeyer J, Royal MA. A review of the literature on the effects of acetaminophen on pregnancy outcome. *Reprod Toxicol* 2010;30(4):495-507.
8. Babb M, Koren G, Einarson A. Treating pain during pregnancy. *Can Fam Physician* 2010;56:25-7.
9. Clemente-Fuentes RJ, Pickett H, Carney M. How can pregnant women safely relieve low-back pain? *J Fam Pract* 2013;62(5):260-8.
10. Koren G, Florescu A, Costei AM, Boskovic R, Moretti ME. Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. *Ann Pharmacother* 2006;40(5):824-9.
11. Ofori B, Oraichi D, Blais L, Rey E, Bérard A. Risk of congenital anomalies in pregnant users of non-steroidal anti-inflammatory drugs: a nested case-control study. *Birth Defects Res B Dev Reprod Toxicol* 2006;77(4):268-79.
12. Nielsen GL, Sørensen HT, Larsen H, Pedersen L. Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study. *BMJ* 2001;322(7281):266-70.



Tools for Practice articles in *Canadian Family Physician (CFP)* are adapted from articles published on the Alberta College of Family Physicians (ACFP) website, summarizing medical evidence with a focus on topical issues and practice-modifying information. The ACFP summaries and the series in *CFP* are coordinated by Dr G. Michael Allan, and the summaries are co-authored by at least 1 practising family physician and are peer reviewed. Feedback is welcome and can be sent to toolsforpractice@cfpc.ca. Archived articles are available on the ACFP website: www.acfp.ca.