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SYSTEMATIC REVIEW AND META-ANALYSIS

Effect of Acetaminophen use during pregnancy on adverse pregnancy outcomes: a systematic review and meta-analysis

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ABSTRACT

Introduction: A high number of women are exposed to acetaminophen during pregnancy worldwide. This drug safety during pregnancy regarding preterm birth, birth weight, and fetal development has not been well described. This study investigated the effect of acetaminophen use during pregnancy on selected adverse pregnancy outcomes.

Areas covered: Databases were searched to identify studies reporting the effects of acetaminophen use during pregnancy on preterm birth, low birth weight, and small for gestational age. The studies' quality was assessed by the Newcastle-Ottawa Scale and the Methodological Index for Non-Randomized Studies. Risk ratios with 95% confidence intervals were estimated using a fixed or random-effects model. Six studies were included for final review, four cohort and two case-control studies. We found no increased risk of preterm birth (RR 0.97; 95% CI 0.59–1.58), and decreased risks of low birth weight (RR 0.65; 95% CI 0.59–0.72) and small for gestational age (RR 0.69; 95% CI 0.50–0.97). Acetaminophen exposure during the third trimester revealed non-significantly in the outcomes.

Expert opinion: Exposure to acetaminophen during pregnancy appears to not increase the risk of the outcomes analyzed. However, there is a lack of information regarding the exposure dose and frequency of acetaminophen use.

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KEYWORDS
Acetaminophen; low birth weight; meta-analysis; pregnancy; preterm birth; small for gestational age; systematic review

1. Introduction

Acetaminophen is a non-steroidal anti-inflammatory drug (NSAID) that has analgesic and antipyretic activities, being the most used drug for the treatment of pain or mild to moderate fever in pregnant women [1]. For decades it was the only recommended analgesic for use during pregnancy and breastfeeding, due to the supposed safety of its use [2,3]; however, the safety of its use during pregnancy regarding preterm birth, birth weight, and fetal development has not been well described in the literature.

Acetaminophen is one of the most consumed drug in the world, either by prescription or self-medication, reaching a proportion of use among pregnant women of 65.1% [4]. Despite the decrease in the consumption of acetaminophen among pregnant women in recent years, its prevalence of use remains high [5] and some studies show that its use increase throughout gestational trimesters [6,7] which is not observed with other NSAIDs [8,9].

Considering the high number of women exposed to acetaminophen during pregnancy and the potential of this drug to affect the health of both the pregnant woman and the fetus, as it crosses the placenta after the administration of therapeutic doses and its fetal concentration reaches levels very close to the maternal ones [10,11], it is necessary to investigate any potential risks arising from its use during pregnancy.

Adverse pregnancy outcomes as preterm birth, low birth weight, and small for gestational age are the leading causes of perinatal and neonatal mortality and contribute to childhood morbidities [12–16]. Moreover, exposure to acetaminophen during pregnancy has been associated with adverse childhood outcomes, as asthma [17], attention deficit hyperactivity disorder (ADHD) [18], and autism [19]. Therefore, the development of childhood disorders associated with prenatal exposure to acetaminophen may be mediated by adverse pregnancy outcomes [20,21].

According to scientific literature, there are two hypotheses by which acetaminophen influences preterm birth. The first hypothesis states that acetaminophen reduces prostacyclin production by endothelial cells through prostaglandin production inhibition. Thus, acetaminophen reduces uterine contractions and prolongs pregnancy [22,23]. The second states that the reduction in prostacyclin synthesis causes an imbalance in thromboxane (TXA2) which may increase the risk of pre-

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Article highlights

- Acetaminophen is the most used drug for pain and fever in pregnancy.
- The safety and consequences of this drug use during pregnancy regarding pregnancy duration and fetus development are not well described.
- This systematic review demonstrated that acetaminophen use during pregnancy was not associated with an increased risk of preterm birth, low birth weight, or small for gestational age.
- No evidence of an increased risk for adverse pregnancy outcomes in women exposed to acetaminophen in the third trimester was found in our analysis.

This box summarizes key points contained in the article.

eclampsia [24,25] and, consequently increase the risk of induced preterm birth [2].

