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General

Prenatal Acetaminophen Exposure and its Associated Risk for Attention Deficit Hyperactivity Disorder

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Acetaminophen is one of the most commonly used over-the-counter antipyretic and analgesic drugs on the market and has been relevant in the medical world for almost a hundred years. It has maintained an excellent reputation as a safe therapeutic in several types of patient profiles. However, the number of children diagnosed with neurodevelopmental disorders, namely ADHD, have been on the rise. Recent findings have indicated an association between in utero exposure to acetaminophen and an increased risk of developing neurodevelopmental disorders such as ADHD in offspring. The mechanism by which this potential side effect occurs is difficult to pinpoint. However, it is known that the metabolism of acetaminophen is known to cause oxidative stress, which has been shown to influence the developing fetus. This review highlights the epidemiological data indicating the correlation between prenatal acetaminophen exposure and ADHD and discusses several proposed theories by which this phenomenon may occur. While there is not yet enough clinical evidence to prove that acetaminophen may cause ADHD, there is a strong enough correlation to indicate a warning to pregnant patients of the potential risks. The risks and benefits of treatment should be considered so that the patient may continue with the course of action with the most favorable outcome. This review was mainly based on manuscripts pulled from Google Scholar and PubMed. The purpose of this literature review is to assist clinicians to better understand lesser-known risks in acetaminophen usage in pregnant patients.

BACKGROUND

Acetaminophen is one of the most commonly used over-the-counter drugs, available by itself or in combination with other agents.[1] Almost 1 in 4 Americans use an acetaminophen-containing product each week.[2] It is the preferred medication for patients that cannot take NSAIDs due to its known safety profile.[1] For years it has been widely accepted as one of the only pain medications safe to use during pregnancy and is used by about 65% of pregnant women.[3] It is also used worldwide in babies and children, with pediatric exposure of up to 90% in certain populations.[4]

One unfortunate facet of acetaminophen metabolism is the generation of the toxic metabolite NAPQI.[4] At therapeutic doses in healthy individuals, it is readily reduced by glutathione before it can cause damage to the patient.[4] However, in patients who are already experiencing excessive oxidative stress, there is less glutathione available, which markedly increases the toxicity of acetaminophen.[4] What was once a therapeutic dose of acetaminophen may now contribute to more oxidative stress in the patient.[4] Oxidative stress has been named as one of the main culprits in the pathology of many diseases, especially neurodegenerative disorders.[5]

According to the CDC, an estimated 6 million children living in the United States have been diagnosed with ADHD, and numbers are on the rise.[6,7] ADHD has been associated with a significant reduction in quality of life, and children diagnosed with ADHD report lower levels of happiness with their family.[8] Those diagnosed with ADHD also tend to suffer from other psychological comorbidities such as depression, anxiety, and substance abuse.[9] The treatment of ADHD by pharmacological agents generally results in a better long-term prognosis for the patient; however, there is no definitive cure for the disorder.[9]

Recent studies have indicated that acetaminophen may not be as harmless as once believed, and that prenatal exposure to the drug may be linked to a higher risk of ADHD in children.[10] Of 29 observational studies conducted, 26

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have found a positive association between acetaminophen use and developmental disorders in children.[7] Several mechanisms attempting to explain this association have been suggested. It is known that acetaminophen crosses the placental barrier and blood-brain barrier of the fetus, and therefore may remain in the infant's bloodstream for some time.[11] There is enough evidence of the association to counsel pregnant patients of the proposed risk of taking the medication.[7] Since the specific pathophysiologic mechanism of ADHD potentially caused by acetaminophen has not been clearly identified, it is important for pregnant patients to heir on the side of caution when given the choice between acetaminophen and another medication for common indications. These patients should be advised to avoid acetaminophen until it is medically indicated and to only take as much of the medication needed to be effective for as little time as possible.[7]

METHODOLOGY

This was a narrative review. The sources for this review are as follows: searching on PubMed, Google Scholar, Medline, and ScienceDirect; using keywords: ADHD, Acetaminophen, Paracetamol. The sources were gathered using standard PRISMA guidelines. Sources were accessed between February 2023 and May 2023.

