SMFM Statement: *Prenatal Acetaminophen Use and Outcomes in Children*

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Acetaminophen is the most widely used medicine during pregnancy\(^1\). While the rate of use in pregnancy is difficult to determine because it is an over-the-counter medication, large surveys have reported that 40-65\% of pregnant women use acetaminophen sometime during their pregnancy. The most common uses are for headache and fever.\(^2\) Acetaminophen crosses the placenta relatively easily and has been reported in umbilical cord blood after maternal administration in labor.\(^3\) While largely considered to be safe during pregnancy, a few recently published observational studies have reported an association between prenatal acetaminophen use and potential increased risk for adverse neurological outcomes in childhood. The purpose of this SMFM statement is to review the nature and findings of these recent studies and put them into context with the available scientific literature in order to provide guidance to practicing obstetric care providers as they discuss these issues with their patients.

Two retrospective cohort studies published within the last year have reported an association between prenatal acetaminophen use and increased risk for adverse neurological outcomes in childhood. Stergiakouli and colleagues studied the relationship between perinatal acetaminophen exposure and behavioral disorders in children including ADHD using the Avon Longitudinal Study of Parents and Children (ALSPAC).\(^4\) In the ALSPAC study, women (n=7,796) were asked at 18 and 32 weeks of gestation about acetaminophen use in the previous 3 months. Childhood behavioral issues were assessed at age 7 by the Strengths and Difficulties Questionnaire (SDQ). Maternal prenatal acetaminophen use was associated with higher odds of having conduct problems (risk ratio [RR], 1.42; 95\% CI, 1.25-1.62) and hyperactivity symptoms (RR, 1.31; 95\% CI, 1.16-1.49). Limitations for this study include the fact that acetaminophen use was self-reported (e.g. potential for recall bias) and that there was no information on dosage and duration of the exposure. Finally, the outcome was measured at one point at age 7 using a parental survey rather than assessment by healthcare professionals.

Another study published in this past year was based on data from the Danish National Birth Cohort in which women with singleton livebirths (n = 64,322) were prospectively asked about acetaminophen use in computer-assisted telephone interviews at 12 and 30 weeks of gestation, as well as at 6 months postpartum.\(^5\) Review of hospital records and psychiatric registries were performed to identify diagnoses of ASD. In this study, any prenatal use of acetaminophen was associated with an increased risk for ASD with a hyperkinetic disorder.
(Hazard ratio [HR] 1.51; 95% CI 1.19–1.92) among the offspring but not ASD without hyperkinetic disorder (HR 1.07; 95% CI 0.92–1.24). There are three other large retrospective cohort studies that have been published in the last few years (2013-2014) which examined the potential association between maternal acetaminophen use and ADHD in their offspring, all finding a mild association. However, each of these studies were limited by maternal self-report of acetaminophen use, lack of quantification of the doses, and measurement of the outcome using questionnaires assessing child and adolescent behavior. Another recently published observational study, a longitudinal study of maternal analgesic use and the subsequent occurrence of psychotic symptoms and schizophrenia in their children, found no association with acetaminophen use but did find a positive association with aspirin use (adjusted OR 2.79; 95% CI 1.27–6.07).

On January 9, 2015, the FDA announced it has reviewed possible risks of pain medicine use during pregnancy and stated: “Based on our evaluation of these studies, we believe that the weight of evidence is inconclusive regarding a possible connection between acetaminophen use in pregnancy and ADHD in children.” They determined that the existing studies had flawed designs and the results were conflicted, precluding any reliable conclusions about maternal acetaminophen use and the occurrence of ADHD. Two systematic reviews of the existing studies have both determined that evidence is insufficient to conclude that there is an association between maternal acetaminophen use and ADHD in offspring.

While correlating exposures during pregnancy with childhood outcomes is problematic, it is especially difficult with regard to neurobehavioral disorders. The definition and diagnosis of these illnesses, especially ADHD, continues to evolve. Furthermore, since the cause or causes of ADHD are unknown, there is the potential for other prenatal and postnatal confounders, such as environmental exposures and genetic predisposition, that these retrospective analyses are not able to measure. Finally, drawing conclusions on teratogenicity of a drug or other exposure based on retrospective cohorts or birth defect registries requires extreme caution. Such studies have inherent methodological limitations, including the inability to determine or control for all potential confounders, as well as recall bias, interview bias, and failure to adjust for multiple testing.
The SMFM publications committee has reviewed these new studies along with the prior literature including the FDA Drug Safety Communication. Similar to prior studies reporting an association between prenatal acetaminophen and increased odds for childhood neurobehavioral issues, these newer studies have significant methodologic and design limitations. Based on our evaluation of these studies, we believe that the weight of evidence is inconclusive regarding a possible causal relationship between acetaminophen use and neurobehavioral disorders in the offspring. As with all medication use during pregnancy, communication regarding the risks versus the benefits of prescription and other-the-counter medications use should occur between patient and provider. SMFM continues to advise that acetaminophen be considered a reasonable and appropriate medication choice for the treatment of pain and/or fever during pregnancy.
References:


