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Prenatal Acetaminophen Use and Autism

Summary: Prenatal Acetaminophen Use and Autism

- Acetaminophen has been the drug of choice for treatment of fever and pain during pregnancy for decades.
- The US Department of Health and Human Services has issued an announcement expressing concern about a potential link between acetaminophen exposure *in utero* and neurodevelopmental disorders such as autism.
- Data from observational studies have been conflicting, but higher-quality studies have been less likely to show an association between maternal acetaminophen use and neurodevelopmental disorders in their offspring.
- Fever during pregnancy has itself been associated with adverse neurodevelopmental outcomes, and it can cause neural tube defects during the first trimester.
- Alternative drugs for treatment of fever or pain (e.g., NSAIDs, opioids) have been associated with significant toxicity when used during pregnancy.
- Major professional organizations continue to recommend acetaminophen for first-line treatment of fever and pain during pregnancy.

Acetaminophen has been considered the drug of choice for treatment of fever and pain during pregnancy for decades, but a recent announcement by the US Department of Health and Human Services (HHS) has prompted discussion about its effects on fetal neurodevelopment and the risk of autism.

THE ANNOUNCEMENT — The HHS announcement claims that chronic acetaminophen use in pregnant women, especially late in pregnancy, may cause long-term neurological effects such as autism in their children.[1] The announcement cites a "consensus statement" that calls for minimizing use of acetaminophen during pregnancy.[2] The consensus statement has not been endorsed by any professional organizations and has been criticized for misrepresenting the studies that it references and failing to account for potential confounding variables.[3]

In conjunction with the HHS announcement, the FDA has issued a letter to physicians stating that it will add information on neurodevelopmental risks to the labels of acetaminophen products.[4,5] The letter suggests that acetaminophen toxicity could be caused by the inability of the fetus' developing liver to metabolize the drug adequately.[4] Some scientists have theorized that depletion of maternal glutathione levels during pregnancy could result in excessive fetal exposure to the toxic acetaminophen metabolite NAPQI.[6]

CLINICAL STUDIES — Data from observational studies evaluating whether acetaminophen exposure *in utero* is associated with neurodevelopmental disorders have been conflicting.[6-13]

FDA-Cited Studies – The FDA cited two studies to support its decision to amend the labels of acetaminophen products.[4]

One study included 8856 children born in the US between 1993 and 2005 to women in the Nurses' Health Study II cohort. Regular acetaminophen use during pregnancy (defined as ≥2 days/week before 1995 and ≥1 day/week afterwards) was associated with an increased risk of an attention-deficit/hyperactivity disorder (ADHD) diagnosis in the child (10.2% vs 7.8% without regular use), but in complete case analyses that adjusted for confounding variables (e.g., maternal age, household income, drinking or smoking during pregnancy), the difference was not statistically significant. This study did not evaluate rates of autism.[7]

In a study from the Boston Birth Cohort in a subgroup of 996 children born between 1998 and 2018, increased levels of acetaminophen or its metabolites in cord plasma were associated with higher rates of autism diagnosis. Use of cord plasma levels, which only reflect perinatal acetaminophen exposure, as a proxy for overall exposure *in utero* has not been validated, and the population studied was unrepresentative of the general population (100% of tested samples contained acetaminophen or its metabolites; 37% of subjects were ultimately diagnosed with autism or ADHD).[8] This study has also been criticized for having weak analytical methods.[3]

Other Studies – In a population study of ~2.5 million children born in Sweden between 1995 and 2019, maternal use of acetaminophen was associated with an increased risk of autism (absolute risk difference 0.09% vs no acetaminophen use; HR 1.05 [95% CI

1.02-1.08]). In an analysis that compared matched full siblings to reduce the effect of confounding variables, *in utero* acetaminophen exposure was not associated with an increased risk of autism (HR 0.98).[9]

In a population study of 217,602 children born in Japan between 2005 and 2022, maternal use of acetaminophen was not significantly associated with development of autism spectrum disorder in either the overall population (adjusted HR 1.06; 95% CI 0.98-1.15) or a sibling-matched analysis (adjusted HR 0.85; 95% CI 0.64-1.13).[10]