RESULTS

CLINICAL IMPLICATION OF ACETAMINOPHEN ASSOCIATED WITH ADHD

Recent reports have shown an observed association with neurodevelopment implications, hyperactivity, and behavioral changes from prenatal exposure to acetaminophen (Table 1). Acetaminophen is often preferred over other antipyretics due to the classification of being considered safe by the FDA. Several studies reported findings with the increased likelihood that the development of ADHD would occur in prenatal exposure to acetaminophen alongside exposures at different trimesters. The third trimester has been associated to experience the most implications due to the fetal brain undergoing rapid development.[12] In one study, a sibling-controlled cohort study compared the difference in the siblings' neurodevelopmental outcomes with exposure to acetaminophen in-utero and duration of exposure. This design was meant to control genetic confounding predispositions. After a three-year follow-up, the children with prenatal exposure to acetaminophen longer than 28 days experienced poor motor function, communication skills, and difficult temperament control when compared to the short term exposure and the non-exposure groups.[13]

A collaborative birth cohort of six different subset populations in Europe was conducted to measure the potential adverse effects of early exposure to acetaminophen with ADHD. Pregnant mothers were required to self-report acetaminophen use within the parameters set from one month pregestational to 32 weeks of pregnancy to be placed within the prenatal exposure period and a control group of non-exposed. Researchers assessed the behavioral outcomes through a Strengths and Difficulties Questionnaire (SDQ), Diagnostic and Statistical Manual of Mental disorders questionnaire (DSM), Connor's parent rating scale (CPRS-R:S) to be classified within the borderline/clinical range of ADHD, or hospital diagnosis records. A risk ratio report of 1.21 infers a 21% higher association of prenatal exposure to acetaminophen with ADHD symptoms compared to non-exposed groups.[17] The findings across eight cohort studies seem to repute similar findings in the association between ADHD and in-utero exposure to acetaminophen with a risk ratio report of 25%.[12] A meta-regression analysis done in 2018 was able to narrow down the possible covariates to the children's age at follow-up and the duration of exposure to acetaminophen to significantly provide a stronger association[18]. Conversely, multifactorial implications should still be considered due to findings of increased environmental risk factors such as smoking, alcohol, other medications, maternal age, fever present in both maternal and offspring, and maternal socioeconomic status.[19-21]

THERAPEUTIC OPINION

ACETAMINOPHEN: INDICATIONS FOR USE, PHARMACOKINETICS, MECHANISM OF ACTION, ADVERSE EFFECTS

Acetaminophen is indicated for use in pain management and fever reduction.[22] It may be used as the primary therapy in mild to moderate pain, or in combination with opioids in severe pain.[22] It is recommended for long-term use in the treatment of chronic pain and is an ideal choice for patients who may have contraindications for NSAIDs, like pregnant women, patients with gastric ulcers, or patients with coagulation disorders.[1] The FDA outlines dosing of acetaminophen as 650-1000 mg every 4-6 hours, without exceeding 4000 mg per day for adolescents and adults.[22] For children, effective dosing is 12.5 mg/kg every 4 hours or 15 mg/kg every 6 hours without exceeding 75 mg/kg per day.[22] It has a bioavailability of 88% and reaches peak concentrations in the blood after 90 minutes.[23] The drug has a half-life of 1.5 - 2.5 hours at therapeutic doses, which is extended to 4-8 hours in overdose.[23] Because acetaminophen can be found in many over the counter products marketed for several indications, patients should be shown what to look for in products to avoid taking more acetaminophen than they intend (54). It is important to stress to the patient the importance of adhering to their recommended dosing regimen, as overdose can cause hepatic damage.[22]

Acetaminophen is the most common cause of drug-related acute liver failure, responsible for about 500 deaths and 50,000 ER visits in the US per year.[24] In recommended doses of acetaminophen, 60-90% of the drug is metabolized to form glucuronic acid- and sulfate-conjugate metabolites.[24] Only 5-15% of the drug is metabolized by the cytochrome P450 system (CYP450).[24] Metabolism by the CYP450 pathway leads to the formation of the toxic intermediate N-acetyl-p-benzoquinone imine (NAPQI) which is

Table 1. Recent comparative studies of prospective cohorts to associate if prenatal exposure to acetaminophen is related with an increasing risk of ADHD.

