Paracetamol Use in Pregnancy: Safety Concerns

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Introduction

Paracetamol (acetaminophen) is the most widely used medicine in pregnancy [1]. Large surveys have reported that 40-65% of women take this drug sometime during their gestation [2,3]. Even though paracetamol is considered the safest analgesic and antipyretic medicine, its improper use in pregnancy may lead to serious consequences to mother and fetus/child.

Paracetamol safety concerns in pregnancy

Paracetamol is a drug with a narrow therapeutic index causing potentially fatal liver damage in overdose. Pregnant women may be more vulnerable to hepatotoxic reactions due to a change in the metabolism of the drug [4]. Increased activity of oxidative pathways of paracetamol metabolism during pregnancy contributes to the formation of toxic NAPQI metabolite [5]. Increase in its clearance can lead to a more rapid reduction in analgesic effect, which may require higher doses whereas higher doses may result in even higher oxidative toxic metabolites [4]. Unfortunately, paracetamol overdose is the most common drug overdose in pregnancy [6,7]. Fulminant liver failure was described in pregnant women both with a large single dose ingestion and with chronic administration of supra-therapeutic doses of paracetamol [8,9]. Paracetamol freely crosses the placenta and could not only affect maternal, but also fetal hepatocytes [10]. Hepatotoxicity may pose an even increased threat for the fetus, because fetal liver transiently functions as the main hematopoietic organ and the source of hematopoietic stem cells. Impairment of the pool of hematopoietic stem cells may affect immune development in other fetal organs to which they seed, e.g. the thymus [10]. Experimental data provide evidence that paracetamol can cause cytotoxic effects in human stem cells [11,12] and that prenatal paracetamol interferes with maternal immune and endocrine adaptation to pregnancy, affects placental function and impairs fetal maturation and immune development [13]. This may have long-lasting consequences on offspring immunity [13].

Epidemiological studies suggest a link between fetal exposure to paracetamol and atopy (nutrition, eczema, wheezing) in early infancy [14]. Several retrospective and cohort studies revealed a positive correlation between prenatal paracetamol exposure and children’s asthma [15-17]. Meta-analysis of 5 studies (2015) showed that any paracetamol use during the first trimester was related to increased risk of childhood asthma (pooled OR=1.39, 95% CI 1.01 to 1.91) but there was marked between-study heterogeneity and only one of these studies was adjusted for maternal respiratory tract infections [18]. Stronger evidence for the link between prenatal exposure to paracetamol and the risk of developing asthma was obtained in the Norwegian Mother and Child Cohort Study published in 2016, which found that in utero exposure increased risk of asthma at 3 and 7 years by 13% regardless of indications (pain, respiratory tract infections/ influenz and fever) [19]. Another confirmation for causality between prenatal paracetamol exposure and childhood asthma is the finding that it can be modified by maternal antioxidant gene polymorphisms [17]. There is a need for further studies aimed at the clarification of paracetamol role in the pathogenesis of asthma, establishing its optimal dose, duration of exposure, time of gestational exposure, patient genotypes that predispose to the development of asthma.

Paracetamol may impair fetal testicular hormone production [20,21] and increase the risk of cryptorchidism in the offspring [22,23]. Generation R Study found the incidence of cryptorchidism after in utero exposure to paracetamol at 14-22 weeks of gestation was 4.8%; NNH (number needed to harm) – 32 [24]. This risk may increase even further if paracetamol is taken during the masculinisation programming window (gestational weeks 8-14) [22] or in combination with other analgesics [20]. Maternal paracetamol intake during the masculinisation programming window was also associated with a shorter anogenital distance in male infants, which may adversely affect male reproductive development [25,26].
Three experimental studies published in 2016 suggest that prenatal paracetamol exposure could disrupt female reproductive development, resulting in decreased follicle number in adulthood [27-29]. There is an urgent need to verify these data in epidemiological studies [30].

Paracetamol use in the third trimester of gestation was associated with increased risk of preterm birth in women suffering from preeclampsia [31]. It has been suggested that the increased risk of preeclampsia and thromboembolic diseases shown in the analysis of data from the Danish National Birth Cohort [32] is triggered by reduced prostacyclin production in endothelial cells caused by paracetamol.

Several epidemiological studies found a link between prenatal paracetamol intake and behavioral/functional defects in the exposed offspring years later. An association between maternal paracetamol use with increased risk of autism spectrum disorder, attention deficit hyperactivity disorder and lower performance intelligence quotient (IQ) was observed in at least 9 prospective cohort studies [33]. The strongest association was demonstrated with exposure to paracetamol in the third trimester of pregnancy [34]. Findings from two large studies suggest that the association between prenatal paracetamol exposure and childhood behavioral problems cannot be explained by confounding factors [34,35]. Evidence against confounding is also supported by the results of a sibling-controlled cohort study [36]. A significant association between maternal paracetamol intake in the first trimester and language delay in children particularly girls at the age of 30 months was reported [37]. The mechanisms of paracetamol adverse effects on fetal neurodevelopment are not well understood. They may involve endocrine disruption, interference with normal immunologic development of the fetal brain or impairment of brain development through oxidative stress [38].

Conclusion

Paracetamol may be not as safe in pregnancy as previously thought. Some of above-mentioned findings are conflicting and require further interdisciplinary studies to reveal mechanisms underlying paracetamol impact on mother and fetus. Nevertheless, given a high prevalence and wide-spread use of paracetamol during pregnancy even small magnitude of excess risk may have serious public health consequences. At present there might be no safer analgesic-antipyretic for pregnant women. Paracetamol remains the drug of choice in pregnancy but measures should be taken to limit its unnecessary use. Both health care professionals and patients should be aware about paracetamol safety concerns and consider its use only in conditions which may affect maternal and child health, such as high fever or chronic pain. Paracetamol should be used at the lowest effective dosage and for the shortest time. Physicians should follow short- and long-term consequences of paracetamol use during pregnancy and report them to the pharmacovigilance authorities.

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