The association of prenatal exposure to paracetamol and neurodevelopmental disorders in childhood

A systematic review

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Abstract

Background: Paracetamol is the most commonly used over-the-counter pain reliever and antipyretic among pregnant women. Paracetamol has been considered to be one of the safest analgesics, even for pregnant women. It is known that paracetamol crosses the placenta and that paracetamol and its metabolites enter the fetal blood flow. However, it is not yet well understood how this prenatal paracetamol exposure could affect the fetus. The aim of this review is to investigate what is known in the existing literature about prenatal exposure to paracetamol and child brain development, focusing on the development of Attention Deficit Hyperactivity Disorder/Hyperkinetic Disorder (ADHD/HKD) and Autism Spectrum Disorders (ASD).

Methods: The PubMed database has been systematically searched for existing literature investigating prenatal paracetamol exposure and the effects on neurodevelopment in children.

Results: A total of 6 articles met the inclusion criteria. Two studies suggested that prenatal paracetamol use was associated with an increased risk for ADHD and HKD; one study showed an increased risk for ASD. Further, an ecological study showed a positive correlation between prenatal paracetamol exposure and the prevalence of autism. One study demonstrated an association between prenatal paracetamol exposure and different adverse developmental outcomes. Finally, there was one study that showed no association with child intelligence.

Discussion: This systematic review suggests that there is an association between prenatal exposure to paracetamol and an increased risk of neurodevelopmental disorders such as ADHD, HKD and ASD. More research on prenatal paracetamol use and the potential consequences on child development is needed before evidence-based recommendations can be developed.

Introduction

Paracetamol, also known as acetaminophen, is the most commonly used over-the-counter pain reliever and fever reducer among pregnant women, with reported use between 65% to 75% in the USA and more than 50% in Europe[1]. The use of paracetamol during pregnancy increased after 1980, when evidence was found that use of prenatal salicylates, such as aspirin, was associated with Reyes syndrome[2,3]. Paracetamol has been considered one of the safest analgesics, even for pregnant women[4]. It is known that paracetamol crosses the placenta and that paracetamol and its metabolites enter the fetal blood flow[5]. However, it is not yet well understood how this prenatal paracetamol exposure could affect the fetus.

Worldwide, the brochure of paracetamol instructs consultation with the physician before taking the drug, that it is safe to breastfeed the child while taking paracetamol and that paracetamol is not recommended for children younger than 6 years. The Dutch brochure even states that paracetamol use during pregnancy is not harmful for the pregnancy or to the health of the unborn child. However, recent animal and human studies have demonstrated delayed adverse effects of paracetamol. Prenatal paracetamol use has been shown to have endocrine-disrupting functions[6-9], which increases the risk of cryptorchidism[10], as well as immune modulating characteristics, increasing the risk of asthma[11,12]. Moreover, high doses of paracetamol can also cause trauma to fetal liver cells, resulting in long term liver failure[13,14]. Even therapeutic doses of paracetamol have been proven to be harmful for the fetus since it may have important effects on (anti)oxidant balance[15,16]. There is no evidence for other adverse effects of paracetamol on birth outcomes, such as malformation, risk of miscarriage, low birth weight or prematurity[17]. However, Rebordosa et al. reported an association between prenatal paracetamol exposure and preterm birth in women with pre-eclampsia[18].

Hormones, (anti)oxidant balance and a regulated immune system are very important for brain development of the fetus. Thus maternal use of paracetamol during pregnancy could po-
potentially be related to neurological and behavioral disorders[19]. It has been suggested that the endocrine-disrupting functions of paracetamol could play a role in the development of Attention Deficit Hyperactivity Disorder (ADHD) and Hyperkinetic disorder (HKD)[20,21]. Moreover, it has also been suggested that maternal paracetamol use plays a role in the etiology of autism spectrum disorders (ASD) due to its immune modulating characteristics and disruption of the anti-oxidant balance[12,22]. The prevalence of ADHD and HKD varies from 2% to 18% and 0.5 to 1% respectively. The global prevalence of ASD is estimated to be 7.6 per 1000. As the prevalence and incidence of these diseases have been increasing since 1970, a good understanding of the underlying etiology and risk factors is important to prevent further exposure and development of these disorders.

