REVIEW ARTICLE

Evaluating the Association Between Maternal Paracetamol Intake and Childhood Asthma: A Review for Prenatal Nursing Management

Nurul Hayati Mohamad Zainal[1], Jovita Ann Noel[2], Wan Nazatul Shima Shahidan[3], Tuan Nadrah Naim T Ismail @ T Manah[4], Nurulezah Hasbullah[4], Rosmaliza Ramli[4]

[1] Department of Human Anatomy, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia.
[2] Klinik Pergigian Bandar Tasek Mutiara, 14120 Penang, Malaysia
[3] Department of Pharmacology, School of Medical Sciences, Universiti Sains Malaysia, 16150, Kelantan, Malaysia
[4] Basic and Medical Sciences Unit, School of Dental Sciences, Universiti Sains Malaysia, 16150, Kelantan, Malaysia

ABSTRACT

Nurses are integral members of the healthcare team and play an important role in providing healthcare information to pregnant women. Recent evidence suggests that the use of paracetamol in pregnant women increases the risk for childhood asthma in offspring. This review aimed to provide an updated evaluation of maternal paracetamol intake and its association with childhood asthma in offspring. Using PubMed, Scopus, and Web of Science scientific databases, we screened relevant articles on maternal paracetamol use and childhood asthma. After applying inclusion and exclusion criteria, 19 articles were selected for review. Most studies support the association between maternal paracetamol use and childhood asthma in offspring. However, interpreting these findings requires caution, as factors such as maternal asthma history, emotional state, and pain levels may influence the observed associations. Therefore, the use of paracetamol for fever and pain management in pregnant women should be approached judiciously.
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Corresponding Author:
Rosmaliza Ramli, PhD
Email: rosmalizakk@usm.my
Tel : +609-7675835

INTRODUCTION

WHO highly recommends that healthcare professionals including nurses, set regular appointments with pregnant women for their antenatal check-ups (1). Being part of the healthcare team, nurses play an important role in delivering key elements of information as summarized in the WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience which include the use of supplements and drugs during pregnancy to achieve positive pregnancy outcomes (2). Paracetamol which is also known as acetaminophen, is an over the counter (OTC) drug which makes it easily accessible without the prescription by healthcare providers. Known for the management of fever and pain, paracetamol has been used by over 50% of pregnant women globally (3,4). Thus, knowledge updates on the use of paracetamol among healthcare providers including nurses are crucial to ensure maternal and foetal health are not compromised by the use of this drug.

The history of paracetamol has been described excessively in many review articles (5,6). Paracetamol was first synthesised in 1873 by Harmon Northrop Morse but its antipyretic property was only discovered in 1893 by Von Mering. However, it was not until the 1950s that paracetamol was commercially accepted and available on the market as an antipyretic and analgesic. In 1979, the US Food and Drug Administration established a system to assess the teratogenic risk of drugs based on studies conducted in both animals and humans. This system classifies paracetamol as a drug in Pregnancy Category B which indicates that its use is safe in pregnant women as supported by the lack of foetal risk when administered to animals, although there is not enough evidence from well-controlled studies in pregnant women. Due to its long history of use and relatively safe profile, it is not surprising that paracetamol is commonly used by more than half of pregnant women worldwide (3,4). The use of paracetamol during pregnancy is crucial especially for the treatment of high-grade fever and severe pain that may harm both the foetus and the mother if left untreated (7–10). The use of

paracetamol and other antipyretics have been shown to minimise the risk of these potential harms in the majority of clinical trials, albeit not all (11–13).

Although paracetamol had an unvarying safety profile during routine usage, there was a rising concern on its toxicity especially when taken by pregnant women. Growing evidence suggests that prenatal paracetamol exposure due to maternal paracetamol intake could lead to various but significant postnatal morbidities including childhood asthma (14). Although inconsistencies exist in the literature, many researchers recommend precautionary measures regarding paracetamol use during pregnancy (14,15). This article aims to review relevant studies that evaluated and reported the association between maternal paracetamol intake and childhood asthma in offspring and highlight the factors and mechanisms that may explain this association.

MATERIALS AND METHODS

The search engines used to retrieve relevant articles for this review were PubMed, Scopus, and Web of Science. Relevant articles were searched using the keywords “paracetamol”, “acetaminophen”, “childhood asthma”, and “prenatal exposure” from 2002 until 2023. All articles found and chosen for this review were peer-reviewed full journal articles with original data, written and published in English. Non-peer-reviewed articles, conference abstracts, letters, and articles without full-text available articles found in other languages were not included in this review. The articles were selected according to PRISMA criteria (16) (Fig 1). The final total number of articles included in this review was 19 articles.

