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Review article

Prenatal paracetamol exposure and child neurodevelopment: A review

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Highlights

- All nine studies suggest prenatal APAP is associated with adverse neurodevelopment.
- These neurodevelopmental endpoints include ADHD, ASD and lower IQ.
- Associations were strongest for hyperactivity and attention-related outcomes.
- Controlling for indication for use, when possible, did not explain associations.
- Given these findings, pregnant women should be cautioned against indiscriminate APAP use.

Abstract

Background

The non-prescription medication paracetamol (acetaminophen, APAP) is currently recommended as a safe pain and fever treatment during pregnancy. However, recent studies suggest a possible association between APAP use in pregnancy and offspring neurodevelopment.

Objectives

To conduct a review of publications reporting associations between prenatal APAP use and offspring neurodevelopmental outcomes.

Methods

Relevant sources were identified through a key word search of multiple databases (Medline, CINAHL, OVID and TOXNET) in September 2016. All English language observational studies of pregnancy APAP and three classes of neurodevelopmental outcomes (autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and intelligence quotient (IQ)) were included. One reviewer (AZB) independently screened all titles and abstracts, extracted and analyzed the data.

Results

64 studies were retrieved and 55 were ineligible. Nine prospective cohort studies fulfilled all inclusion criteria. Data pooling was not appropriate due to heterogeneity in outcomes. All included studies suggested an association between prenatal APAP exposure and the neurodevelopmental outcomes; ADHD, ASD, or lower IQ. Longer duration of APAP use was associated with increased risk. Associations were strongest for hyperactivity and attention-related outcomes. Little modification of associations by indication for use was reported.

Conclusions

Together, these nine studies suggest an increased risk of adverse neurodevelopmental outcomes following prenatal APAP exposure. Further studies are urgently needed with; precise indication of use and exposure assessment of use both in utero and in early life. Given the current findings, pregnant women should be cautioned against indiscriminate use of APAP. These results have substantial public health implications.

Introduction

The number of women taking medications during pregnancy has more than doubled over the past 30 years, and now nine out of ten women take at least one medication while pregnant (Mosley II et

al., 2015). Pregnant women are generally excluded from clinical trials so the vast majority of maternal medications have not been adequately studied in human pregnancy and the risks to the fetus are often poorly understood (Adam et al., 2011). Emerging research suggests that medication use during pregnancy may increase the risk of long-term adverse neurodevelopmental outcomes including autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) (Landrigan, 2010; El Marroun et al., 2014).

Paracetamol (APAP, Acetaminophen), an analgesic and antipyretic generally available without prescription, is the most commonly used medication in pregnancy (Werler et al., 2005). APAP has been estimated to be used by up to 65% of US, and >50% of European women during their pregnancies (Brandlistuen et al., 2013; Servey and Chang, 2014). Although APAP has a narrow therapeutic index and is the leading cause of acute liver injury (Guggenheimer and Moore, 2011), it is considered among the safest options during pregnancy (Thiele et al., 2013). This is in part because there has been no strong evidence associating APAP with structural birth defects (Servey and Chang, 2014). However, a growing body of research suggests APAP may alter fetal development in a number of ways. Research has shown APAP may have endocrine disruptive properties capable of altering reproductive function (Kristensen et al., 2016; Holm et al., 2015; Kristensen et al., 2011; Snijder et al., 2012; Fisher et al., 2016). APAP use during pregnancy has been associated with an increased risk of asthma (Lourido-Cebreiro et al., 2016), immune alterations (Prymula et al., 2009; Thiele et al., 2015), and, most recently, functional changes in behavior and cognition (Andrade, 2016).

Long-term neurodevelopmental consequences of APAP were first hypothesized fourteen years ago by Dr. Anthony Torres who noted that ASD was associated with infection during pregnancy (Torres, 2003). He proposed that antipyretics might interfere with normal immunological development in the brain leading to neurodevelopmental disorders, such as ASD, in those genetically and immunologically predisposed. This hypothesis was followed by two supportive ecological analyses (Becker and Schultz, 2010; Bauer and Kriebel, 2013), but this question has only recently been investigated in well-conducted studies.

The purpose of this review is to summarize and assess the findings of observational studies evaluating the association between prenatal exposure to APAP and offspring adverse neurodevelopmental outcomes and to provide an overview of plausible biological mechanisms for such a relationship.

Section snippets

Search strategy

Relevant studies were identified by searching several online databases: the database of the National Library of Medicine (MEDLINE/PubMed); the Cumulative Index to Nursing and Allied Health Literature (CINAHL); University of Massachusetts Lowell collection of 66 health related journals

(OVID UML Journals@OVID); and the National Institute of Health Toxicology Network (TOXNET) September 28–29, 2016. The search was limited to English language studies. For the MEDLINE and CINAHL Boolean searches …

Results

Sixty four records were initially identified. Overlapping studies were compared and only the study with the earliest publication date was selected for full text review, the additional studies were excluded. After exclusion of non-relevant articles, twelve full text articles were screened and nine eligible studies in five populations were identified. The search flowchart is presented in Fig. 1.

Due to the large variation in outcomes and outcome measurement methods we could not combine the results …

Discussion

In the nine studies from five cohorts in this review, over 50% of children were exposed to APAP in utero consistent with other estimates of exposure (Kristensen et al., 2016). Because of heterogeneity of study outcomes it was not possible to use meta-analytic methods to provide a quantitative summary estimate of the effects of included studies. There was, however, consistency of results as all nine prospective cohort studies suggested prenatal APAP exposure moderately increased risk of adverse …

Conclusions

There were consistent findings in the nine prospective cohort studies within five cohorts suggesting adverse neurodevelopmental outcomes in children following APAP use in pregnancy. These findings suggest APAP alters neurodevelopment most strongly in relation to a hyperactive and attention related functions. The greatest risk of ASD and ADHD symptoms appeared to be from prolonged exposure late in pregnancy. The relatively modest risks may be the result of residual confounding but the …

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Eur. J. Paediatr. Neurol. (2015)

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Environmental risk factors, protective factors, and peripheral biomarkers for ADHD: an umbrella review

2020, Lancet Psychiatry

> *Citation Excerpt :*
>
> ...Maternal acetaminophen exposure during pregnancy was associated with a higher risk of ADHD in offspring with convincing evidence, retaining the level of evidence in all three subset analyses. Various potential mechanisms have been suggested, including excess toxic N-acetyl-p-benzoquinoneimine formation, oxidative stress due to inflammation-induced immune activation, brain-derived neurotropic factor alteration, endocannabinoid dysfunction, Cox-2 inhibition, and endocrine disruption.55,63 Although the exact biological mechanism has not yet been identified, one hypothesis is that prenatal acetaminophen exposure affects normal neurodevelopment, which is consistent with the evidence that acetaminophen readily crosses the placenta64 and blood–brain barrier,65 and that prenatal acetaminophen exposure during the third trimester of pregnancy (when the fetal brain grows rapidly and is highly sensitive to stimulation)66 is associated with a higher risk of ADHD than exposure in earlier trimesters.55,67,68...

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Paracetamol use during pregnancy — a call for precautionary action ↗

2021, Nature Reviews Endocrinology

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Investigating the Use of Machine Learning Models to Understand the Drugs Permeability Across Placenta ↗

2023, IEEE Access

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