The aim of this systematic review is to investigate in the existing literature about prenatal exposure to paracetamol and child brain development with a particular focus on the development of disorders including ADHD/HKD and ASD.

**Methods**

**Search strategy**

On January 6th 2016, the PubMed database has been systematically searched for English-language articles, using the following Medical Subject Headings (MeSH Terms): (acetaminophen [MeSH Terms] OR analgesics[MeSH Terms]) NOT narcotics[MeSH Terms]) AND (prenatal exposure delayed effects[MeSH Terms] OR prenatal[title/abstract] OR antenatal[title/abstract] OR perinatal[title/abstract] OR intrauterine[title/abstract] OR in utero[title/abstract] OR pregnancy[title/abstract] OR fetal[title/abstract]) AND humans[MeSH Terms]) AND (mental disorders [MeSH Terms] OR child behavior [MeSH Terms] OR behavioral symptoms [MeSH Terms] OR cognition [MeSH Terms] OR intelligence [title/abstract] OR IQ [title/abstract] OR neuropsychology [MeSH Terms]) OR ((acetaminophen [Title/abstract]) AND autism [Title/abstract] AND maternal [Title/abstract]). The last three terms (in italic) were added to the search to include a relevant article that was not included to the first search. All results were limited to human subjects.

**Selection criteria**

The articles were first screened by title and abstract. Articles without full text or inaccessible articles were excluded. Inclusion criteria were studies that concerned the use of paracetamol during pregnancy and the potential long-term effects that this prenatal exposure could have on childhood brain development in the broadest sense. Articles were excluded if they were case reports, reviews or a reply to articles. Articles that investigated the use of paracetamol during pregnancy and health problems other than alteration of brain development (e.g asthma) were also excluded. As the aim was to investigate the effect of prenatal paracetamol use on neurodevelopmental disorders in children only, a maximum age of 13 years was set on included subjects within the articles. Articles that met the inclusion criteria were read in full text.

**Analysis**

The primary outcome measure was the association between prenatal exposure to paracetamol and anomalies of the brain development in the offspring. An overview of the included articles is produced in Figure 1 and Table 1.

**Results**

**Description of studies**

Figure 1 shows that the systematic search in PubMed lead to 59 articles. One article has been published in December 2015 and has not yet been indexed in PubMed. Thus this article could not be found in the initial search in PubMed. To be able to include this article, a few Mesh Terms were added to the search (see Methods section) but it is expected that in a few months, this addition will not be required. After the first screening, 20 of the articles were potentially relevant. After the second screening, 6 articles remained to be included in the review (see Figure 1). The included studies are described in Table 1[23-28].

![Flow chart of study selection progress](image-url)
Subjects

The 6 studies were conducted in the Western world. The follow-up period varied from birth to 13 years. Five of these studies were cohorts. Most of the children were European.

In each study, the results were adjusted for several confounders, such as diseases or conditions that may trigger paracetamol use during pregnancy (fever, infections, inflammations), smoking and alcohol drinking during pregnancy, self-reported maternal psychiatric illnesses, concomitant use of any other medication, baseline characteristics of mother and child, including child’s birth year, birth weight, sex, maternal age at child’s birth, parity, gestational age at delivery and socioeconomic status. Maternal use of paracetamol during pregnancy was assessed using different methods, mostly using questionnaires or interviews via telephone. The prevalence of maternal paracetamol use during pregnancy varied between 43.5% and more than 50% in these studies.

ADHD/HKD

Two studies investigated the relation between prenatal paracetamol exposure and ADHD symptoms[24,26].

