Clinical and Practical **Psychopharmacology**

Use of Acetaminophen (Paracetamol) During Pregnancy and the Risk of Autism Spectrum Disorder in the Offspring

Chittaranjan Andrade, MD

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.

Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, India (candrade@psychiatrist.com).

ABSTRACT

Acetaminophen (paracetamol) is available over the counter in most countries and is widely considered to be safe for use during pregnancy; studies report gestational exposures to acetaminophen that lie in the 46%–65% range. Acetaminophen influences inflammatory and immunologic mechanisms and may predispose to oxidative stress; these and other effects are hypothesized to have the potential to compromise neurodevelopment in the fetal and infant brain. Two ecological studies suggested that population-level trends in the use of acetaminophen were associated with trends in the incidence/prevalence of autism; one of these studies specifically examined acetaminophen use during pregnancy. One large prospective observational cohort study found that gestational exposure to acetaminophen (especially when the duration of exposure was 28 days or more) was associated with motor milestone delay, gross and fine motor impairments, communication impairment, impairments in internalizing and externalizing behaviors, and hyperactivity, all at age 3 years; however, social and emotional developmental behaviors were mostly unaffected. A very recent large cohort study with a 12.7-year follow-up found that gestational exposure to acetaminophen was associated with an increased risk of autism spectrum disorder, but only when a hyperkinetic disorder was also present. In the light of existing data associating acetaminophen use during pregnancy and subsequent risk of attention-deficit/hyperactivity disorder, this new finding suggests that the predisposition, if any, is toward the hyperkinetic syndrome rather than to autism. In summary, the empirical data are very limited, but whatever empirical data exist do not support the suggestion that the use of acetaminophen during pregnancy increases the risk of autism in the offspring.

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Introduction

The association between maternal antidepressant use during pregnancy and the risk of autism spectrum disorder (ASD) in the child has been the subject of considerable research; positive associations, when identified, have received much adverse media publicity even though causality remains unproven.[1] In contrast, it is not commonly known that acetaminophen (paracetamol), a medication that is available over the counter in most countries and that is widely regarded as a safe drug for use during pregnancy,[2,3] has also been associated with neuropsychiatric risks, with neurodevelopmental delay,[4] ASD,[5] and even attention-deficit/hyperactivity disorder (ADHD)[6] described as possible consequences of prenatal use. This article examines the possible association between prenatal use of acetaminophen and ASD in the offspring. The subject is important because acetaminophen use is common in pregnancy, with exposures of 46%–65% reported.[4,5,7] The subject is particularly important because if the oft-cited rising incidence of ASD is due to a genuine increase in the number of new cases as opposed to use of looser diagnostic criteria or increased ascertainment, then environmental factors that might be responsible need to be identified and addressed.

Background

Over a decade ago, Torres[8] noted that autism is associated with maternal infection during pregnancy and, separately, that acetaminophen, used to treat fever associated with infection, interferes with cytokines that are important for brain development. Putting these 2 observations together, Torres[8] proposed the intriguing hypothesis that prenatal use of antipyretics such as acetaminophen can interfere with normal immunologic development of the fetal brain, leading to neurodevelopmental disorders, such as autism, in children who have other genetic and immunologic predispositions. This hypothesis later received support from more detailed, theoretical discussions on inflammatory, immunologic, and genetic mechanisms that might lead to autism, and the possible contribution of acetaminophen thereto.[9,10] Other hypotheses have also been advanced, such as acetaminophen-related oxidative stress[11] and acetaminophen-related endocrine and cannabinoid receptor effects[5] predisposing to ASD. However, as with other psychiatric disorders, the etiopathogenesis of ASD is incompletely understood, and so the mechanisms proposed by these authors[8–11] must be recognized to be speculative.