In a prospective observational study of 64,322 children born in Denmark between 1996 and 2002, maternal use of acetaminophen during pregnancy was associated with an increased risk of a subsequent autism spectrum disorder diagnosis compared to no acetaminophen use (incidence rate 1.36 vs 1.12 cases/1000 person years; adjusted HR 1.19 [95% CI 1.04-1.35]), but not with a significant increase in the risk of infantile autism. The association was statistically significant in children who had been diagnosed with hyperkinetic disorders, such as ADHD, but not in those without hyperkinetic disorders. This study did not perform a sibling-matched analysis.[11]

In a prospective study of 2644 children born in Spain between 2004 and 2008, maternal use of acetaminophen during pregnancy was associated with increased scores on the Childhood Autism Spectrum Test (CAST) in males, but not in females or in the overall population. The study did not evaluate overall rates of autism diagnosis or perform a sibling-matched analysis.[12]

A recently published review article asserts that evidence supports a link between acetaminophen exposure *in utero* and neurodevelopmental disorders,[13] but the review uses an atypical methodology ("Navigation Guide") and its assessments of evidence quality and risk of bias are suspect.

An article published after the HHS announcement evaluated 9 systematic reviews (40 studies in total) that reported on prenatal acetaminophen exposure and a subsequent diagnosis of autism or ADHD in the offspring. Based on the results of an assessment using a validated appraisal tool (AMSTAR 2), the authors expressed low to critically low confidence in the findings of the reviews and concluded that available evidence is insufficient to definitively link *in utero* acetaminophen exposure and autism and ADHD in childhood.[14]

EFFECT OF FEVER — Fever during pregnancy has itself been associated with neurodevelopmental disorders in the offspring.[15] In a prospective study of 114,500 children born in Norway between 1999 and 2009, maternal prenatal fever was associated with an increased risk of autism spectrum disorder (adjusted odds ratio 1.34; 95% CI 1.07-1.67). The correlation was weaker among children whose mothers took acetaminophen than in those whose mothers did not.[16] Maternal hyperthermia during the first trimester of pregnancy has also been associated with development of neural tube defects, such as spina bifida.[17]

ALTERNATIVES — Acetaminophen is an effective antipyretic and a modestly effective analgesic. It has been recommended for treatment of pain and fever in pregnant women for decades because other drugs for fever or musculoskeletal pain have been associated with toxicity when taken during pregnancy.

Exposure to **NSAIDs** (including aspirin) around the time of conception or during pregnancy has been associated with an increased risk of miscarriage,[18] but the data are weak. Use of NSAIDs after 20 weeks' gestation can cause fetal renal dysfunction, which could lead to low amniotic fluid levels and neonatal renal impairment. Use after 30 weeks' gestation can cause premature closure of the ductus arteriosus.[19]

Opioid use during pregnancy has been associated with preterm delivery, poor fetal growth, stillbirth, birth defects (e.g., neural tube defects, congenital heart defects, gastroschisis), poor physiological development, and neurodevelopmental disorders.[20,21] It can also lead to neonatal opioid withdrawal syndrome. Opioid withdrawal during pregnancy has been associated with spontaneous abortion and premature labor.[22]

Suzetrigine (*Journavx*), a sodium channel blocker that was approved by the FDA earlier in 2025 for treatment of moderate to severe acute pain, has not been studied adequately in pregnant women. In animal studies, it has been associated with pre- and post-implantation loss and postnatal mortality.[23]

SOCIETY RECOMMENDATIONS — Major professional organizations, such as the American College of Obstetricians and Gynecologists, the Society of Obstetricians and Gynaecologists of Canada, and the European Network of Teratology Information Services, continue to recommend acetaminophen for first-line treatment of fever and pain during pregnancy.[24-26]

CONCLUSION — Data from observational studies evaluating whether acetaminophen exposure *in utero* is correlated with subsequent neurodevelopmental disorders have been conflicting, but higher-quality studies have been less likely to show an association. A causal relationship has not been established. Since no acceptable pharmacologic alternatives are available, acetaminophen should remain the drug of choice for fever and pain during pregnancy. As with any drug, it would be prudent to advise pregnant women to take acetaminophen in the lowest effective dose for the shortest possible duration of time. ■

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