Table 1 - Characteristics and outcomes of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Type study</th>
<th>Follow-up</th>
<th>(Assessment of) paracetamol use (%)</th>
<th>Tests used</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD/HKD</td>
<td>n= 64 322</td>
<td>Longitudinal</td>
<td>13 years</td>
<td>Three telephone interviews at 12 and 30 weeks gestation as well as 6 months postnatal (&gt; 50%)</td>
<td>Strengths and Difficulties Questionnaire (SDQ) to measure symptoms of ADHD</td>
<td>Prenatal paracetamol use was related to an increased risk for ADHD-like behaviors</td>
</tr>
<tr>
<td>Liew Z et al. 2014</td>
<td>n= 871</td>
<td>Longitudinal population based prospective cohort study</td>
<td>11 years follow-up</td>
<td>Interviewer-administered questionnaires soon after giving birth</td>
<td>Strengths and Difficulties Questionnaire</td>
<td>Prenatal paracetamol use was associated with the prevalence of autism</td>
</tr>
<tr>
<td>Bauer &amp; Kriebel 2013</td>
<td>n= 8 (countries)</td>
<td>Ecological analysis</td>
<td>-</td>
<td>Usage rates were extracted from studies examining the use of paracetamol during pregnancy</td>
<td>-</td>
<td>Prenatal paracetamol use was positively correlated with the prevalence of autism</td>
</tr>
<tr>
<td>Liew Z et al. 2015</td>
<td>n= 64 322</td>
<td>Longitudinal population based prospective cohort study</td>
<td>13 years follow-up</td>
<td>Telephone interviews at 12 and 30 weeks gestation</td>
<td>Classification of paracetamol use was associated with a higher risk for autism in children</td>
<td>Prenatal paracetamol use was associated with adverse outcomes for gross motor development &amp; Child Behavior and communicative development, behavior and activity</td>
</tr>
<tr>
<td>Diverse developmental outcomes</td>
<td>n= 22 418</td>
<td>Sibling-controlled prospective cohort study</td>
<td>3 years follow-up</td>
<td>Two prenatal questionnaires and one postnatal (&gt;50%) (6 months) questionnaire (46.1%)</td>
<td>Ages and Stages Questionnaire</td>
<td>Prenatal paracetamol use was not related to child IQ or attention</td>
</tr>
<tr>
<td>Brandlistuen et al. 2013</td>
<td>n= 1529</td>
<td>Longitudinal population based prospective cohort study</td>
<td>4 years follow-up</td>
<td>Self-report at 5 months gestation (43.5%)</td>
<td>Wechsler Preschool and Primary Scale of Intelligence (WPPSI)</td>
<td>Prenatal paracetamol use was not related to child IQ or attention</td>
</tr>
</tbody>
</table>

In Thompson et al.[24], symptoms of ADHD were assessed using the Strengths and Difficulties Questionnaire (SDQ). In this study, higher total difficulty scores were observed when paracetamol was used during pregnancy, but not if other drugs (e.g., antibiotics, analgesics) were used (parent SDQ at 7 (OR= 2.1; 95% CI 0.0-5.0), parent SDQ at 11 (OR= 1.2; 95% CI 0.6-2.5) and child SDQ at 11 (OR= 1.0; 95% CI 0.6-1.6)). Children of mothers who used paracetamol during pregnancy were also at increased risk of ADHD-problems at 7 and 11 years of age[26]. Particularly problematic were emotional and conduct problems at age 7[24].

In a Danish cohort, children’s ADHD-like behaviors were assessed using the standardized Strengths and Difficulties Questionnaire (SDQ) and all HKD diagnoses were based on the International Statistical Classification of Diseases, 10th revision (F90.0-F90.9)[26]. Relying on the civil registration number, they also searched for children who used ADHD medications. An increased risk for ADHD-like behaviors was observed in children aged 7 years with maternal paracetamol use during pregnancy (RR, 1.13; 95% CI 1.01-1.27) as well as an increased risk for HKD diagnosis or ADHD medications. When women reported having used paracetamol for 20 weeks or more during...
pregnancy, the risk for HKD diagnosis in children almost doubled (HR, 1.84; 95% CI, 1.39-2.45) and the risk of receiving ADHD medication increased by 50% (HR, 1.53; 95% CI 1.21-1.94). Thus, the risks increased with increasing frequency of paracetamol use throughout pregnancy. Correction for maternal use of ibuprofen and aspirin during pregnancy did not change the results, showing a specific effect of paracetamol.

ASD
Two studies examined the association between prenatal exposure to paracetamol and autism[23,27].