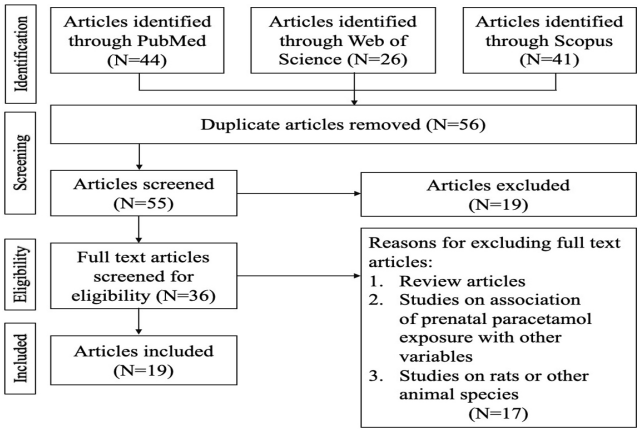

Fig. 1: Article selection process including the number of records identified, included and excluded, and the reasons for exclusions using PRISM 2020 flow diagram

MATERNAL PARACETAMOL INTAKE AND CHILDHOOD ASTHMA IN OFFSPRING: DATA FROM LITERATURE

Although the prevalence of asthma is decreasing in high-income countries, its prevalence in middle- and lower-income countries remains unchanged for the past three decades (17). Asthma is a chronic respiratory disease that affects all stages of human life—childhood, adulthood, and elderly. Asthma has been listed as one of the top ten causes of Disability-adjusted Life Years (DaLY) in children aged 10 – 15 years (18). Childhood asthma imposes a significant burden on both parents and children. Parents need to avoid places with carpets when looking for accommodation during holidays, take leave from work when their children have asthma exacerbation and hospital admission, and may face additional financial burden if they opt for private clinics to avoid long waiting times (19). Meanwhile, children with asthma have limited activities particularly in sports, and may face teasing from peers as "sickboy" or "sickgirl." They also lose valuable learning time due to being absent from school during asthma exacerbations (19).

Following an observation that the use of paracetamol was associated with asthma and rhinitis in children, a group of clinicians and scientists conducted an ecological survey on international paracetamol sales and the prevalence of atopic diseases in children and adults (20). Their findings were published in the year 2000 reporting that paracetamol sales were parallel with the increase in the prevalence of wheeze in both adults and children of 13-14 years old. As paracetamol is the most commonly used drug by the world population, this article raised concerns among the scientific community and sparked a wealth of small- and large-scale epidemiological studies to investigate further this observation. Although there are conflicting data from these studies, most researchers agreed that prenatal paracetamol exposure is associated with childhood asthma (Table I) (21–34). However, this positive association becomes less significant when adjusted for confounding factors such as paternal smoking status, maternal history of asthma, and maternal psychosocial history including stress due to pain (Table I) (31,34–36).

Notably, when compared to other common analgesics such as aspirin and ibuprofen, these medications did not show any association with childhood asthma (Table I) (35), (Table II) (32). This finding suggests that this association is specific to paracetamol and not with other common analgesics used.

Table I: Studies that showed association between maternal paracetamol intake and childhood asthma in offspring

Study time	Study type	Cohort	Data collection method	Trimester investigated	Paracetamol dose and frequency	Main study results	Study
Early in pregnancy with EDD between 1 April 1991 and 31 December 1992 until children aged 42 months	Prospective study	14 541 pregnancies with 14 062 live-born children	Questionnaires	Data collection: Early and late Association seen during: Late pregnancy	Not at all, sometimes, most days, every day	Frequent use paracetamol in late pregnancy (20-32 weeks) was associated with an increased risk of wheezing in the offspring at 30-42 months	Shaheen *et al.* 2002 (21)
Early in pregnancy with EDD between 1 April 1991 and 31 December 1992 until children 81 months	Prospective study	14 541 pregnancies with 14 062 live-born children	Questionnaires	Data collection: Early and late Association seen during: Late pregnancy	Not at all, sometimes, most days, every day	Use of paracetamol in late pregnancy was positively associated with asthma in children aged 69 – 81 months	Shaheen *et al.* 2005 (22)
October 2005– February 2006	Cross-sectional study	38 asthmatic patients aged between 3 and 10 years old	Questionnaire	Not reported	Not reported	Usage of paracetamol during pregnancy was associated with allergic asthma (p=0.03)	Riece *et al.* 2007 (23)
Years not clearly stated. Started during the first trimester and followed up children 3-5 years	Randomised controlled study	345 females recruited in the first trimester	Questionnaires	Data collection: First, second, and third trimesters Association seen during: Middle to late pregnancy	Not reported	Use of paracetamol in middle to late pregnancy was significantly related to wheezing	Persky *et al.* 2008 (24)
1996-2003	Prospective study	66445 women	Questionnaires	Data collection: First, second, and third trimesters Association seen during: First trimester	Total number of weeks exposed within each trimester. Number of pills per week.	Paracetamol use during any time of pregnancy was associated with increased risk of asthma at 18 months, hospitalisation due to asthma up to 18 months, and diagnosed asthma at 7 years. The highest risk was observed for paracetamol use in the first trimester and persistent wheezing at 18 months and 7 years.	Rebordosa *et al.* 2008 (25)
1998 - 2006	Prospective study	1442 eligible mothers, 714 children enrolled	Questionnaires	Data collection: First, second, third trimester Association seen during: Second and third trimesters	Not reported	Prenatal exposure to paracetamol predicted current wheeze and the risk increased monotonically with increasing number of days of prenatal paracetamol exposure	Perzanowski *et al.* 2010 (26)
Early in pregnancy with EDD between 1 April 1991 and 31 December 1992 until children aged 7.5 years	Prospective study	14 541 pregnancies with 14 062 live-born children	Questionnaires	Data collection: Third trimester at 32 weeks Association seen during: Late pregnancy	Not at all, sometimes, most days, every day	The univariate effect of maternal use of paracetamol in late pregnancy on doctor-diagnosed asthma in children was stronger than the effect of postnatal use	Shaheen *et al.* 2010 (27)
2003 until children aged 4.5 years	Prospective, longitudinal study	Children born in the region of western Sweden in 2003, 8176 families	Questionnaires at 6 and 12 months, 4.5 years of age	Not reported	Note reported	Prenatal paracetamol exposure increased the risk of inhaled corticosteroid treated wheeze at preschool age	Goksur *et al.* 2011 (28)

