

Pre-natal Acetaminophen & ADHD: Small Risk, But Unwarranted Fear



By Chuck Dinerstein — April 25, 2018

A recent meta-analysis of the impact of prenatal acetaminophen on Attention Deficit Hyperactivity Disorder and Autism vacillates between the academic need to publish a positive finding, and the clinical need to put findings into context for patients.



Courtesy: Nina Matthews derivative
work: Babypedia [1]

The *Journal of Epidemiology* published a meta-analysis of the possible relationship between prenatal exposure to acetaminophen and subsequent attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in their offspring. You know how these “studies” work, they reviewed the literature, identified seven papers with a total of more than 132,000 “mother and child pairs,” pooled the data and reported relative risks. For ADHD, acetaminophen use resulted in a 30% increase, for ASD 24%.

There are problems in the selection of studies on two accounts, which they explicitly report. All of the papers had a high or intermediate risk of bias, and there was a lot of heterogeneity among the studies. In short, they were often comparing apples to oranges, and because positive results are published more often than negative results, there was a thumb on the scale. To their credit, the authors point these difficulties out repeatedly. Let us suspend our disbelief, accept the findings, and get to the heart of the problem – the way in which they frame the clinical effect and the

narrative that follows.

Relative vs. Absolute Risk

The pooled results are given as a ratio or relative risk. This is often the measure of scoundrels because it makes an effect sound more significant. Nowhere in the paper are actual numbers of children affected by ADHD or AUD provided. You have to know that yourself. According to the CDC ADHD can affect 8-11% of our population, ASD 0.6%. So let us try and put their finding of a 30 and 24% increased risk respectively in context. For the 132,000 mother-child pairs, taking acetaminophen increased the absolute risk by 3% for ADHD (4,000 additional cases) and by 0.14% for ASD (190 additional cases). Which sounds more dramatic? More importantly, which number describes the clinical effect of acetaminophen more appropriately? I would argue that it is these much smaller, by a factor of 10, increases in the absolute risk.

Having their cake and eating it too

They conclude that “our analysis of the available evidence indicates that acetaminophen exposure during pregnancy is associated with a 20-30% increased risk for neurodevelopmental disorders.” But in the very next sentence, they begin to walk back that position, recommending that “results should be interpreted with caution.” Amongst the reasons they cite,

- The lack of studies resulted in selections that were heterogeneous (the apples to oranges comparison) concerning outcomes and definitions.
- Acetaminophen “exposure assessment and validation is limited” – it was recalled rather than prospectively measured and acetaminophen in an over the counter product found in many “combined medical products.”
- There was confounding, e.g., acetaminophen may have been taken by women who had more comorbid conditions or who were taking other medications that might affect neurodevelopment. That is especially true for the women taking acetaminophen for the more extended time periods, the women where the effect was seen
- That the diagnosis of ADHD and ASD were not always made by trained individuals, but by parents, teachers and even the responses of children – “add difficulty in interpreting the clinical significance of the results.”
- That the observed effect decreased with maternal age, a known risk factor for ADHD and ASD
- ASD is strongly associated with advancing paternal age, none of the studies reported this variable.

Here is the statement from one of the authors

*“Our findings suggest an association between prolonged acetaminophen use and an increase in the risk of autism and ADHD. However, **the observed increase in risk is small and existing studies have significant limitations.** While unnecessary use of any medication should be avoided in pregnancy, we believe **our findings should not alter current practice and women should not avoid use of short term acetaminophen when clinically needed**”*

.” (*Emphasis added*)

What is the clinical value of such a flawed meta-analysis? It doesn't change care, and it raises “concern” that the casual reader may believe is more valid than a careful reading of the evidence supports. The measures they report and their subsequent equivocating around their conclusion frame sheds more shadow than light.

Source: Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autism Spectrum Disorder: A Systemic Review, Meta-Analysis, and Meta-Regression Analysis of Cohort Studies American Journal of Epidemiology DOI:10.1093/aje/kwy086

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[1] https://upload.wikimedia.org/wikipedia/commons/3/3f/Silhouette_or_a_pregnant_woman_and_her_partner-14Aug2011_clean.jpg