In the ecological study of Bauer and Kriebel in 2013, population weighted average autism prevalence rates and paracetamol usage rates were compared. They used the Autism Prevalence Summary Table which summarized the results of 59 prevalence studies conducted worldwide. In this study prenatal use of paracetamol was correlated with autism prevalence with a correlation of r=0.80[23]. Within the limits of the small datasets, the normality assumption was not seriously violated and so Pearson’s parametric correlation coefficient was used with an information weighted (1/variance) linear regression model. Although a positive correlation between autism prevalence and indicators of prenatal paracetamol exposure were found, this ecological study did not address causation.

In Liew et al. in 2015, an ASD was assessed using the International Classification of Diseases 10th edition (ICD-10 F84.0-F84.9 for ASD). The association between maternal paracetamol use during pregnancy and offspring ASD diagnosis was investigated[27], using the same Danish cohort as the previous study of Liew et al. in 2014[26]. Their analysis suggested that prenatal exposure to paracetamol was associated with a higher risk for ASD and infantile autism in children. An increased risk for ASD and infantile autism was found if the mother reported paracetamol use during all three trimesters (HR, 1.39; 95% CI 1.14-1.70 and 1.49; 95% CI 1.07-2.07 respectively). The effect estimates for paracetamol use in pregnancy were stronger for ASD with hyperkinetic symptoms, and no associations were observed for ASD or infantile autism alone[27]. Maternal use of paracetamol during pregnancy was also associated with other subtypes of ASD, but only in those children with hyperkinetic symptoms. Effect estimates were similar in models including co-medication[27].

Diverse developmental outcomes
One sibling-controlled cohort study revealed that paracetamol use during pregnancy was associated with several adverse developmental outcomes[25]. Children prenatally exposed to paracetamol for more than 28 days had poorer gross motor development (β 0.24, 95% CI 0.12-0.51), poorer communication skills (β 0.20, 95% CI 0.01-0.39), increased externalizing behavior (β 0.28, 95% CI 0.15-0.42), internalizing behavior (β 0.14, 95% CI 0.01-0.28), and higher activity levels (β 0.24, 95% CI 0.11-0.38). The effect estimates were lower if the mother reported short-term (less than 27 days) paracetamol use. There was no association found between prenatal ibuprofen use and neurodevelopmental outcomes. This sibling-controlled analysis showed stronger effects than the cohort analysis of Liew et al[26,27].

Finally, the last study reported that maternal paracetamol use was not significantly related to child intelligence or attention variables at the age of 4 years (p= 0.48 and p= 0.28, respectively)[28].

Discussion
This systematic review suggests an association between prenatal exposure to paracetamol and ADHD, HKD and autism/ASD in young children. A brief discussion of each study used in this review will follow.

Two studies focused on the association between maternal paracetamol use and ADHD-like behavior of the child. Both studies showed a significant association and used reliable ADHD assessment data[24,26].

Thompson et al. analyzed possible confounding by multiple drugs use and showed specific effects of paracetamol on ADHD. In addition, the study showed a stronger association with ADHD when paracetamol was used to suppress fever. Liew et al. 2014 and Brandlistuen et al. suggested that the longer the paracetamol is used, the higher the risk of potential adverse effects.

Each study has its own limitations which can be complemented by the strengths. Strengths are the large sample size, the prospective design, the database used to detect ADHD and correction for important confounders such as co-medication, baseline characteristics of both mother and child, diseases or conditions that may trigger paracetamol use during pregnancy and smoking and alcohol use during pregnancy (these strengths apply for all studies mentioned in the current review, except the article of Bauer and Kriebel). These strengths make small effects detectable, limit maternal recall bias and are reliable for diagnosing disorders such as ASD and ADHD.

However, these two studies (Thompson et al. and Liew et al. 2014) also have similar limitations: they have a potential source of selection bias due to dropout, they did not have information on dosage of paracetamol use and the findings have to be limited to children of European ethnicity. The possibility of residual confounding or confounding by indication for these studies also exists as is often the case with observational studies.

Two studies focused on the association between maternal paracetamol use and ASD[23,27]. However, these studies are completely different and complement each other.

