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Original article

Prenatal exposure to acetaminophen and children's language development at 30 months

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ABSTRACT

Objective: To examine prenatal APAP exposure in relation to language development in offspring at 30 months of age.
Method: A population-based pregnancy cohort study including 754 women who enrolled in the Swedish Environmental Longitudinal, Mother and child, Asthma and allergy (SELMA) study in pregnancy week 8–13. Two exposure measures were used: (1) maternally reported number of APAP tablets taken between conception and enrollment; (2) APAP urinary concentration at enrollment. Language development at 30 months was assessed by nurse's evaluation and parental questionnaire, including the number of words the child used (<25, 25–50 and >50). Main study outcome; parental report of use of fewer than 50 words, termed language delay (LD).
Results: 59.2% of women enrolled in weeks 8–13 reported taking APAP between conception and enrollment. APAP was measurable in all urine samples and urinary APAP was correlated with the number of APAP taken during pregnancy ($P < 0.01$). Language delay was more prevalent in boys (12.6%) than girls (4.1%) (8.5% in total). Both the number of APAP tablets and urinary APAP concentration were associated with greater LD in girls but not in boys. The adjusted odds ratio (OR) for LD among girls whose mothers reported >6 *vs.* 0 APAP tablets was 5.92 (95% confidence interval (CI) 1.10–31.94). The OR for LD in girls whose mothers' urinary APAP was in the highest compared to the lowest quartile was 10.34 (95% CI 1.37–77.86). While it cannot be ruled out, our available data do not support confounding by indication.
Conclusions: Given the prevalence of prenatal APAP use and the importance of language development, these findings, if replicated, would suggest that pregnant women should limit their use of this analgesic during pregnancy.

1. Introduction

Acetaminophen (acetyl-para-aminophenol, abbreviated as APAP) is sold under multiple formulations (including but not limited to Tylenol in the United States, Canada and Japan, Paracetamol in Europe and Panadol in South America) and widely used as an analgesic and antipyretic. A recent study found that 56% of pregnant women in the USA used APAP during their first trimester; ibuprofen (IBP) and acetylsalicylic acid (ASA) were used by 24% and 5% [1]. Multiple human and rodent studies report a range of adverse outcomes following prenatal analgesic exposure including hormonal and reproductive tract changes [2–4] and increased risk of airway disease [5]. Several studies report associations with behavioral, attentional and social deficits [6–9] but few have examined cognitive development.

Among 1529 pregnant women in the US in 1974–1975, APAP or ASA use in the first half of pregnancy was reported by 46% and 41%, respectively. In that study use of ASA (not APAP) in the first half of pregnancy was significantly related to IQ and attention decrements, with stronger associations in girls [10]. In the Norwegian Mother and Child Cohort Study (MOBA) mothers reported APAP and IBP use at 17 and 30 weeks gestation and developmental outcomes in 2919 same-sex sibling pairs. In that study, which did not examine sex-specific effects, long term (≥28 days) prenatal use

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of APAP (but not IBP) was associated with poorer communication at three years of age [11]. A recent MOBA study reports that long-term (≥28 days) prenatal APAP exposure was also associated with impaired communication skills at 18 months [12]. A study of the Danish National Birth Cohort investigated 1491 mothers and their children and found that maternal fever and APAP use in pregnancy were independently associated with reduced IQ in 5 year olds [13], but exposure to both was not. Children born to mothers who used APAP during pregnancy and had no fever had significantly lower Full Scale IQ and Performance IQ. This study found no modification of associations by child sex.

Because impaired language development is an early marker of impaired cognitive development [14], the current study examined sex-specific associations between estimated APAP exposure in weeks 8–13 of pregnancy and language development at 30 months of age.

2. Methods

2.1. Study population

The Swedish Environmental Longitudinal, Mother and child, Asthma and allergy (SELMA) study is a pregnancy cohort study designed to investigate early life exposure and growth, development and chronic diseases (www.selmastudy.se). SELMA recruited pregnant women in the county of Värmland, Sweden between September 2007 and March 2010 [15]. Women who could read Swedish and were not planning to move out of the country were recruited at their first prenatal visit. Of the 8394 pregnant women identified, 6658 were eligible; and 2582 (39%) agreed to participate.

