Journal of
Gynecology and Women's Health
ISSN 2474-7602

Juniper Publishers
key to the Researchers

Mini Review
Volume 8 Issue 5 - March 2018
DOI: 10.19080/JGWH.2018.08.555748

J Gynecol Women's Health

Paracetamol Use in Pregnancy: Safety Concerns

Ushkalova EA* and Zyryanov SK

RUDN University, Russia

Submission: February 11, 2018; **Published:** March 12, 2018

***Corresponding author:** Ushkalova EA, RUDN University, 11-115, Moscow, 119331 Russia, Tel: +79166021030; Email: eushk@yandex.ru

Keywords: Paracetamol pregnancy; Safety

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/influenza 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.

References

1. Chambers C (2015) Over-the-counter medications: Risk and safety in pregnancy. Semin Perinatol 39(7): 541-544.
2. Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA (2005) Use of over-the-counter medications during pregnancy. Am J Obstet Gynecol 193(3 Pt 1): 771-777.
3. Society for Maternal-Fetal Medicine (SMFM) Publications Committee (2017) Prenatal acetaminophen use and outcomes in children. Am J Obstet Gynecol 216(3): B14-B15.
4. Allegaert K, van den Anker JN (2017) Perinatal and neonatal use of paracetamol for pain relief. Semin Fetal Neonatal Med 22(5): 308-313.
5. Miners JO, Robson RA, Birkett DJ (1986) Paracetamol metabolism in pregnancy. Br J Clin Pharmacol 22(3): 359-362.
6. Wilkes JM, Clark LE, Herrera JL (2005) Acetaminophen overdose in pregnancy. South Med J 98(11): 1118-1122.
7. McClure CK, Katz KD, Patrick TE, Kelsey SF, Weiss HB (2011) The epidemiology of acute poisonings in women of reproductive age and during pregnancy, California, 2000–2004. Matern Child Health J 15(7): 964-973.
8. Craig DG, Bates CM, Davidson JS, Martin KG, Hayes PC, et al. (2011) Overdose pattern and outcome in paracetamol-induced acute severe hepatotoxicity. Br J Clin Pharmacol 71(2): 273-282.
9. Thornton SL, Minns AB (2012) Unintentional chronic acetaminophen poisoning during pregnancy resulting in liver transplantation. J Med Toxicol 8(2): 176-178.
10. Thiele K, Kessler T, Arck P, Erhardt A, Tiegs G (2013) Acetaminophen and pregnancy: short- and long-term consequences for mother and child. J Reprod Immunol 97(1): 128-139.
11. Yiang GT, Yu YL, Lin KT, Chen JN, Chang WJ, et al. (2015) Acetaminophen induces JNK/p38 signaling and activates the caspase-9-3-dependent cell death pathway in human mesenchymal stem cells. Int J Mol Med 36(2): 485-492.
12. Bremer L, Goletzke J, Wiessner C, Pagenkemper M, Gehbauer C, et al. (2017) Paracetamol medication during pregnancy: insights on intake frequencies, dosages and effects on hematopoietic stem cell populations in cord blood from a longitudinal prospective pregnancy cohort. EBio Medicine 26: 146-151.
13. Thiele K, Solano ME, Huber S, Flavell RA, Kessler T, et al. (2015) Prenatal acetaminophen affects maternal immune and endocrine adaptation to pregnancy, induces placental damage, and impairs fetal development in mice. Am J Pathol 185(10): 2805-2818.
14. Langhendries JP, Allegaert K, Van Den Veyckemans, Smets F (2016) Possible effects of repeated exposure to ibuprofen and acetaminophen on the intestinal immune response in young infants. Med Hypotheses 87: 90-96.
15. Shaheen SO, Newson RB, Smith GD, Henderson AJ (2005) Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. Clin Exp Allergy J Br Soc Allergy Clin Immunol 35(1): 18-25.
16. Rebordosa C, Kogevinas M, Sørensen HT, Olsen J (2008) Pre-natal exposure to paracetamol and risk of wheezing and asthma in children: a birth cohort study. Int J Epidemiol 37(3): 583-590.
17. Shaheen SO, Newson RB, Ring SM, Rose-Zerilli MJ, Holloway JW, et al. (2010) Prenatal and infant acetaminophen exposure, antioxidant gene polymorphisms, and childhood asthma. J Allergy Clin Immunol 126(6): 1141-1148.
18. Cheelo M, Lodge CJ, Dharmage SC, Simpson JA, Matheson M, et al. (2015) Paracetamol exposure in pregnancy and early childhood and

How to cite this article: Ushkalova EA, Zyryanov SK. Paracetamol Use in Pregnancy: Safety Concerns. J Gynecol Women's Health 2018; 8(5): 555748. DOI: 10.19080/JGWH.2018.08.555748

development of childhood asthma: a systematic review and meta-analysis. Arch Dis Child 100(1): 81-89.

