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Review article

Prenatal paracetamol exposure and child neurodevelopment: A review

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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.

1. 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.,

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Table 1
Cohort studies summary characteristics - pregnancy APAP and offspring neurodevelopmental outcomes.

Study author date	Population	Prevalence of APAP use	Exposure assessment	Outcome and assessment tools	Main Outcomes	Effect estimates (95% CI) - ever exposed	Effect estimates (95% CI) -prolonged exposure
Brandlistuen et al. (2013)	**Norwegian Mother and Child Cohort Study (MoBA)** 2919 3 year old sibling control pairs discordant on exposure within cohort of 48,631 born 1999–2008	46%	**APAP -Maternal report** -gestation weeks 17 and 30 & 6 months postpartum questionnaires w/ 10 exposure windows to name med, days of use & indication. Exposure divided into short-term (1–27 days use) and long term (28 days or more)	**Adverse Neurodevelopment at 3 yrs** Maternal report using: 1) Psychomotor Development - Norwegian Ages and Stages 2) Externalizing and Internaling behaviors - Child Behavior Checklist (CBCL/11/2–5/LDS) 3) Temperament - Emotionality, Activity and Shyness Temperament Questionnaire (EAS)	**Measures in Sibling control analysis:** 1) Gross motor 2) Communication 3) Externalizing behaviors 4) Internalizing behaviors 5) Hyperactivity 6) Motor/walking delay	**Less than 28 days:** 1) β = 0.10 (0.02–0.19) 6) β = 0.10 (0.02–0.18)	**More than 28 days:** 1) β = 0.24 (0.12–0.51) RR~1.67 2) β = 0.20 (0.01–0.39) RR ~ 1.57 3) β = 0.28 (0.15–0.42) RR ~ 1.69 4) β = 0.14 (0.01–0.28) RR ~ 1.40 5) β = 0.24 (0.11–0.38) RR ~ 1.67 6) β = 0.26 (0.06–0.45)
Vlenterie et al. (2016)	**Norwegian Mother and Child Cohort Study (MoBA)** 51,200 mother & child pairs from MOBA version 6 born 1999–2008	41%	**APAP -Maternal report** -gestation weeks 17 and 30 & 6 months postpartum questionnaires w/ 10 exposure windows to name med, days of use & indication. Exposure divided into short-term (1–27 days use) and long term (28 days or more)	**Adverse neurodevelopment at 1.5 yrs** Maternal report using; 1) Psychomotor Development - Norwegian Ages and Stages Questionnaire (ASQ) 2) Externalizing and Internaling behaviors - Child Behavior Checklist (CBCL/11/2–5/LDS) 3) Temperament - Emotionality, Activity and Shyness Temperament Questionnaire (EAS)	**Measures in propensity score matched cohort:** 1) Communication problems 2) Motor/walking delay		**More than 28 days:** 1) OR = 1.38 (0.98–1.95) 2) OR = 1.35 (1.07–1.70)
Liew et al. (2014)	**Danish National Birth Cohort (DNBC)** 64,322 children & mothers enrolled 1996–2002	56%	**APAP-Maternal report** -Telephone interview gestation weeks 12, 30, 6 months after birth. Provided w/ list of 44 med, asked gestation weeks of use on week by week basis.	**ADHD/hyperkinetic disorder at 7 yrs** using: 1) Hospital records-hyperkinetic disorder (HKD) 2) ADHD medications −2+ prescriptions 3) Parent report ADHD like behavior- Strengths and Difficulties Questionnaire (SDQ)	**3 measures:** 1) HKD diagnosis 2) Use of ADHD med 3) SDQ total difficulties	1) HR 1.37 (1.19–1.59) 2) HR 1.29 (1.15–1.44) 3) HR 1.13 (1.01–1.27)	> **20 weeks:** 1) HR 1.84 (1.39–2.45) 2) HR 1.53 (1.21–1.94) 3) HR 1.46 (1.16–1.85)

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