CONTINUE

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Table I: Studies that showed association between maternal paracetamol intake and childhood asthma in offspring. (CONT.)

Study time	Study type	Cohort	Data collection method	Trimester investigated	Paracetamol dose and frequency	Main study results	Study
1996-2009	Registry-based cohort study	All singleton born alive in Northern Denmark from 1 January 1996 to 31 December 2008 and were followed from birth until date of asthma diagnosis or end of follow-up date 31 December 2009	Data on maternal by-prescription paracetamol was extracted from the Aarbus University Prescription Database (AUPD). Data on asthma was extracted from Danish National Patient Registry (DNPR)	Data collection: First, second, and third trimester Association seen during: All trimesters	At least 1 maternal paracetamol prescription from 30 days before the first day of the last menstrual period and until delivery	Prenatal exposure to maternal use of prescription paracetamol was associated with an increased risk of asthma in children	Andersen *et al.* 2012 (29)
1999-2002	Longitudinal prebirth cohort study	2128 women who delivered live infant, only 1490 mother-child pairs enrolled in Project Viva	Interviews and questionnaires	Not reported	Never, intermediate (1-9 times), high (≥10 times)	Paracetamol intake during pregnancy was associated with increased risk of early childhood recurrent wheeze and asthma	Sordillo *et al.* 2014 (30)
2005- enrolled for 18 months	Ongoing web-based birth cohort study	4252 children of mothers who have access to internet	Questionnaires	Data collection: First and third trimester Association seen during: First and third trimester	Number of days (1-2 days, 3-7 days, more than 7 days per month, actual number of days)	The risk of wheezing was higher in infants exposed to paracetamol in first and third trimester **Adjustment for potential confounders reduces this risk*	Migliore *et al.* 2015 (31)
1 March 1996 – 1 November 2002 follow-up until 2010	Prospective study	63652 live-born singleton	Interviews and questionnaires	Data collection: First, second, and third trimester Association seen during: Not mentioned	Not reported	Maternal paracetamol use during pregnancy was associated with a modest increased risk for asthma	Liu *et al.* 2016 (32)
1999-2008 follow-up until 7 years old	Prospective study	95200 mothers and 114500 children	Questionnaires	Data collection: 18 and 30 gestational weeks Association seen during: Not mentioned	Not reported	There were independent modest associations between asthma at 3and 7 years with prenatal paracetamol exposure	Magnus *et al.* 2016 (33)
1 January 2003 – 31 December 2003 follow-up until 6 months old	Prospective study	58316 singleton births	Interviews and Questionnaires	Data collection: First, second, and third trimester Association seen during: Second and third trimesters	Once per month or less, once per week, about 3 days per week, or every day	Paracetamol exposure during pregnancy was associated with childhood asthmatic symptoms	Liew *et al.* 2021 (34)

*EDD: Estimated due date

Table II: Studies that show no association between maternal paracetamol intake and childhood asthma in offspring

Study time	Study type	Cohort	Data collection method	Trimester investigated	Paracetamol dose and frequency	Main study results	Study
1 March 1991 – 30 June 1992, follow-up for 18 months	Prospective study	4811 mothers and 3329 children	Questionnaires	At 20 weeks of pregnancy	Not at all, sometimes, most days, and every day	A higher but non-significant risk of asthma was observed for those whose mothers used paracetamol during pregnancy compared with those who used aspirin	Piler *et al.* 2018 (35)
July 2005 – end of 2010	Prospective study	Population of 492999	Data from National Patient Register and Swedish Prescribed Drug Register	Not reported	Not mentioned	Paracetamol use in pregnancy does not cause childhood asthma/wheeze.	Shaheen *et al.* 2019 (36)
April 1997 – June 2000	Prospective study	3413 women, 1871 children	Interviews and Questionnaires	First and third trimesters	1-7 days per month, 8-14 days per month, more than 14 days (but not every day) per month, and everyday	Paracetamol use during both the first and the third trimester was not associated with increased risk of asthma in children. There was no evidence of dose response, and paracetamol consumption of more than 10,400 mg month did not increase risk of asthma in children	Kang *et al.* 2009 (45)
1 January 1992, follow-up for 10 years	Prospective study	3754 children	Questionnaires	First, second, and third trimesters	Paracetamol intake throughout pregnancy: "Yes" or "No"	Paracetamol exposure in pregnancy was not associated with asthma at ten	Bakkeheim *et al.* 2011 (46)
1999-2007	Prospective study	685015 children	Interviews	Second and third trimesters	Not mentioned	Maternal use of paracetamol did not seem to increase the risk of childhood asthma	Kallïn *et al.* 2013 (47)