	Table 1: Searches' Data Extraction					
Year	**Author**	**Study Type**	**Focus**	**Sample**	**Measures**	**Results**
2022	Sznajder et al. [14]	Prospective cohort study	Child Behavior Checklist (CBCL) was indicated to be scored significantly higher under the "attention problems" with prenatal exposure to acetaminophen	1011 women	Child behavioral problems at the age of 3 years, using the 7 syndrome scale scores fromt (CBCL) for ages 1 ½ to 5	This study concludes that prenatal exposure to acetaminophen is associated with ADHD
2022	Ji et al. [15]	Prospective cohort study	Detectable cord plasma in the fetus was analyzed and separated into a first, second, or third tertile. An increasing odds ratio was found in a dose dependent manner when comparing the tertiles.	996 pregnant women	Cord plasma metabolites of acetaminophen and ADHD	Prenatal exposure to acetaminophen is significantly associated with an increased risk to ADHD
2020	Baker et al. [16]	Prospective cohort study	An odds ratio of 2.43 was reported between the meconium detection of acetaminophen in children that were diagnosed with ADHD by ages 6-7. They also showed an increased loss of connectivity in the frontoparietal regions that could be attributed to hyperactivity.	394 Children	Resting state brain connectivity at ages 9-11 with ADHD	Negatively impacted neurodevelopment is significantly found with prenatal acetaminophen exposure.

neutralized by glutathione to nontoxic metabolites.[24] However, in overdose of acetaminophen, the CYP450 pathway metabolizes a larger portion of the drug, which leads to depletion of glutathione stores and the buildup of toxic compound NAPQI.[24] This excessive amount of NAPQI reacts with cellular macromolecules, which leads to cell death and liver damage.[24]

Acetaminophen's precise mechanism of action has been up for debate since its introduction to the pharmacological market in 1955.[1] The analgesic and antipyretic effects of acetaminophen are likely due to its ability to act on antinociceptive processes by activating the endogenous cannabinoid system and by inhibiting COX.[1,25,26] Acetaminophen is deacylated in the brain and spinal cord to form p-aminophenol, which is conjugated with arachidonic acid to form N-arachidonylphenolamine (AM404).[26] AM404 then indirectly increases activity of the endocannabinoid system by activating TRPV1 (a cannabinoid receptor ligand) and by inhibiting anandamide reuptake, which leads to increased amounts of endogenous cannabinoids.[25,26] Endogenous cannabinoids may then lower body temperature by activating BC1 receptors in the preoptic area.[1,26] Another mechanism by which acetaminophen may lower body temperature is through COX inhibition in the brain. Acetaminophen can inhibit COX as long as the surrounding concentrations of peroxides are kept relatively low.[1,26] Concentrations of peroxides are low in the brain, but high at sites of inflammation.[26] This may explain why acetaminophen's anti-inflammatory properties are negligible.[26]

ACETAMINOPHEN AND ITS ASSOCIATION WITH ADHD

Attention deficit hyperactivity disorder (ADHD) is an early onset neurodevelopmental disorder.[27] ADHD is characterized by inadequate attention spans, impulsivity, and hyperactivity which can continue into adulthood .[27] Although studies have shown that ADHD prevalence in developed countries has decreased in recent years, prescriptions for ADHD have suggested otherwise.[27] This increase in prescriptions is thought to be due to an increase in awareness for ADHD in both parents and teachers who interact with the affected children. The opposite can be said about underdeveloped countries, implying that this condition often goes underdiagnosed in such places. ADHD is a multifactorial disorder where many different traits influence the development and severity of the disorder.[28] There is a male bias of around 3-4:1 which can be used to deduce that males are at an increased risk of developing ADHD.[27] Ge-

netic variation such as single nucleotide polymorphisms (SNPs) have been shown to be associated with risk with ADHD but only where there are large numbers of SNPs present.[27] Another genetic factor associated with risk of ADHD development are small chromosomal duplications or deletions named copy number variants (CNV). CNV have a larger effect size on ADHD development but are uncommon.[27] However, most of the risk factors associated with ADHD are environmental exposures. Premature birth, low birthweight, and in utero exposures to smoking, alcohol, and illicit drugs are factors that increase risk of ADHD in newborns.[28] In utero environmental exposures to pesticides have also been shown to be linked to ADHD development. Additionally, both nutritional inadequacies and nutritional surpluses have also been correlated to ADHD development.[27] Psychosocial risks such as low income, family adversity, and hostile parenting have also been proven to predispose children to ADHD.[27]

