Clinical and Practical **Psychopharmacology**

Use of Acetaminophen (Paracetamol) During Pregnancy and the Risk of Attention-Deficit/Hyperactivity Disorder in the Offspring

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Prenatal exposure to acetaminophen may result in compromised neurodevelopment through inflammatory and immunologic mechanisms, through predisposition to oxidative stress, and through endocrine, endogenous cannabinoid, and other mechanisms. Several small and large prospective studies have found an association between gestational acetaminophen exposure and attention-deficit/hyperactivity disorder (ADHD)-like behaviors, use of ADHD medication, and ADHD diagnoses in offspring during childhood; the only negative study was a small investigation that examined only one aspect of attention as an outcome. Creditably, most of the studies adjusted analyses for many (but not all) confounds associated with ADHD risk. Importantly, one pivotal study also adjusted for pain, infection, inflammation, and fever to reduce confounding by indication; this study found a dose-dependent risk. In the light of the finding of a single study that infection and fever during pregnancy by themselves do not raise the ADHD risk, it appears possible that the use of acetaminophen during pregnancy is itself responsible for the increased risk of ADHD. This suggests that acetaminophen may not be as safe in pregnancy as is widely believed. However, since fever during pregnancy may itself be associated with adverse gestational outcomes, given the present level of uncertainty about the ADHD risk with acetaminophen, it is suggested that, until more data are available, the use of acetaminophen in pregnancy should not be denied in situations in which the need for the drug is clear.

J Clin Psychiatry 2016;77(3):e312–e314
dx.doi.org/10.4088/JCP.16f10721

Introduction

Infections may occur during any trimester of pregnancy, and an infectious organism that crosses the placental barrier may harm the developing fetus. Inflammation, which can also occur during pregnancy, and infection are each associated with inflammatory and immunologic changes in blood and tissues, and elements of the maternal host response may also cross the placental barrier; it is theoretically conceivable that these too may compromise fetal neurodevelopment. Finally, drugs used in the treatment of fever and pain, which are symptoms of infection and inflammation, may also cross the placenta and affect the fetus.

Acetaminophen (paracetamol), which is available over the counter in most countries, is commonly used to treat fever and pain. Many recent studies have identified an association between acetaminophen use during pregnancy and adverse neurodevelopmental outcomes during childhood. Do the data suggest a causal link? This article presents a qualitative review of one specific aspect of the subject: the relationship between prenatal use of acetaminophen and the risk of attention-deficit/hyperactivity disorder (ADHD) in the offspring. Articles for this review were sourced through a PubMed search conducted on February 3, 2016, using combinations of the search terms *acetaminophen* (or *paracetamol*), *fever, pregnancy*, and *ADHD*.

Acetaminophen in Pregnancy

Acetaminophen is widely considered to be safe for use during pregnancy,[1,2] and gestational exposures have been found to lie in the 46%–65% range.[3–5] Acetaminophen is hypothesized to have the potential to compromise neurodevelopment in the fetal and infant brain through its effects on inflammatory and immunologic mechanisms, through possible predisposition to oxidative stress, and through endocrine, endogenous cannabinoid, and other mechanisms.[2,5–9] Possible adverse consequences include neurodevelopmental impairments,[4] autism spectrum disorder (ASD),[5] and ADHD. Mechanisms and possible association with ASD were examined in an earlier article in this column[10] and will not be repeated in this article.

Prenatal Acetaminophen Exposure, Attention, and Hyperactivity

Streissguth et al[11] examined the effect of prenatal exposure to acetaminophen, ascertained during the fifth month of pregnancy, on intelligence and attention in the offspring at age 4 years. The sample sizes were 421 and 355, respectively, for these two outcome variables. The analysis adjusted for several potential confounds, including demographics, other prenatal exposures, and lifestyle and environmental variables. The authors found that acetaminophen exposure was not associated with either IQ scores on a standard scale or errors of commission and omission in a computerized vigilance task.

Brandlistuen et al[4] examined data drawn from the prospective Norwegian Mother and Child Cohort Study. Gestational exposure to acetaminophen was recorded around weeks 17 and 30 of pregnancy. There were 48,631 children, including 2,919 same-sex sibling pairs. Neurodevelopmental outcomes were assessed at age 3 years. Analyses

Clinical Points

- There are many theoretical mechanisms through which gestational exposure to acetaminophen (paracetamol) may compromise neurodevelopmental outcomes in the offspring.
- Many studies suggest that prenatal exposure to acetaminophen increases the risk of attention-deficit/hyperactivity disorder (ADHD) in the offspring during childhood. The risk may be dose-dependent.
- Fever does not raise the ADHD risk but is associated with other adverse gestational outcomes. It may therefore be best to not restrict the use of acetaminophen during pregnancy in situations in which the need for the drug is clear.

were adjusted for potential confounds, such as maternal age, alcohol use, smoking, febrile illness, infections, and other medication use during pregnancy. In the sibling-control analysis (134 discordant pairs, 1,346 concordant pairs), 28 or more days of gestational exposure to acetaminophen was associated with impairments in externalizing behaviors and with higher activity level. In the exposed versus unexposed analysis (n = 26,213), gestational exposure to acetaminophen was associated with impairments in externalizing behaviors after exposures of 1 to 27 days as well as > 27 days. Ibuprofen exposures, in contrast, were not associated with neurodevelopmental outcomes.