Although most studies define childhood asthma by referring to the presence of wheezing and doctor's diagnosis, two studies considered the presence of wheezing only as an indirect indicator of asthma (Table I) (21,26) which could contribute to the inconsistent primary end point and outcome measured in each of the studies included in this review. Perzanowski et al. (2010) justify wheezing as the primary end point in their study due to the potential bias in physician-diagnosed asthma in young children as reported by The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee (37,38). In addition, earlier studies reported that 50% of children may have at least one episode of wheezing before the age of six due to viral respiration infection and not due to asthma (39–41).

METHODS OF ASSESSMENT FOR MATERNAL PARACETAMOL INTAKE

The assessment of maternal paracetamol intake in studies varies in methodology, which can impact the reliability and validity of the data. In this review, three studies (Table I) (7,36), (Table II) (29), obtained data on maternal paracetamol intake from prescription registers, while all other studies used questionnaires and maternal recall, ranging from 3 weeks to one-year study period (Table I) (21–28,30–34), (Table II) (35,42,43). While obtaining data from the existing hospital records can avoid bias in memory recall, it also reduces the sample size of pregnant women taking paracetamol. As paracetamol is an OTC drug worldwide, maternal paracetamol intake could be underreported as unprescribed paracetamol intake by these pregnant women may be missed out from their data. In this context, assessing maternal paracetamol intake via questionnaires does provide a larger sample size, however, as recall may be subjective and depends on the recall ability of the pregnant women and mothers involved, the data on the paracetamol intake among these subjects must be interpreted with caution. Interestingly, studies among academics have shown that although the ability to recall memories declines by age and time recall interval, most people can still provide highly detailed information across age and time of up to two years when it comes to life events (44).

Therefore, while questionnaires can capture a broader range of maternal paracetamol intake, including OTC purchases, the data must be interpreted with caution due to potential recall bias. Conversely, prescription register data, although more accurate, may underestimate the total intake.

FACTORS THAT LINK MATERNAL PARACETAMOL INTAKE AND CHILDHOOD ASTHMA IN OFFSPRING

Pregnancy trimester

The correlation between paracetamol use during specific trimesters of pregnancy and its potential link

to asthma in offspring lacks a clear trend. Moreover, conflicting data exists between earlier and more recent studies regarding the influence of trimester timing. One of the factors that may affect the results of these studies is the definition of asthma used in each of the studies as explained above. Nevertheless, the majority of studies indicate that childhood asthma predominantly develops in children whose mothers had consumed paracetamol during their second and third trimesters (Table 1) ((21,22,24,26,27,34).

Significance of drug dose, intake frequency and gestation age

The teratogenic effect of a drug relies on five principles; drug dose, drug mode of administration, gestation age, genotype, and mechanism of action of the drug (45,46). Out of these five principles, the majority of the articles reviewed focused on gestation age as one of the factors that link maternal paracetamol intake with childhood asthma (Table I) (21,22,24–27,29,31,34) (Table II) (35,42,43,47) with only one article (Table I) (42) included drug dose in their study. Most studies evaluated paracetamol consumption in pregnant women by classifying intake frequency into various categories, a methodology that varies across studies (Table I and Table II). However, these categories may also serve as proxies for the quantity of paracetamol ingested by the pregnant women. The significance of drug dosage, frequency, and gestational age will be explained further below.

Drug dose

As paracetamol crosses the placental and gets to the foetal circulation, the dose and frequency of paracetamol taken by the pregnant women can be an indicator of foetal paracetamol exposure. When termed pregnant women take paracetamol, its concentrations in these women are comparable to the concentration of paracetamol found in the infant's blood cord (48). A paracetamol pregnancy pharmacokinetic model developed to study the placental foetal-maternal transfer after paracetamol exposure further confirms this finding (49). Theoretically, a therapeutic dose of a given drug for an adult is a toxic dose for paediatric patients, which may explain why even a therapeutic amount of paracetamol taken by pregnant women may disrupt the normal physiology and tissue development of the foetus. However, a low dose of paracetamol intake during pregnancy may still be safe for the foetus. A study conducted in Southern New England, US involving 1871 children reported that maternal paracetamol consumption of 10,400 mg per month (or approximately one tablet per day) did not increase the risk of childhood asthma in the offspring (Table II) (42).

