Commentary

Meconium Testing for Prenatal Acetaminophen Exposure and Attention Deficit Hyperactivity Disorder- Considering Confounding by Indication

Gideon Koren¹ and Jacob V. Aranda²

¹Department of Pharmacology, Adelson School of Medicine, Ariel University, Israel  
²Department of Ophthalmology, SUNY Downstate Health Sciences University, USA  
*Corresponding author: Gideon Koren, MD, FRCPC, FACMT, Professor and Head of Pharmacology, Adelson School of Medicine, Ariel University, Israel, Tel: +972587194777; E-mail: gidiup_2000@yahoo.com

Received: October 15, 2020; Accepted: October 28, 2020; Published: November 05, 2020

Copyright: ©2020 Koren G. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

On September 28, 2020, Baker and colleagues reported on a prospective study showing an association between meconium acetaminophen measures and the diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) in the offspring. They concluded that “caution should be used in administering acetaminophen during pregnancy” based on the fact that the use of meconium is a “biological marker” strengthens the association to the verge of causation.

We believe that this “biological assumption” may be wrong. Meconium measurements of acetaminophen are merely a proof of exposure. We argue that it is very likely that the association between acetaminophen and ADHD are the result of bias by indication.

Keywords: acetaminophen, attention deficit hyperactivity disorder, meconium, fetus, pregnancy

Introduction

For decades acetaminophen has been regarded the drug of choice for pain and fever during pregnancy, with numerous studies documenting lack of safety issue [1]. However, during the last decade repeated studies and meta analyses have suggested an association between maternal exposure to the drug and different neurodevelopmental problems, such as ADHD and autism spectrum disorder [2-4].

On September 28, 2020, Baker and colleagues reported the results of a prospective birth cohort study probing these previously observed association between in utero exposure to acetaminophen and neurodevelopment by using levels of the drug in meconium, claiming that it more objectively captures exposure of the fetus than maternal reports [5]. At age 6-8 years they completed a series of tests and found a correlation between meconium acetaminophen and evidence of ADHD. Among 345 children included in the analysis, acetaminophen was detected in 199 meconium samples (57.7%) and ADHD was diagnosed in 33 children by age 6-8 years. Compared with no acetaminophen, detection of acetaminophen in meconium was associated with increased odds of ADHD (odds ratio [OR], 2.43; 95% CI, 1.41-4.21). The authors calculated that each doubling of exposure increased the odds of ADHD by 10%. Children with acetaminophen detected in meconium showed increased negative connectivity in the sensorimotor cortices, which the authors believed is mediating an indirect effect on increased child hyperactivity. Despite of this new evidence, acetaminophen is not contraindicated in pregnancy [6]. Baker et al. suggested that this is possibly due to the fact that prior studies have relied on maternal self-report, failing to quantify acetaminophen dose, and lacking mechanistic insight.
Meconium as a biomarker for fetal drug exposure

Meconium is a fetal precursor to feces or post-natal stool, which is evacuated from the neonatal bowel over the first several days of post-natal life. The first meconium evacuation occurs within 48 hours of parturition in ninety-nine percent of neonates, with complete evacuation and transition to post-natal feces generally occurring within a maximum of 125 post-natal hours; however in very low birthweight infants, the time to passage of first meconium can be much longer [9,10]. Meconium has been extensively used for the detection of chronic in utero exposure to a wide range of drugs of abuse and ethanol metabolites [11]. The first milestone of drugs in meconium was the discovery of cocaine and metabolites in early gestational fetuses (17 weeks) leading to an initial assumption that meconium offered a detection window capable of identifying any exposures that occurred beyond first trimester of pregnancy [12]. A controlled clinical study examining cocaine and buprenorphine use in a very small number of pregnant women (N=11) suggested that maternal use of cocaine and opiates must occur within approximately 30-60 days of delivery to produce positive meconium findings. These data suggested that meconium is in fact a dynamic matrix, with its contents subject to some degree of intestinal reabsorption and/or in situ metabolism. It should be noted however that while meconium likely represents third trimester exposures, earlier exposures occurring in the second trimester cannot be clearly ruled out: only a limited range of self-dosing patterns and drugs have been examined in a very small number of women. The vast majority of research and clinical application of meconium is for detection of in utero drug abuse, including cocaine, heroin, methamphetamine, ethanol, to mention a few [11]. Detection of medicinal drugs in meconium included mostly nonsteroidal anti-inflammatory agents and antiretroviral drugs [13-14], but this research did not end up being used clinically as there are typically no toxicological or clinical questions involved.

Meconium is estimated to start depositing in the fetal intestine at approximately 12 weeks of gestation, when fetal swallowing is thought to initiate [11]. Drugs entering the fetal circulation via the umbilical cord may directly enter the meconium through the biliary system following fetal hepatic elimination or may be deposited into the meconium through the fetal gastrointestinal system following the swallowing of drugs and/or metabolites present in the amniotic fluid that were excreted through fetal urine [15]. Fetal swallowing (i.e. entero-renal cycling) is considered to be the primary mechanism by which drugs concentrate in the meconium, leading to relatively high levels that are easily detected [16]. Once drugs are incorporated into meconium, it is suggested that the matrix offers a certain degree of protection from biotransformation and elimination [18].

Hence, a positive detection of acetaminophen in meconium does not disclose either the time or length of exposure, nor the dose used, whereas this information can be collected from medical charts and maternal interviews [7]. Because
the drug is considered legitimate, there is no risk of false negative reports, as is often the case with drugs of abuse and alcohol. Yet, women’s recall may be an issue, especially regarding dose and time of use.

We believe that the big elephant in the room is the role of confounding by indication, i.e. the possibility that it is not the acetaminophen but the indications for taking it in general, and in large amounts in particular. The present meconium study does not help even minimally to address this issue. Previous studies have examined the extent and length of exposure to acetaminophen and putative neuronal damage [3]. Women who experience prolonged fever and receive more acetaminophen may do so because of infections that affect fetal brain development. Moreover, increased duration of acetaminophen exposure has been associated with smoking, obesity, depression and anxiety, and use of antidepressants [7]. The difference in BMI in Baker study in the group using the drug and the group not using the drug was not statistically significant, but quite close to it and the difference was quite big. There are known associations between maternal depression, SSRIs use and risk of ADHD in the offspring [18].

We are concerned that the quasi “biological” evidence presented by Baker et al. may lead women not to manage optimally pain and fever. Acetaminophen is the only analgesic-antipyretic medication recommended for early and late pregnancy [6]. Scaring the medical community and pregnant women against acetaminophen may lead many not to manage pain effectively during pregnancy, or to use opioid analgesics.

In conclusion, the meconium biomarker is merely a rough indicator of maternal exposure to acetaminophen. Presenting it as a biological evidence of causation of acetaminophen damage may not be scientifically justified.

References