An Ecological Link

Becker and Schultz[9] drew attention to a possible ecological link between acetaminophen use and autism enrollment (by year of birth, 1960–1990) in California. The autism enrollment graph showed a steep rise from the late 1970s onward. There were 3 occasions, however, when the graph briefly leveled out, and 2 of these occasions were associated with a drop in acetaminophen sales because of public scares related to drug tampering. Prenatal use of acetaminophen has also been linked to an increased risk of asthma in the offspring,[12] and Becker and Schultz[9]

Clinical Points

- There are theoretical grounds to support the hypothesis that gestational exposure to acetaminophen (paracetamol) increases the risk of autism spectrum disorder (ASD), and there is support for this hypothesis from studies that compare trends in population-level use of acetaminophen with trends in the incidence/prevalence of ASD.
- One large prospective observational study found that gestational exposure to acetaminophen was associated with risk of neurodevelopmental impairments at age 3 years; longer duration of gestational exposure was associated with worse neurodevelopmental outcomes. However, the impairments excluded social deficits that are the core features of ASD.
- Another large prospective observational study found that gestational exposure to acetaminophen was associated with an increased risk of ASD, but only in cases with a comorbid hyperkinetic syndrome diagnosis.
- Although the data are very limited, the data that do presently exist do not implicate acetaminophen exposure during pregnancy as an etiologic risk factor for the development of ASD.

suggested that there also seemed to be a leveling in the graph of asthma rates by year, corresponding to the periods of acetaminophen sales drop. A limitation of this study is that for both associations (with autism and asthma) the link was based on eyeball impressions, and perhaps not all readers would share those impressions.

Bauer and Kriebel[10] compared country-level acetaminophen usage with population-weighted average autism prevalence rates. Using all available country-level data for 1984–2005 (8 countries), they found a high correlation ($r = 0.8$) between prenatal use of acetaminophen and autism/ASD prevalence. The regression analysis suggested that a 10% increase in population prenatal acetaminophen use would be associated with a 0.053% (95% CI, 0.13–0.93) increase in the autism population prevalence. Interestingly, there was an even higher, near perfect country-level correlation ($r = 0.98$) between the circumcision rates and the autism/ASD rate in males born after 1995 (9 countries); in this context, it must be noted that acetaminophen use in male children increased from 1995 when guidelines recommended its use for analgesia during circumcision, so circumcision rates were a proxy for acetaminophen use. A similar pattern was seen in an analysis of data from 14 US states and a comparison of the 3 main racial/ethnic groups in the United States.[10]

A limitation of Bauer and Kriebel's[10] interpretation of their data is that the pre-1995 country-level correlation between circumcision and autism rates was almost the same ($r = 0.89$) as the post-1995 value (0.98); this finding ($r = 0.89$) was obtained from an analysis of data from 12 countries. A limitation of the 2 ecological studies[9,10] presented here is that acetaminophen use in the population may have merely been a marker for an unmeasured ASD risk factor.

Empirical Data: Effects on Neurodevelopment

Using data drawn from the prospective Norwegian Mother and Child Cohort Study, Brandlistuen et al[4] examined child neurodevelopmental outcomes at age 3 years in relation to acetaminophen exposure identified through questionnaires administered around gestational weeks 17 and 30, as well as at 6 months postpartum. The sample comprised 48,631 children, including 2,919 same-sex sibling pairs; data from the latter were used to correct for familial and genetic factors. Analyses were adjusted for potential confounders, including maternal age, alcohol use, smoking, febrile illness, infections, and other medication use during pregnancy.

In the sibling-control analysis, pairs discordant for gestational acetaminophen exposure were compared with concordant pairs. In this analysis, 28 or more days of gestational exposure to acetaminophen (discordant, n = 134; concordant, n = 1,346) was associated with impairments in motor milestones, gross motor development, communication, externalizing behavior, and internalizing behavior and with higher activity level. Shorter (1–27 day) acetaminophen exposure (discordant, n = 805; concordant, n = 1,980) was associated with impairments in motor milestones and gross motor outcomes, but the effects were smaller. Shorter exposure was also associated with impairment in fine motor outcomes. Emotionality, sociability, and shyness were not associated with either duration category of acetaminophen exposure. There was no trimester-of-exposure effect on outcomes.

In the exposed vs unexposed (n = 26,213) analyses, 1 to 27 days of gestational exposure to acetaminophen (n = 20,587) was associated with impairments in gross motor development, externalizing behavior, and emotionality; exposure for 28 days or more (n = 1,831) was associated with impairments in motor milestones, gross motor development, communication, externalizing behavior, and emotionality.

In contrast with exposure to acetaminophen, gestational exposure to ibuprofen was not associated with neurodevelopmental outcomes. This finding suggests that the outcomes with acetaminophen were not due to confounding by indication, but such a conclusion is limited by differences in the reasons why acetaminophen and ibuprofen may have been prescribed. Another concern is that the ibuprofen-exposed sample was small, raising the possibility of a type 2 error.

Brandlistuen et al[4] estimated that 28 or more days of gestational exposure to acetaminophen increases the risk of adverse psychomotor and behavioral outcomes by almost 70% and doubles the risk of language problems at age 3 years. Their study, however, was not designed to provide information about risks associated with continuous vs intermittent use of acetaminophen during pregnancy, or dose-dependent risks. Although they did not explicitly say so, many of the neurodevelopmental impairments they recorded are common to those observed in ASD. However, they properly observed that the developmental impairments identified were not specific to ASD and that social impairments, which might be expected in ASD, were

not associated with acetaminophen exposure.[13] Readers interested in a conceptual and methodological critique of this article could consult a commentary[14] and the response thereto.[15]

Empirical Data: Risk of Autism

Only 1 study appears to have specifically examined the risk of ASD in the context of maternal use of acetaminophen during pregnancy. In this study, Liew et al[5] drew data from the Danish National Birth Cohort in which mothers with singleton livebirths (n = 64,322) were prospectively asked about acetaminophen use in computer-assisted telephone interviews at gestational weeks 12 and 30 and at 6 months postpartum. The children were followed up for 10.4–15.6 (mean, 12.7) years. Registry-linked data were used to identify *ICD-10* diagnoses of ASD; this was previously shown to have high validity.

There were 1,027 (1.6%) children with ASD, of whom 345 (0.5%) were diagnosed with infantile autism, 306 (0.5%) with Asperger syndrome, and 518 (0.8%) with pervasive developmental disorder, not otherwise specified (PDD-NOS). Some cases received more than 1 ASD subtype diagnosis. Of note, 31% of the ASD cases and 26% of the infantile autism cases also received a hyperkinetic disorder diagnosis. Acetaminophen use during pregnancy was reported by 56.3% of the women.

Liew et al[5] adjusted analyses for variables that might influence the ASD risk, including gender, birth year, maternal age, parity, socioeconomic status, maternal body mass index, maternal use of alcohol and tobacco, maternal medical and psychiatric illness, and maternal use of medications, including antidepressants. They found that, relative to no use of acetaminophen, prenatal use of acetaminophen at any time during gestation was associated with a small increase in the risk of ASD (hazard ratio [HR], 1.19; 95% CI, 1.04–1.35); use during all 3 trimesters was associated with a higher risk (HR, 1.39; 95% CI, 1.14–1.70). No trimester-specific risk was evident, but the risk was dose-dependent, based on cumulative weeks of exposure during pregnancy.

ASD was comorbid with an *ICD-10* hyperkinetic condition in 31% of cases; this figure was 26% for cases with a diagnosis of infantile autism. Despite the far smaller comorbidity sample sizes, acetaminophen use during pregnancy increased the risk of ASD only when ASD was comorbid with a hyperkinetic condition. Also, the risk was greater with greater cumulative weeks of exposure only when ASD was accompanied by a hyperkinetic disorder diagnosis. Similar findings were obtained in separate analyses for infantile autism, Asperger syndrome, and PDD-NOS. Importantly, the findings were similar when analyses were restricted to women who did not experience infection or fever during pregnancy, diminishing the likelihood of confounding by indication. Thus, this study appeared to associate gestational use of acetaminophen with the hyperactive behavioral phenotype rather than with ASD. This is in line with research that has linked gestational acetaminophen exposure to ADHD risk.[6]

Summary

Many biological mechanisms have been proposed to explain why use of acetaminophen during pregnancy may increase the risk of ASD in the offspring. In 2 studies, population-level use of acetaminophen was associated with trends in the incidence/prevalence of ASD. In one study, gestational exposure to acetaminophen was linked to poorer neurodevelopment and hyperactivity, but not to social and emotional deficits. In one study, gestational exposure to acetaminophen was associated with an increased risk of ASD; the risk increased with greater cumulative duration of exposure. However, the increase in risk was evident only when ASD cases had a comorbid hyperkinetic disorder diagnosis. Thus, the limited evidence available at present does not support the conjecture that use of acetaminophen during pregnancy contributes to the suggested secular increase in autism incidence.

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