Several studies categorised the frequency of maternal paracetamol intake (Table I) (21,22,25,27,30,31,34), (Table II) (35,42)while other studies only assessed the intake by asking the pregnant women whether they had taken paracetamol at any time during their pregnancies, and recorded their responses only as "yes" or "no" accordingly (Table I) (29) (Table II) (43). Although these studies revealed that the majority of pregnant women use paracetamol sparingly or intermittently during their pregnancies, with one study indicating that those who consumed paracetamol most days or daily comprised of less than 1% of all participants (Table II) (35), the notable link between maternal paracetamol usage and childhood asthma suggests that prenatal exposure to paracetamol increases the risk of childhood asthma irrespective of the frequency of maternal paracetamol intake. Not surprisingly, this risk is increased with the increased frequency of maternal paracetamol intake (34).

Gestational age

The transfer of nutrients, and other maternal blood constituents including drugs from maternal blood to foetal circulation occurs via the placenta. Although the placental barrier functions to filter harmful constituents from the maternal circulation, the transfer differs between trimesters. The early-stage placental barrier (in the first trimester) lacks vascularisation and has selective permeability, while in the later stage of the placental barrier (in the second and third trimesters), the vascularisation increases (50,51) allowing more blood constituents from mothers to get transferred to the foetus during later pregnancy. The changes in placental barrier vascularisation may explain why most studies reported a significant association between maternal paracetamol intake and childhood asthma in the offspring occurs when paracetamol was taken during the second and third trimester (Table I) (21,22,24,26,27,34)

Other confounding factors that link maternal paracetamol intake with childhood asthma in offspring

Maternal asthma

The link between maternal asthma and childhood asthma in the offspring has been reported in many studies (52,53). This association may be contributed by both genetic inheritance and prenatal exposure. However, one study reported maternal asthma as a stronger predictor than paternal asthma for childhood asthma in their offspring (54). Although reports from numerous preclinical studies investigating the association between maternal asthma and childhood asthma in offspring are available (53), the exact mechanisms of this association remain largely unknown. A review on maternal asthma and its impact on foetal lung summarises the potential mechanisms that may link maternal asthma with asthma in offspring. These mechanisms involve changes in the foetal lung (impair in surfactant synthesis and airway development), foetal immune system (affecting T helper/T helper 2 (Th/Th2) balance and bronchial innervation), and the placenta (reduced signals for lung maturation and placental signalling) (55). However, it is worth to note that mothers with uncontrolled asthma

during pregnancy are more likely to give birth to children with early onset of asthma (56). In this regard, improving control of maternal asthma during pregnancy has been shown to reduce the risk of childhood asthma in offspring (57).

Coffee Consumption

Interestingly, for pregnant women who took coffee, the risk of childhood asthma was found to be lower compared to those without coffee consumption (32). Findings from more recent studies showed that high maternal level of coffee and its related metabolites prevent childhood asthma in the offspring (58,59). Interestingly, similar finding was also observed in children; the high coffee-related metabolites reduced the risk of asthma in children of 6 years of age (59). However, this data should be interpreted with caution as taking coffee during pregnancy may affect fertility and cause preterm birth, metabolic disorders (such as diabetes mellitus and hypertension), and new born health problem (low birth weight and childhood obesity (60). The observed lower risk of childhood asthma among offspring of coffee-consuming pregnant women might be due to antioxidant and immune-protective properties of coffee (61,62), which could potentially counteract oxidative stress and protect the immune body system. An initial study on caffeine activity on 5 lipoxygenase (5-LOX), an enzyme involved in the synthesis of an inflammatory mediator involved in asthma leukotriene, demonstrated that caffeine has an inhibitory effect on 5-LOX (63) thus it may prevent asthma development. Caffeine may also reduce bronchial hyperresponsiveness in asthma; as shown in a study in murine asthma model, where nebulised caffeine reduced airway hyperresponsiveness in mouse model of asthma (64). However, given the potential adverse effects of coffee intake during pregnancy, further research is needed to better understand this association and confirm these findings.

Stress and Pain

Pregnant women who took paracetamol and had a history of mental stress and pain during their pregnancies showed a higher risk of their children developing asthma (Table I) (26,34,36). The association of maternal stress with cognitive, behavioural and health problem in the offspring is well-documented in the literature (65–67). However, the mechanism to explain this association remains unclear. The increased risk of childhood asthma among offspring of mothers who experienced stress and pain during pregnancy could be related to the effects of stress hormone—cortisol on foetal development. Both psychological and physiological stresses elevate cortisol levels by activating the hypothalamus-pituitary axis. Prolonged elevated cortisol level has been associated with behavioural, endocrine and immunological functions (68). In animal studies, the increase in cortisol level has been shown to inhibit the release of interleukin 4 (IL-4) an anti-inflammatory cytokines and administration of IL-4 ameliorates chronic mild stress in mice (69). High cortisol level also caused airway inflammation driven by Th2 cell (70) and decrease in CD4+, CD25+ and Foxp3 expression (71) in bronchial lymph nodes of murine models of stressed asthma. Collectively, these events disrupt the respiratory immune system leading to allergic asthma. In human, transplacental transfer of maternal cortisol foetus has also been reported following maternal stressful events (72,73). In addition to the aforementioned mechanisms that relate the elevated cortisol release with asthma, epigenetic pathway involving methylation of ADCYAP1R1 and CRHR1 was found to increase cortisol level in foetus (74) and children (75). Altogether, these mechanisms could contribute to the development of asthma in the offspring.

