Paracetamol and Asthma: is the evidence is robust enough to change the guidelines: an overview of systematic reviews

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Abstract

Objective: To conduct an umbrella review collating the existing evidence to determine whether there is an association between exposure of paracetamol in utero or in infancy, and the development of childhood asthma.

Methods: In this review, systematic reviews with or without meta-analysis that reported the association between paracetamol and asthma in children were included. To identify relevant reviews, a search was performed in the electronic databases PubMed, the Cochrane Central Register of Controlled Trials Library, and Ovid.

Results: The search strategy in various databases identified 1913 conceivably significant studies for inclusion. After removal of 493 duplicates ,1420 studies were screened for titles and abstracts against a standard eligibility criterion. Full text screening yielded four systematic reviews to be

included in this review. Prenatal paracetamol exposure is associated with an increased risk of Asthma in the offspring. Of the four systematic reviews, 2 have an unclear risk of bias, one has a high risk and one has a low risk of bias. Association does not imply causation and we recommend further research to answer this very important question. In the absence of any other alternative, paracetamol will have to continue to be the safest and the most widely prescribed analgesic and antipyretic in pregnancy.

Conclusions: We recommend further research to answer this very important question. In the absence of any other alternative, paracetamol will have to continue to be the safest and the most widely prescribed analgesic and antipyretic in pregnancy.

Keywords: Paracetamol, Prenatal, Asthma, Umbrella review

Key Messages: Prenatal paracetamol exposure is associated with an increased risk of Asthma in the offspring. This statement is based upon the results of four systematic reviews, 2 of which have an unclear risk of bias, one has a high risk and one has a low risk of bias. Association does not imply causation and we recommend further research to answer this very important question. In the absence of any other alternative, paracetamol will have to continue to be the safest and the most widely prescribed analgesic and antipyretic in pregnancy.

Background and Description:

Asthma is a chronic respiratory disorder, which causes episodic wheezing ranging from mild symptoms to life-threatening episodes. [1]. Common symptoms of asthma in children include coughing and whistling or wheezing sounds when breathing [2].“As indicated by the Centers for Disease Control and Prevention (CDC), 1 of every 13 individuals have asthma “[3].

Asthma is the most common cause of chronic morbidity in children. At present, 1 out of 12 children have asthma. It is the significant reason behind missed school days[3].The risk factors of asthma are divided into Genetic factors and Environmental factors. Genetic factors include a

positive family history for atopy and environmental factors include exposure to allergens, dust, toxic chemicals and some drugs include Paracetamol, Aspirin, Ibuprofen etc [4].

Paracetamol (acetaminophen) is a frequently used over-the-counter analgesic for the self-management of some of the common disorders in children. Several epidemiologic observational studies suggested that paracetamol use can be a risk factor for asthma development [5,6]. It is believed that the metabolite of paracetamol diminishes glutathione levels in the respiratory tract and thus leads to susceptibility to oxidative stress. This process causes airway inflammation, which is leads to bronchoconstriction, and subsequently, symptoms of asthma [7].

Why it is important to do this overview

Paracetamol has been used commonly during all stages of pregnancy for pain relief and fever[8].Paracetamol is easily available over the counter and therefore readily accessible for self-medication [8,9]. Three is no specific guideline/policy brief reporting the association of paracetamol and development of asthma in children. It is necessary to shed some light on the effects of early-life exposure to paracetamol on the respiratory health during childhood.

Methods

All the Systematic reviews with or without meta-analysis that reported the association between the exposure of paracetamol and asthma were included. The protocol of this review was registered in PROSPERO CRD42020156023. The Population of interest was pregnant women and children less than 1 year of age. Paracetamol given by any route, any dose and any duration was the exposure. The comparater was any other analgesic or placebo. The outcome was childhood asthma. We included systematic reviews of cohort and cross-sectional studies . We included all the Systematic reviews that utilized explicit and efficient techniques to limit the bias. No time and language restrictions were applied.