Liew et al. 2015 showed a significantly increased risk of ASD with hyperkinetic symptoms among children who were prenatally exposed to paracetamol. This association cannot be made for ASD alone. Together with the previous studies focusing on ADHD and HKD, it is more likely that paracetamol use causes hyperactivity, and not ASD. This study is also possibly residually confounded by indication, selection bias and genetic factors that could play a role in the etiology of ASD. This study cannot be generalized for ethnicities other than European ones and also did not have information about dosage of paracetamol use.

Bauer and Kriebel performed a different type of study, linking ecological trends to the prevalence of ASD. This ecological analysis showed a positive correlation between prenatal paracetamol use and ASD prevalence. This correlation is plausible, this ecological link cannot be used to infer causality. According to the authors, the study is possibly confounded and subjected to bias and misclassification. However, this study has the strength that it is generalizable.
Only Brandlistuen et al. focused on different neurodevelopmental outcomes. This sibling-controlled cohort study adjusted for familial confounding (which is a major strength of this study). The relation of prenatal paracetamol exposure and childhood neurodevelopment was stronger when comparing siblings. The outcomes in this study were too broad to be directly related to ADHD. Furthermore, as with the other studies, confounding by indication could be an issue. Also this study did not inform about dosage of paracetamol use and is only generalizable for European children.

Only Streissguth et al. focused on the influence of prenatal paracetamol use on the child intelligence, but the findings were not significant. However, this study only focused on paracetamol use in the first half of pregnancy, while the other studies mentioned that the third trimester is also an important period for brain development in children. Further, this study did not collect information about dosage of paracetamol use. Results of this study are only generalizable to the Northern-American population. This study is also subject to confounding by indication and like the other studies, does not predict causal relations.

In this systematic review, 6 articles were included, of which both studies of Liew et al. showed the strongest evidence for the effects of prenatal paracetamol exposure on the development of ADHD/HKD and possibly ASD. Brandlistuen et al. also provides strong evidence for adverse neurological outcomes after prenatal exposure to paracetamol, mostly because this study corrected for familial confounding. The ecological link of Bauer and Kriehoevel shows the least strong evidence, because it has only linked the paracetamol use trends to the ASD prevalence trends over time, without examining if this increased prevalence of ASD was found among children prenatally exposed to paracetamol. It is, however, striking that both trends follow each other.

**Conclusion**

Based on the existing literature, an association between prenatal exposure to paracetamol and a higher risk of neurodevelopmental disorders like ADHD and HKD has been suggested. This potential association also holds for ASD. Although the literature suggests a relation between prenatal exposure to paracetamol and childhood neurodevelopment, studies are sparse. More information on prenatal paracetamol use and the potential consequences on child development are needed before evidence based recommendations can be made.

Studies that further investigate the exact mechanisms of paracetamol and how these mechanisms are involved in the etiology of these neurodevelopmental disorders are essential. Studies should register the dosage of the paracetamol use and should adjust for several environmental factors that could influence neurodevelopment, such as timing, frequency, and duration of paracetamol use during pregnancy.

It is also suggested that other studies examining the effects of paracetamol in adolescence and adulthood should be reviewed. The current review only holds associations between prenatal paracetamol exposure and adverse neurodevelopmental outcomes in children up to 13 years, thus the conclusions of this review are not generalizable to other neurodevelopmental disorders that present later in lifetime, such as schizophrenia, psychotic symptoms, and depression.

A few studies have examined the relation between prenatal exposure to analgesics and schizophrenia/psychotic symptoms, but have not investigated paracetamol specifically.[29,30]

To move forward, observational studies should be improved. First, human studies could be combined with experimental animal studies to show a plausible causal relation. Next, observational cohort studies examining maternal paracetamol use during pregnancy could also be combined with investigating paternal paracetamol use in the same period in order to adjust for shared familial and genetic confounding. Further, minor improvements could be to include different ethnicities in the study population for generalizability. This is important because the worldwide paracetamol use during pregnancy is high.

In conclusion, further research is needed into the long-term neurodevelopmental effects of prenatal exposure to paracetamol to provide information in order to make evidence-based recommendations.

**Acknowledgements**

We would like to thank Hanan El Marroun for her supervision during the writing of this review. She has been of significant importance in the process of defining the aim of our review, providing us with literature, knowledge and her opinion.

**References**