Liew et al[5] examined data from the Danish National Birth Cohort in which gestational exposure to acetaminophen was assessed at weeks 12 and 30 in 64,322 mothers with singleton livebirths. Autism spectrum disorder (ASD) diagnoses were ascertained in the children at a mean age of 12.7 years. Analyses were adjusted for confounds such as demographics, maternal medical and psychiatric health, maternal use of alcohol and tobacco, and exposure to other medications, including antidepressants. Acetaminophen exposure (reported by more than half of the mothers) was associated with ASD only when ASD was comorbid with a hyperkinetic condition, and the risk was higher with greater cumulative weeks of exposure only when ASD was accompanied by a hyperkinetic disorder diagnosis. The studies of Brandlistuen et al[4] and Liew et al[5] were examined in greater detail in the previous article in this column.[10]

Prenatal Acetaminophen Exposure and ADHD

Using the same sources as in their study[5] described in the previous section, Liew et al[12] examined the association between prenatal acetaminophen exposure and a registry diagnosis of ADHD. Analyses were adjusted for a large number of potential demographic-, maternal-, paternal-, and child-derived confounds, including those related to pain, fever, infection, and inflammation (however, family history of ADHD was not adjusted for). The authors[12] found that prenatal exposure to acetaminophen was associated with an increased risk of an *ICD-10* hyperkinetic disorder diagnosis (hazard ratio [HR] = 1.37; 95% CI, 1.19–1.59), an increased use of ADHD medications (HR = 1.29; 95% CI, 1.15–1.44), and an increased risk of ADHD-like behaviors (risk ratio [RR] = 1.13; 95% CI, 1.01–1.27) at age 7 years. A dose-dependent relationship appeared possible: when acetaminophen exposure occurred during > 1 trimester, and with greater frequency (in weeks), the strength of the associations was observed to increase.

Thompson et al[13] studied members of the Auckland Birthweight Collaborative Study, which comprised 871 infants disproportionately sampled for being small for gestational age. Drug use during pregnancy was ascertained through inquiry from the mother after childbirth. Analyses were adjusted for confounds such as demographics, birthweight, and antenatal maternal stress. The authors found that acetaminophen, used prenatally by 49.8% of the mothers, was associated with higher ADHD-like behaviors in the offspring at ages 7 and 11 years, as assessed using the Strengths and Difficulties Questionnaire. Gestational acetaminophen use was also associated with an increased risk of hyperactivity/impulsivity (but not inattention), as assessed using the Conners' scale at age 7 but not 11 years. No significant associations were identified between gestational exposure to aspirin, antacids, or antibiotics and the risk of ADHD behavior. However, in this study a formal diagnosis of ADHD was not made, and analyses were not corrected for multiple hypothesis testing.

Prenatal Infection/Fever Exposure and ADHD

The preceding sections suggest that there is a probable relationship between prenatal exposure to acetaminophen and increased risk of ADHD with hyperactivity (but perhaps not inattention) in the offspring. Acetaminophen is most likely to be used in pregnancy to treat fever, which in turn is most likely to result from an infection. So, might acetaminophen exposure merely be a proxy for infection and fever in the relationship described?

Dreier et al[14] used data from the Danish National Birth Cohort to determine whether there was an association between fever/infection and the risk of childhood ADHD (N = 89,146 pregnancies). Information about fever/infection was ascertained twice during pregnancy, between weeks 7 and 40 (mostly at weeks 12 and 30). ADHD was registry-ascertained in the offspring with follow-up to a mean age of 10.6 years. Analyses were adjusted for demographics, maternal illness, maternal smoking, maternal stress, gestational age at birth, birth weight, and other potential confounds. Importantly, analyses were also adjusted for antipyretic use.

Fever was reported by 28% of women, and infection, by 60%. ADHD was identified in 2% of the sample. Neither fever (adjusted hazard ratio [aHR] = 1.03; 95% CI, 0.93–1.13) nor infection (aHR = 1.01; 95% CI, 0.92–1.11) during pregnancy was associated with ADHD risk. Additionally, a higher degree or longer duration of fever was also unassociated with ADHD risk. In exploratory analyses, only genitourinary infection, and fever specifically during weeks 9–12 of gestation, were associated with small but significant increases in ADHD risk; these findings cannot be discounted, but could be a false-positive error resulting from multiple hypothesis testing.

The authors[14] presented a good discussion on the limitations of their study; additionally, this single study cannot discount the possibility that acetaminophen use is merely a marker for ADHD risk with infection/fever as the contributory factor. Nevertheless, as the literature stands, the possibility that prenatal exposure to acetaminophen itself increases the risk of childhood ADHD cannot be ruled out.

Implications

As stated in the introduction, acetaminophen is commonly used during pregnancy. Given that randomized controlled trials of the safety of the drug during pregnancy will probably never be conducted, it becomes important for prospective birth cohort studies, similar to those of Liew et al,[5,12] to carefully examine the effects of gestational exposure to pain, infection, fever, inflammatory markers, acetaminophen, and other analgesic and antipyretic drugs on the risk of ADHD in the offspring. Potential confounds, including genetic risk and postnatal variables, will need to be comprehensively identified, measured, and adjusted for.

Until such a time as new information becomes available, the literature examined in this article suggests a review of the widespread opinion that acetaminophen is safe during pregnancy.[1,2] Whereas there is certainly no cause for alarm, as yet, perhaps a case can be made to limit the use of acetaminophen during pregnancy to only those situations in which the need for the drug is clear. Wherever feasible, nonpharmacological approaches should be considered, such as for pain management.

Fever during pregnancy, especially during the first trimester, is associated with adverse gestational outcomes.[15,16] It is not clear whether the adverse outcomes are a consequence of the fever or of whatever it was that caused the fever (eg, an infectious organism). Nevertheless, due consideration must be given to the possibility that the judicious use of acetaminophen to control fever might be protective during gestation.

Readers interested in a critical commentary on technical aspects of the subject are referred to the scholarly article of Cooper et al.[17]

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