

# Acetaminophen in pregnancy and future risk of ADHD in offspring

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### 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,<sup>1</sup> 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,<sup>2</sup> 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  $\beta$  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.<sup>1,2</sup>
- 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.<sup>3</sup>

### 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 ADHD<sup>4</sup> and a possible 13% to 37% relative increase,<sup>1</sup> the absolute increase might be 0.7% to 2%, if real.
- Acetaminophen is used by 55% to 65% of pregnant women.<sup>1,5,6</sup>
- Acetaminophen is believed to be safe in pregnancy<sup>7</sup> and is first-line treatment for pain owing to safety<sup>8,9</sup>; these statements precede the recent research.<sup>1,2</sup>

### Implementation

There are few options for analgesia that are safe in all 3 trimesters.<sup>10-12</sup> 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. 🌿

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