Confounding factor and its effect on study outcomes

Confounding factors could introduce data misinterpretation and bias in the study outcome. The effects of confounding factors could be eliminated or reduced before the study is performed by establishing a good study design or after the completion of data collection, during data analysis (76–78). The former includes sample selection by either randomisation, restriction, matching, or stratification while the latter requires data on the anticipated confounding factors also included during data collection. As paracetamol is commonly used by pregnant women, eliminating confounding factors is imperative to confirm cause-effect relationship on the association between maternal paracetamol intake and childhood asthma with minimal bias.

With regard to the association between maternal paracetamol intake and childhood asthma in offspring, analysing the confounding factors could help validate the accuracy of the study's findings. Some studies reported that even after the adjustment for a set of confounding factors such as maternal asthma or other atopic diseases, migraine, and infections during late pregnancy, the association between maternal paracetamol intake and childhood asthma remained strong (Table I) (21,22,24,26,27). Other studies reported that adjusting for confounding factors decreased the effect estimates for childhood asthma (Table I) (25,30–32) although the association remained significant. Interestingly, some studies reported that the significant association between maternal paracetamol intake and childhood asthma was confounded by other factors such as anxiety and pain (Table II) (36) and therefore, following adjustment for confounding factors, the association became not significant.

It is worth to note that these conflicting findings on the effects of confounding factors could be contributed by sample size and study design. Studies that showed negative association had smaller sample size (Table II) (35,42,43) and the data collected on maternal paracetamol intake was limited to prescription records (Table II) (36,47) potentially leading to underreporting of

paracetamol use and impacting the statistical significance in the data analysis. A well-constructed study design, emphasizing on the methods and procedures for data collection and clearly defining exclusion and inclusion criteria for subject recruitment are critical (79). A hierarchy for non-randomised studies for controlling confounders suggests that non-randomised studies are least biased when they employ longitudinal designs that assess exposure prior to the outcome and account for confounders measured at baseline, preferably including baseline measurements of both the exposure and the outcome (80).

Further research is needed to explore the association between the factors mentioned above with childhood asthma. Understanding the underlying mechanisms can help in developing guidelines for safe medication use to minimize the risk of asthma in the offspring. In this regard, a few studies have made attempts to propose the possible mechanisms for this association which are explained below.

MECHANISMS FOR MATERNAL PARACETAMOL INTAKE AND CHILDHOOD ASTHMA IN OFFSPRING

Although the link between prenatal paracetamol exposure and childhood asthma is still debatable, several studies have made attempts to explain the mechanisms of this association (81–85). The roles of N-acetyl-ρ-benzoquinone imine (NAPQI), cytochrome P450 (CYP450) super family and nuclear factor erythroid 2-related factor 2 (Nrf2) in paracetamol metabolism during prenatal paracetamol exposure and childhood asthma will be further elucidated in this section. Most of the mechanisms explained in the literature emphasised the role of the by-product of paracetamol metabolism, NAPQI, as the precursor for the development of asthma in children via prenatal paracetamol exposure.

The role of N-acetyl-ρ-benzoquinone imine (NAPQI) in the antioxidant pathway of paracetamol metabolism

There are two main pathways in paracetamol metabolism which include detoxification and oxidation pathways (Fig 2). Upon ingestion, paracetamol is biotransformed to acetaminophen- sulphate and acetaminophen-glucuronide by the action of enzymes sulfotransferase, 3′- phosphoadenosine-5′-phosphosulfate (PAPS) and uridine-5′-diphospho-glucuronosyltransferase (UGT). These pathways are considered the detoxification pathway for paracetamol. Paracetamol metabolites produced via detoxification pathway have recently been used to study the association between maternal paracetamol intake and childhood asthma in Boston population. This study measured several paracetamol metabolites including acetaminophen glucuronide in the blood cord and revealed positive association between maternal paracetamol intake and childhood asthma, particularly in children without allergic co-morbidities (86). Another pathway involves the oxidation process mediated by human CYP450 enzymes, a membrane-bound haemoproteins which generates an electrophilic intermediate known as NAPQI (87). Under normal physiological conditions, NAPQI, which is a toxic metabolite, undergoes conjugation by binding to the sulfhydryl group of glutathione to form mercapturic acid and other non -toxic related products, before they are excreted in the urine (88,89).