Recent studies have postulated that acetaminophen exposure in utero increases risk to children developing ADHD. Acetaminophen is the number one over the counter drug used in pregnant women for its analgesic and antipyretic effects. Although the safety profile of acetaminophen in pregnant patients is exceptional for its intended use, there may be future consequences, particularly on neurodevelopment, postpartum to their children.[11,29] The fetal brain undergoes a 30-fold surface area increase between 24 and 40 weeks' gestation.[30] This rapid development makes it exceptionally vulnerable to injury.[30] There are a few theories on the mechanism of how acetaminophen acts to damage this susceptible organ, and several of these theories point to oxidative stress as the main culprit. Acetaminophen becomes toxic to vital proteins at lower doses in patients who are already under oxidative stress.[4] A wide range of factors from infection and treatment with antibiotics to chromosomal disorders to simply being in a fasted state may all be causes of oxidative stress.[4] Combinations of genetic and environmental factors may increase susceptibility of a fetus or newborn to experience damage caused by excessive oxidative stress after a dose of acetaminophen.[4] Inflammation caused by oxidative stress in the metabolism of acetaminophen may then prevent microglial cells from properly interacting with neurons in order to maintain their proper function which could cause neurologic disorders like ADHD.[31] Because acetaminophen clearance significantly increases during pregnancy, patients may be more likely to exceed recommended doses because the therapeutic effects go away faster.[31] This increase in dosing then leads to even more oxidative stress through the buildup of toxic metabolites.[31]

One study conducted careful analysis of DNA methylation patterns in blood samples from umbilical cords of fetuses exposed to at least 20 days of acetaminophen compared to a control with no exposure.[32] Differences in DNA methylation patterns in genes known to be involved in oxidative stress and neural transmission were found in children who were diagnosed with ADHD who had also experienced long-term prenatal acetaminophen exposure. These findings indicate a dosage effect of acetaminophen on DNA methylation pattern disruptions, which is also observed in mice where long-term acetaminophen exposure was associated with altered cognitive function.[32] Another study also suggests that oxidative stress mechanisms may explain the association between perinatal acetaminophen use and ADHD.[33] This study analyzed umbilical cord data for the presence of unmetabolized acetaminophen, glutathione (the antioxidant that detoxifies NAPQI) precursors, and 8-hydroxy-deoxyguanosine, a known biomarker for oxidative stress[4,33] (12). They found that high levels of unmetabolized acetaminophen present in the umbilical cord corresponded to higher levels of glutathione precursors and 8-hydroxy-deoxyguanosine. They also found that as 8-hydroxy-deoxyguanosine levels increased, the risk for developing ADHD also increased. These findings remained consistent when known risk factors for ADHD, like preterm birth and maternal drinking and smoking, were excluded.[33] One of the analyzed precursors of glutathione, methionine, was found to partially mediate the association between acetaminophen and ADHD.[33] Methionine is also a precursor for S-adenosyl-methionine, which is involved in epigenetic processes and the formation of monoamine neurotransmitters.[33] Animal studies have found that increased levels of methionine can affect the methylation of DNA and proteins, and that restriction of methionine stimulates glutathione levels and reduces oxidative stress.[33] Interestingly, another study also identified the potential underlying explanation for the increased risk of neurodevelopmental disorders in the third trimester of pregnancy.[28] While analyzing the cord blood, there was a remarkable decrease in hematopoietic cell frequency which highlights the increased risk for adverse effects later in the pregnancy.[34] Another study showed increased childhood hyperactivity measures were mediated by the frontal parietal-sensorimotor cortex by analyzing meconium samples. Additionally, animal studies have shown the potential of acetaminophen to alter fetal development by disrupting endocrine pathways and oxidative stress pathways.[33]

CONCLUSION

These various extensive studies highlight the importance of patient information on dosing and frequency of acetaminophen while pregnant to minimize the risk of neurodevelopmental disorders to offspring. However, these studies are observational, and while a positive correlation has been found, causation cannot be inferred. There have been several proposed mechanisms by which prenatal acetaminophen exposure may cause ADHD, and each theory should be thoroughly researched independently before a definitive statement can be made. More research should be conducted to thoroughly outline a differential dosing regimen of acetaminophen for pregnant patients to mitigate adverse outcomes for their offspring. Given recent studies, it may be beneficial for clinicians to inform pregnant patients about the potential risks of taking acetaminophen while pregnant. Patients and clinicians alike should be aware that while acetaminophen is still the preferred analgesic and antipyretic over aspirin or NSAIDs, excessive ac-

etaminophen exposure should also be limited until it is medically indicated.

AREAS OF UNCERTAINTY

Note that the studies referenced in this paper are observational and have their limitations. Epidemiological literature can be used to examine a correlation between two factors but may not provide enough evidence to assume that one causes the other. There is, however, a large enough number of studies conducted on this topic to indicate a warning to pregnant women about the potential risk. Further human epidemiological studies should be designed to control for confounding variables, and animal research should be conducted to attempt to elucidate a mechanism behind the observed association. Until there is a definitive answer to this question, pregnant women should be advised to consult their healthcare providers and to conduct a thorough risk-benefit analysis before taking acetaminophen.

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