19. Magnus MC, Karlstad Ø, Håberg SE, Nafstad P, Davey Smith G, et al. (2016) Prenatal and infant paracetamol exposure and development of asthma: the Norwegian Mother and Child Cohort Study. Int J Epidemiol 45(2): 512-522.

20. Kristensen DM, Lesné L, Le Fol V, Desdoits-Lethimonier C, Dejucq-Rainsford N, et al. (2012) Paracetamol (acetaminophen), aspirin (acetylsalicylic acid) and indomethacin are anti-androgenic in the rat foetal testis. Int J Androl 35(3): 377-384.

21. van den Driesche S, Macdonald J, Anderson RA, Johnston ZC, Chetty T, et al. (2015) Prolonged exposure to acetaminophen reduces testosterone production by the human fetal testis in a xenograft model. Sci Transl Med 7(288): 288ra80.

22. Jensen MS, Rebordosa C, Thulstrup AM, Toft G, Sørensen HT, et al. (2010) Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during for cryptorchidism or hypospadias pregnancy and risk of cryptorchidism. Epidemiology 21(6): 779-785.

23. Gurney J, Richiardi L, McGlynn KA, Signal V, Sarfati D (2017) Analgesia use during pregnancy and risk of cryptorchidism: a systematic review and meta-analysis. Hum Reprod 32(5): 1118-1129.

24. Snijder CA, Kortenkamp A, Steegers EA, Jaddoe VW, Hofman A, et al. (2012) Intrauterine exposure to mild analgesics during pregnancy and the occurrence of cryptorchidism and hypospadias in the offspring: the generation R study. Hum Reprod 27(4): 1191-1201.

25. Fisher BG, Thankamony A, Hughes IA, Dunger DB, Acerini CL (2016) Prenatal paracetamol exposure is associated with shorter anogenital distance in male infants. Hum Reprod 31(11): 2642-2650.

26. Lind DV, Main KM, Kyhl HB, Kristensen DM, Toppari J, et al. (2017) Maternal use of mild analgesics during pregnancy associated with reduced anogenital distance in sons: a cohort study of 1027 mother-child pairs. Hum Reprod 32(1): 223-231.

27. Holm JB, Mazaud-Guittot S, Danneskiold-Samsøe NB, Chalmey C, Jensen B, et al. (2016) Intrauterine exposure to paracetamol and aniline impairs female reproductive development by reducing follicle reserves and fertility. Toxicol Sci 150(1): 178-189.

28. Dean A, van den Driesche S, Wang Y, McKinnell C, Macpherson S, et al. (2016) Analgesic exposure in pregnant rats affects fetal germ cell development with inter-generational reproductive consequences. Sci Rep 6: 19789.

29. Johansson KHL, Jacobsen PR, Hass U, Svingen T, Vinggaard AM, et al. (2016) Perinatal exposure to mixtures of endocrine disrupting chemicals reduces female rat follicle reserves and accelerates reproductive aging. Reprod Toxicol 61: 186-194.

30. Arendrup FS, Mazaud-Guittot S, Jégou B, Kristensen DM (2018) EDC IMPACT: Is exposure during pregnancy to acetaminophen/paracetamol disrupting female reproductive development? Endocr Connect 7(1): 149-158.

31. Rebordosa C, Kogevinas M, Bech BH, Sørensen HT, Olsen J (2009) Use of acetaminophen during pregnancy and risk of adverse pregnancy outcomes. Int J Epidemiol 38(3): 706-714.

32. Rebordosa C, Zelop CM, Kogevinas M, Sørensen HT, Olsen J (2010) Use of acetaminophen during pregnancy and risk of preeclampsia, hypertensive and vascular disorders: a birth cohort study. J Matern Fetal Neonatal Med 23(5): 371-378.

33. Bauer AZ, Kriebel D, Herbert MR, Bornehag CG, Swan SH (2018) Prenatal paracetamol exposure and child neurodevelopment: A review. Horm Behav. pii: S0018-506X(17)30454-30463.

34. Stergiakouli E, Thapar A, Davey Smith G (2016) Association of acetaminophen use during pregnancy with behavioral problems in childhood: evidence against confounding. JAMA Pediatr 170(10): 964-970.

35. Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J (2014) Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr 168(4): 313-320.

36. Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H (2013) Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. Int J Epidemiol 42(6): 1702-1713.

37. Bornehag CG, Reichenberg A, Hallerback MU, Wikstrom S, Koch HM, et al. (2017) Prenatal exposure to acetaminophen and children's language development at 30 months. Eur Psychiatry. pii: S0924-9338(17): 32989-32999.

38. Andrade C (2016) Use of acetaminophen (paracetamol) during pregnancy and the risk of autism spectrum disorder in the offspring. J Clin Psychiatry 77(2): e152-e154.

DOI: 10.19080/JGWH.2018.08.555748

How to cite this article: Ushkalova EA, Zyryanov SK. Paracetamol Use in Pregnancy: Safety Concerns. J Gynecol Women's Health 2018; 8(5): 555748. DOI: 10.19080/JGWH.2018.08.555748