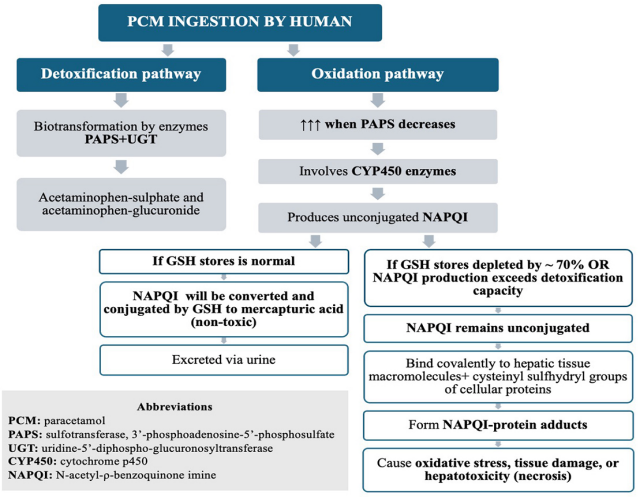

Fig. 2: Paracetamol metabolism in human body via detoxification and oxidation pathways following paracetamol ingestion

Evidence suggests that the low level of PAPS to biotransform paracetamol may cause the paracetamol to undergo the latter oxidation pathway instead (88,90). This oxidation pathway causes more NAPQI to be produced, subsequently depleting the glutathione which results in the accumulation of toxic metabolite NAPQI in the human body. The accumulation of unconjugated NAPQI will occur if glutathione stores are depleted by approximately 70% either by malnutrition or insufficient amount as in alcoholics, or if the production of NAPQI exceeds the capacity of its detoxification. This accumulation of NAPQI causes further depletion of glutathione. The unconjugated NAPQI will bind covalently to hepatic tissue macromolecules and cysteinyl sulfhydryl groups of cellular proteins forming NAPQI-protein adducts causing oxidative stress, tissue damage, or necrosis to the liver especially (90–92). This is because in the absence of glutathione, NAPQI remains in its toxic state and as it is a reactive metabolite, it will bind to mitochondria DNA, leading to cell injury and eventually cell death. In this regard, oxidative stress has also been linked to the pathogenesis of several lung diseases including asthma (93). Therefore, antenatal paracetamol exposure which leads to the presence of NAPQI in foetal circulation could possibly be one of the

mechanisms that lead to childhood asthma.

The role of the CYP450 super family in the antioxidant pathway of the paracetamol metabolism

Several important isoenzymes of the CYP450 super family including human CYP2E1, CYP1A2, CYP2A6, and CYP3A4 are responsible for paracetamol metabolism via the oxidative pathway that produces NAPQI. However, the production of NAPQI is directly caused by two isoenzymes, CYP2E1 and CYP1A2 (82,88,94). Although CYP2E1, an N-nitrosodimethyl-amine demethylase, contributes only 10% of NAPQI production, an increase in its activity has been shown to increase NAPQI and oxidative stress which results in liver cell injuries (94). In agreement with this data, studies on different compounds have shown that inhibition of CYP2E1 leads to the attenuation and inhibition of liver cell injury following paracetamol ingestion (95–98).

The association of childhood asthma and CYP2E1 has been reported in a study on the single nucleotide polymorphisms (SNPs) and toxic environment pollutes with asthma. Choi et al. (2017) reported that children with SNPs CYP2E1 and exposed to the airborne carcinogen benzo[a]pyrene are significantly highly more susceptible to asthma as compared to those without any of these risk factors (81). Inhibition of both CYP1A2 in humans and CYP3A4, which is CYP1A2 analogue in mice has also been shown to protect asthmatic patients who are taking asthmatic medication theophylline (99) and aminophylline (100). However, the effects of these isoenzymes on paracetamol prenatal exposure and childhood asthma are still inconclusive.

The role of the nuclear factor erythroid 2-related factor 2 (Nrf2) in the antioxidant pathway of the paracetamol metabolism

Studies have shown that Nrf2 plays an essential role in protecting the liver cells from hepatotoxicity during paracetamol ingestion and overdose (101). Nrf2 is a transcription factor that upregulates glutamate cysteine ligase (GCL) (102–104), a key enzyme in GSH synthesis critical for detoxifying NAPQI and protecting liver cells from injury. The activity of GCL is regulated by P- c-Jun-N-terminal kinase (P-JNK), a key modulator in paracetamol-induced liver toxicity; whereby the inhibition of P-JNK has been shown to increase GCL activity, thereby promoting GSH recovery following paracetamol ingestion (105).

Disrupted interaction between Nrf2 and Kelch-like ECH-associated protein 1 (KEAP1) (Nrf2 inhibitor protein) permits the suppression of Nrf2 degradation following transcription of a large battery of cytoprotective genes via binding to the antioxidant response element (ARE) (99). Stabilized Nrf2 triggers the expression of cytoprotective genes and anti-oxidative responses following exposure to oxidative stressors like cigarette smoking. This results in an anti- inflammatory expression profile, which is essential for the initiation of the healing process (84). Recent evidence further supports the role of Nrf2 in hepatotoxicity. Substances like caffeic acid, a phenolic compound from many natural products; and tanshinone, the main active ingredients in S. miltiorrhiza have been associated with the activation of the Nrf2 signalling pathway which protects the liver from paracetamol-induced liver injury in mice (106,107).