Search methods

To identify the relevant reviews, an extensive search was performed in three electronic databases: PubMed, the Cochrane Central Register of Controlled Trials Library, and Ovid till November 4, 2020. Search terms included MESH terms and synonyms of ‘‘asthma,’’ ‘‘acetaminophen,’’ ‘‘paracetamol,’’ “children,” ‘‘infants,” “pregnancy,” “prenatal,” and “systematic review”. We did not apply any date or language restrictions in the electronic searches.Two authors (VS, MS) independently screened the abstracts and titles of every record to

identify studies potentially relevant to the predefined eligibility criteria. Full texts of all included studies during primary screening were retrieved and screened by two authors (VS, MS) independently, to determine the eligibility of the study. Where differences in opinion existed, they were resolved through discussion with a third author (MeS).

Data Extraction

For reviews that met the inclusion criteria, two authors (VS, MS) independently extracted data using data extraction templates. Discrepancies were resolved through discussion with the third author (MeS). All the relevant data was extracted from the each included review.

Risk of bias assessment

Two reviewers (VS and MS) used ROBIS tool to assess the risk of bias of each included systematic review. This tool assesses the level of bias presence in four domains namely, eligibility criteria of the study, identification and selection of studies, data collection and study appraisal and synthesis and findings [10].Any discrepancy in quality assessment was discussed and resolved through mutual discussion between authors.

Data synthesis

Due to the existence of heterogeneity and overlap of studies between included systematic reviews,a qualitative evidence synthesis was done instead of pooling the results of the systematic reviews.

Results

The systematic search identified 1913 conceivably significant studies for inclusion. 493 duplicates were identified and removed. 1420 studies were screened for title and abstract against a standard eligibility criterion. The level- I screening identified a total number of 39 studies for full text screening. The full text of all 39 studies were downloaded and screened for the eligibility. Full text screening yielded four systematic reviews to be included in this review. The reasons for exclusion of the 35 studies are presented in PRISMA chart [Fig 1].

The 4 included systematic reviews were published between 2009 and 2016 and originated from three different continents (Asia, Australia and North America). The characteristics of the included reviews are given in table 1.

Risk of Bias in included reviews

Risk for bias was assessed by using the ROBIS tool[12]. Two reviewers (VS and MS) performed the Risk of bias assessment. By appraising the four main domains of each systematic review, one systematic review had a low risk of bias, 2 had an unclear risk of bias and the remaining one review was identified as having a high risk of bias, as it didn't report how the risk of bias was assessed for all the included studies and what efforts were made to minimize the bias.[Table 2]

Mahyar E et al identified five studies by searching in 8 databases (Medline, EMBASE, Cochrane central register of controlled trails, American College of Physicians Journal Club, Database of Abstracts of Reviews of Effects, BIOSIS Previews, International Pharmaceutical Index and Web of Science) up to 2008. This review focussed on paracetamol exposure in pedatrics, adults and prenatal age groups and provided a subgroup analysis for each of these catagories. Out of five included studies in the prenatal subgroup, three were cohort studies and two were the cross-sectional surveys. This review reported the information on paracetamol use in the pregnancy, and development of asthma symptoms in 425140 infants. This review used New Castle-Ottawa scale to assess the risk of bias. This review found high risk for the development of persistent wheeze [OR: 1.50 (1.10-2.05)] and the development of asthma [OR:1.28 (1.13-1.39)] in children [11]. There was no information in the manuscript regarding the number of authors who performed screening of titles and abstracts and what efforts were taken to minimise errors in data collection, due to which we have reported an unclear risk of bias in the review.

Eyers S et al identified six studies by searching in four databases (Medline from 1950 to 2010, EMBASE from 1947 to 2010, Cochrane from 2005 to 2010 and Cochrane central register of controlled trails in 3rd quarter of 2010). This review included five prospective cohorts and one cross sectional survey consisting of 28038 subjects. This review had a high risk of bias, as it did not report any details about the risk of bias assessment of included studies. The authors concluded that paracetamol use in pregnancy was associated with a significant risk of development of wheezing in offspring [OR: 1.21(1.02–1.44)] [12].