Of these, complete data on maternally reported APAP use and all covariates, as well as a 30-month language development assessment, were available for 905 women. These women were enrolled at their first prenatal visit, regardless of pregnancy week (range 4–19, median 10 weeks). To examine exposure in a narrower developmental window and to limit the length of the recall period, our primary analyses are restricted to women enrolled in weeks 8–13, median 10 weeks ($N = 754$). The Regional Ethical Review Board in Uppsala, Sweden approved the SELMA protocol and all participants signed informed consents prior to the start of data collection.

2.2. Language development

Language development is routinely assessed in Sweden when children are 30 months of age. This validated assessment consists of a nurse evaluation and a parental questionnaire on language use. If warranted, the nurse discusses possible referral (to a speech therapist, audiologist, psychologist or pediatrician) with the parent [16]. The questionnaire asks about the number of words the child uses; responses are categorized as <25, 25–50 and >50 words. Our primary study outcome is a parental report of the use of fewer than 50 words, which we denote here as Language Delay (LD).

2.3. Study exposures

2.3.1. Self-reported APAP use

At study entry women were asked whether they had taken non-prescription analgesics (which were categorized as APAP or other (ibuprofen (IBP) or aspirin (ASA)) since the start of pregnancy. Those who responded positively were asked to estimate the number of tablets they had taken since the start of pregnancy. Because only 9.4% of women reported taking IBP/ASA, the current analysis is limited to the use of APAP, the analgesic most commonly used in this population.

2.3.2. Urinary biomarker of APAP

At enrollment, all women were asked to provide a urine sample [17]. Urinary APAP concentration was measured in a subset of 140 women selected to over-represent children with LD. This sample included 60 girls (30 with LD) and 80 boys (50 with LD). APAP was quantified by high performance liquid chromatography with isotope dilution tandem mass spectrometry (HPLC–MS/MS) carried out on an Agilent 1260 HPLC system coupled to an AB Sciex Triple Quad 4500/5500 System [18,19]. Creatinine was analyzed using an enzymatic method [20], and used to adjust for urinary dilution. We compared urinary and self-reported APAP use and the relationship between LD and APAP exposure in the 111 women who were recruited in weeks 8–13 for whom we had with urinary APAP measurements.

2.4. Statistical analysis

Multiple logistic regression analyses were used to model LD as a function of APAP exposure as estimated both by reported use and urinary APAP concentration. Adjusted models were stratified by child sex and included the following covariates which had been selected *a priori*: maternal weight, mother's education, smoking and week of enrollment. Because clinic visits were routinely scheduled at 30 months, age at language assessment varied little and was not included in these models. Data on all covariates were obtained by questionnaire at study entry except mothers' weight at enrollment, which was obtained from the Swedish National Birth Registry.

For those reporting some APAP use from conception to study entry, exposure was categorized in three approximately equal categories (1–3, 4–6, >6 tablets) and women in these categories were compared to women reporting no APAP use.

Urinary APAP was creatinine-adjusted in all analyses and examined as both a continuous and a categorical variable. For the continuous analyses, creatinine-adjusted APAP was $\log_{10}$ transformed to normalize the distribution. In categorical analyses creatinine-adjusted APAP concentration was categorized by quartile and 2nd, 3rd and 4th quartiles compared to 1st. We report crude and adjusted odds ratios (OR) and their 95% confidence intervals (CI). All statistical analyses were conducted independently by two analysts one in SPSS [21] and one in R [22].

3. Results

3.1. Study population

Demographic information is displayed in Table 1. Study participants were young (mean age 31.3 years), well educated (65.4% had completed university), non-smokers during the first trimester (97%), and white. Mean weight for the women was 70 kg at pregnancy start. Among women who enrolled in weeks 8–13, median gestational age at enrollment was 10 weeks. Results for women enrolled at any time in pregnancy are included in STable 1.

3.2. Language delay

Language delay (the use of fewer than 50 words) at 30 months of age was reported for 64 children (8.5%) and was more common among boys (12.6%) than girls (4.1%) (Table 1). Because few children (2 girls and 14 boys) used fewer than 25 words it was not possible to analyze this outcome separately. Similarly, numbers were too few (4 girls and 13 boys) to examine the APAP-associated risk of being referred by the nurse for physician evaluation.

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