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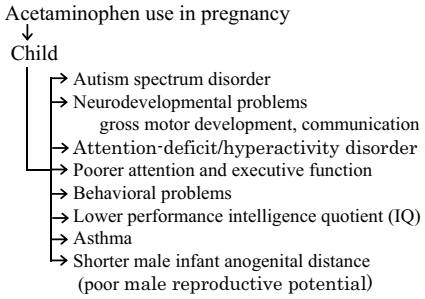
Narrative review

Is acetaminophen safe in pregnancy?

GRAPHICAL ABSTRACT



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ABSTRACT

Acetaminophen is thought to be the safest analgesic and antipyretic medicine for pregnant women, and it is widely used all over the world. However, prenatal acetaminophen was reported to be associated with asthma, lower performance intelligence quotient (IQ), shorter male infant anogenital distance (predicting poor male reproductive potential), autism spectrum disorder, neurodevelopmental problems (gross motor development, communication), attention-deficit/hyperactivity disorder, poorer attention and executive function, and behavioral problems in childhood. Each article has poor power to show risks of acetaminophen, however, the integration of the articles that showed adverse effects of acetaminophen may have power to show them. Acetaminophen use in childhood was associated with autism spectrum disorder, asthma symptoms, wheezing, and allergic disease. Acetaminophen is the safest medicine as analgesics for nociceptive pain and antipyretics in childhood and pregnancy. There is no alternative medication of acetaminophen. Acetaminophen should not be withheld from children or pregnant women for fears it might develop adverse effects. Acetaminophen should be used at the lowest effective dosage and for the shortest time. When we know the possible, rare but serious complications, we should use acetaminophen in pregnancy only when needed and no safer option for pain or fever relief is available. Health care providers should help inform the general lay public about this difficult dilemma.

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Introduction

Acetaminophen is thought to be the safest analgesic and antipyretic medicine for pregnant women, and it is widely used all over the world. However, recently many adverse effects of acetaminophen on the fetus have been reported.

In 2015, the U.S. Food and Drug Administration (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." [1].

The Society for Maternal-Fetal Medicine: Publications Committee made a statement about safety of acetaminophen in pregnancy in 2017 [2]. I am afraid that the cited articles ([3,4], etc.) are only one part of articles which showed risks of acetaminophen in pregnancy. Two articles reported that prenatal acetaminophen was associated with increased asthma in childhood [5,6]. A systematic review and meta-analysis reported that prenatal paracetamol was associated with an increased risk of childhood asthma [7]. Long-term prenatal paracetamol was associated with modestly increased risks of motor milestone delay and impaired communication skills among children at 18 months [8]. Prenatal acetaminophen was associated with lower performance intelligence quotient (IQ) in 5-year olds, however, acetaminophen treatment of maternal fever in preg-

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nancy showed an apparent compensatory association with child IQ scores [9]. Paracetamol exposure during 8–14 weeks of gestation was associated with shorter male infant anogenital distance from birth to 24 months of age, indicating intrauterine paracetamol exposure during the masculinisation programming window (8–14 weeks of gestation) may adversely affect male reproductive development [10]. A longer anogenital distance is associated with fatherhood and may predict normal male reproductive potential [11]. Moreover, many articles including systematic review reported that acetaminophen use in childhood was associated with autism spectrum disorder [12], asthma symptoms [13,14], wheezing [15,16], and allergic disease [17,18].

Each article has poor power to show risks of acetaminophen, however, the integration of the articles that showed adverse effects of acetaminophen may have power to show them.

I would like the Society for Maternal-Fetal Medicine respond to at least reference number 5–10 [5–10]. However, the Society for Maternal-Fetal Medicine (American Journal of Obstetrics & Gynecology) rejected this article. The FDA did not subsequently make a statement about safety (or danger) of acetaminophen in pregnancy.

Acetaminophen is the safest medicine as analgesics for nociceptive pain and antipyretics in childhood and pregnancy. There is no alternative medication of acetaminophen. Acetaminophen should not be withheld from children or pregnant women for fears it might develop adverse effects. Evidence of acetaminophen risks is inconclusive. However, the warning is necessary about acetaminophen use in childhood and pregnancy. For example, few physicians recognise fibromyalgia and some pregnant women with fibromyalgia receive acetaminophen over a long period in Japan. Acetaminophen is not effective for non-nociceptive pain (neuropathic pain) such as fibromyalgia, but effective for nociceptive pain. Acetaminophen should be used at the lowest effective dosage and for the shortest time. We should recognise risks of acetaminophen. When we know the possible, rare but serious complications, we should use acetaminophen in pregnancy only when needed and no safer option for pain or fever relief is available. Health care providers should help inform the general lay public about this difficult dilemma.

Conclusion

Paracetamol use in pregnancy can cause child ADHD, ASD, asthma, decreased IQ, etc.
It can cause shorter male infant anogenital distance, predicting poor fertility.
Longer use by mother, can cause neuromuscular and cognitive deficits in childhood.
Even if uncertain, lay people and physicians should know the adverse effects of it.
No safer option for pain or fever relief is available, causing dilemma.

Conflict of interest

No conflict of interest.

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