Cheelo M et al identified eleven studies by searching in two databases (PUBMED from January 1967 to August 2013and EMBASE from January 1971 to August 2013). This review included retrospective and prospective cohorts studies, as they provide the highest quality of evidence amongst the observational studies. This review included both Prenatal and Infantile paracetamol exposure and reported data of 907751 subjects. This review used the New Castle-Ottawa scale to assess the bias in included studies. Subjects were divided into three sub groups according to the

time of exposure; during infancy, during Pregnancy and in infancy and during Pregnancy. There was more risk of asthma in children when the exposure was prenatal, during 1st trimester [OR: 1.39(1.01-1.91)], during 2nd and 3rd trimester [OR: 1.49(1.37-1.63)], during 3rd trimester [OR: 1.17(1.04-1.31)] and during Infancy [OR: 1.41(0.96-2.08)].The results from this systematic review found that exposure in 2^{nd} and 3^{rd} trimester have more association to develop asthma in childhood followed by infancy exposure [13].The authors concluded that the risk of asthma in cohorts exposed to paracetamol in utero or in early infancy is overstated and confounding factors like the presence of respiratory tract infections, may be causing this association. Overall, this review had a low risk of bias. This review also used the most robust definition of asthma by pre-specifying the age of diagnosis above 5 years.

Fan G et al identified thirteen studies by searching in two databases (PubMed and EMBASE up to 2016). This systematic review included cohort studies reporting the association between prenatal exposure to paracetamol and development of asthma in children. This review reported data from 1043109 subjects. Risk of bias in the included studies for this systematic review was assessed by using New Castle Ottawa scale. The findings of this review reported a significant association between use of paracetamol and asthma[OR 1.19 (1.12-1.27)]. The findings from subgroup analysis suggested that paracetamol use in all trimesters was associated with an increased risk. [14].The results of the risk of bias assessment as well as methods used to minimise error in risk of bias assessment were not reported in the manuscript, making the overall risk of bias unclear.

All the four reviews consisted of 21 different studies. Out of 21 studies 20 studies were found and one study was not available. From 20 studies 15 studies were conducted from Europe, 3 studies from United States of America and 2 studies from Australia [supplementary material].Individual study with highest population and highest duration of follow-up has reported the significant association between paracetamol exposure and development of asthma[1.35 (1.17–1.57)] [15].

Discussion

Association does not imply causation and non causal explanations for such associations cannot be ruled out. However, paracetamol exposure in utero does fulfil most, if not all of Hills criteria for causation with regard to asthma in offspring. If the results of these reviews indeed represent true causation, then the pathophysiology of “PCM associated Asthma”, has been attributed to

increase oxidative stress to the repiratory system due to a paracetamol metabolite, and the endocrine disruption theory according to which, Th2 response is favoured as a result of exposure to paracetamol in the developing fetus. This present umbrella review was conducted to collate and critically appraise the existing evidence to identify gaps in research and the current knowledge of the association of prenatal exposure to paracetamol and development of childhood asthma. All the four reviews have shown a significant association between the development of asthma in childhood and the history of prenatal exposure to paracetamol. Apart from asthma/wheezing some studies have implied that long-term use of paracetamol is also related with risk for development of Attention Deficit Hyperactivity Disorder, Hepatotoxicity and also associated with increased risk for hyperkinetic disorders [12,16]. As all such data is based upon observational studies, it is difficult to base policy recommendations on these findings. However, given the widespread use of paracetamol as an analgesic and antipyretic, there is a definite need to design a sufficiently powered cohort study, adjusting for major confounders, before we implicate paracetamol as causative.

Strength and limitations of the study

The strengths of this umberella review are a rigorous literature search and a meticulous appraisal of the included studies. We followed the methods recommended by the Cochrane collaboration for umbrella review of systematic reviews. The process followed a pre-defined protocol which was registered in PROSPERO. As recommended, we used a validated tool, ROBIS, widely used in previous umbrella reviews, to assess the risk of bias in systematic reviews [10]. The limitations are that we were unable to pool the results because of significant heterogeneity and variable confounders. In conclusion, we believe there is a need to generate high quality evidence to make recommendations about the use of paracetamol on pregnancy. While conducting RCTs of this nature may not be feasible, an approach in which prescription paracetamol is replaced by another analgesic/antipyretic may yield meaningful evidence. Animal studies can also be beneficial in answering this question. It is important to determine the dose and duration of paracetamol exposure which is harmful before any clear recommendations can be made. Till the time that such evidence becomes available, and in the absence of a better alternative, paracetamol will have to continue to play the role of the safest and most commonly prescribed antipyretic and analgesic in pregnancy.

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Tables:

Table 1:Reviews included in this umbrella review

Table 2:Risk of bias assessment in the included reviews using the ROBIS tool

Figure Legends:

Figure 1: PRISMA flow diagram for study selection for this umbrella review

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