The relationship of N-acetyl-ρ-benzoquinone imine (NAPQI) and reduced glutathione (GSH) with T helper cells 2 (Th2) in allergic diseases

NAPQI has been shown to induce T helper (Th) cell activity, which is involved in the adaptive immune response. Th2 is elevated in allergic diseases such as asthma and allergic rhinitis (108–110). Other than NAPQI, glutathione depletion also may cause decreased levels of Th2 in mice with retrovirus-induced immunodeficiency syndrome (AIDS) (111). Moreover, the reduced form which is also the active form of glutathione–GSH has been shown to be involved in a vicious cycle of airway inflammation and injury and thus are related to asthma development and severity. GSH is present in all tissues and fluids throughout the major organs in the human body including the liver and lungs. GSH is ubiquitous in all tissues and fluids across major organs of the human body, notably in the liver and lungs. It is particularly abundant in the airway epithelial lining fluid, where concentrations are 100 times higher than in the plasma. The following are some of the critical roles that GSH plays in relation to asthma: (i) detoxifying electrophilic substances like xenobiotics; (ii) scavenging free radicals; and (iii) regulating cellular processes like DNA synthesis and repair, differentiation, apoptosis, and immunological function (112). During paracetamol metabolism, the depletion of GSH due to the overproduction of NAPQI has been shown to elevate the Th2 response (83). Although the role of GSH in regulating the Th2 levels during paracetamol ingestion has not been fully explored, the depletion of GSH due to conjugation of the toxic metabolism NAPQI may induce Th2 production and consequently the development of asthma.

Mechanisms of maternal paracetamol intake and its effect on the fetus during the intrauterine period

Paracetamol readily crosses the placental barrier with concentration levels almost identical in the pregnant mother and the foetus thus maternal intake of paracetamol can be considered as an indicator of foetal exposure (48). Pharmacokinetics analysis for a 1,000 mg oral paracetamol dose indicate a strong correlation between the contents in maternal venous blood (12.3 μg/mL) and foetal blood (11.2 μg/mL) with pregnant women showing higher paracetamol clearance rates (36.8%–84.4%) and higher volume of distribution (3.5–60.7%) than non-pregnant women (48). Furthermore, pregnant women experience the highest levels of toxic metabolite NAPQI in the first trimester, followed by the

second and third trimesters as compared to non-pregnant women (113). In intrauterine, NAPQI binds to the foetal lung epithelium and causes hyperresponsiveness of bronchial tissues. This further explains why NAPQI/ oxidative stress has been linked to the pathogenesis of several lung diseases including asthma (93). Therefore, antenatal paracetamol exposure which leads to the presence of NAPQI in foetal circulation could be one of the mechanisms that lead to childhood asthma.

Less is known about how prenatal exposure to paracetamol may result in childhood asthma unless the foetus' glutathione levels are sufficiently reduced to impact the lung development (114). Research on adult mice that were administered paracetamol during gestation and were experiencing an allergic airway challenge provides evidence for the effects of maternal paracetamol use on offspring (115). The increment of leukocytes, especially eosinophil infiltration of the airways may indicate a higher risk of developing asthma. A cohort study conducted on 1201 singleton births in Los Angeles (LA) reported that maternal paracetamol use in pregnancy was associated with offspring asthmatic symptoms and wheezing in early childhood (34). In addition, the exposure-outcome relationship in this LA cohort was stronger for women who experienced high psychosocial stress in pregnancy and among Black/ African American and Asian/Pacific Islander children. Asthma in children has already been linked to a rise in maternal illnesses, including respiratory infections and thus, paracetamol was used as the treatment for these mothers (116).

In summary, the evidence suggests that the production of NAPQI, the activity of CYP450 enzymes, Nrf2 signalling, and GSH levels all contribute to the increased risk of childhood asthma following prenatal paracetamol exposure. Further research is necessary to fully elucidate these mechanisms and inform guidelines for safe use during pregnancy.

CONCLUSION

Paracetamol remains a preferred choice among pregnant women for managing fever and mild to moderate pain due to its established safety profile over decades. However, recent concerns linking maternal paracetamol use with childhood asthma in offspring warrant careful consideration. While many studies suggest an association, newer research indicates that the presence of additional confounding factors may influence this relationship, suggesting that paracetamol alone may not significantly elevate the risk of childhood asthma. As such, healthcare professionals should continue recommending paracetamol as primary medication for fever and pain management in pregnant women. Nevertheless, patient counselling is crucial as confounding factors such as history of maternal asthma, maternal infection, as well as pain and stress have been shown to play a major role in the association between maternal paracetamol intake and childhood asthma in offspring. This information needs to be included when advising pregnant women to encourage judicious use, emphasizing the importance of using paracetamol only when necessary to minimize potential risks such as childhood asthma and other health issues in offspring linked to prenatal paracetamol exposure. In this regard, a development of Clinical Practice Guidelines for paracetamol usage among pregnant women will help healthcare providers including nurses to provide a more guided consultation to their patients. Prescription of paracetamol should also be carefully monitored by senior nurses or medical officers to ensure a judicious paracetamol prescribing among junior nurses.

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