Previous studies suggest that therapeutic and toxic doses of acetaminophen can affect not only maternal but also fetal hepatocytes due to this drug hepatotoxicity, which can affect fetal liver function. Since the fetus' liver is responsible for hematopoiesis, injuries in this organ can cause a reduction of stem cells in key organs, impairing the fetus' growth and development [11,26]. Due to ethical issues related to the possibility of harmful events, randomized clinical trials do not allow to answer questions regarding drug safety in pregnancy. In this case, observational studies are the main available source of evidence [27]. Therefore, it is important to perform a systematic review and meta-analysis of all available observational studies of pregnant women exposed to acetaminophen to discuss the amount, quality, and findings of the existing studies.

This systematic review and meta-analysis aimed to investigate the association between acetaminophen use during pregnancy and the risk of adverse pregnancy outcomes.

2. Methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement [28]. The protocol for this systematic review was registered in the International Prospective Register of Systematic Review (PROSPERO) database before starting the literature search (CRD42020159638).

2.1. Eligibility criteria and outcome measures

A study was considered eligible for this systematic review if it met the following criteria: (1) observational study (cohort, case-control, or cross-sectional study); (2) exposure to acetaminophen any time in pregnancy; (3) at least one adverse pregnancy outcome (preterm birth; low birth weight, or small for gestational age) was reported. No language or date restrictions were applied. Review articles, case reports, case series, and animal studies were excluded.

Preterm birth (delivery <37 weeks of gestational age) [29], low birth weight (birthweight <2500 g) [13], and small for gestational age (birth weight <10th percentile) [30] were considered as the main outcomes of interest for the meta-analysis.

2.2. Search strategy

Searches were conducted using PubMed, Embase, Ovid, Scopus, Web of Science, and Virtual Health Library (VHL) databases to identify observational studies that assessed the use of acetaminophen during pregnancy and adverse pregnancy outcomes from inception to 5 April 2020. Published papers registered in these databases were identified using the descriptors 'pregnancy,' 'acetaminophen,' 'preterm birth,' 'low birth weight,' and 'small for gestational age.' Grey literature sources were also searched (Google Scholar, Catálogo de Teses e Dissertações da CAPES, and Open Access Theses and Dissertations) and reference lists of all selected studies were reviewed to identify any studies that were not indexed in the databases but might be pertinent for inclusion in this review.

2.3. Study selection and data extraction

Titles and abstracts were independently examined by 2 reviewers (CTC and RSG) for potentially relevant articles using Rayyan [31], a free web software that helps expedite the initial screening of abstracts and titles. The studies that met the inclusion criteria in the initial phase had their eligibility confirmed by reading the full article. The articles that met all the inclusion criteria were included in the qualitative and quantitative synthesis. If the 2 reviewers could not agree on whether an article should be included in the study, a third reviewer (DBS) was consulted.

Details of the included studies were extracted independently by the reviewers (CTC and RSG) with the use of a data extraction form. The extracted data include information related to publication and design, sample, age of participants, period of study completion, study location, year of study, trimester of exposure, study outcome, confounding control, and statistical measures, as the number of events in each group which allowed the calculation of the summarized risk ratios (RR). Study authors were contacted by e-mail when the selected studies did not provide all the information necessary to calculate the association measures.

2.4. Quality assessment

Two review authors (CTC and RSG) independently assessed the quality of the included studies in the systematic review using two different scales: The Newcastle-Ottawa scale (NOS) and The Methodological Index for Non-Randomized Studies (MINORS).

NOS assesses the quality of non-randomized studies in meta-analyses [32]. This scale has 3 domains and its score is based on a star system, ranging from zero to nine stars: selection (four stars), comparability (two stars), and exposure or outcome of interest (three stars). A score of 0 to 3 stars was considered a low-quality study, a score of 4 to 6 stars was considered a moderate quality study, and a score of 7 or more stars was considered a high-quality study [33].

MINORS is a validated index to assess the quality of observational studies [34]. This tool contains 12 questions, of which

the final four are specific for comparative studies. The global ideal score for non-comparative studies is 16 points, while for comparative studies it is 24 points. Quality assessment of the included studies was considered as follows: very low quality, 0 to 6 points; low quality, 7 to 12 points; moderate quality, 13 to 18 points; and high quality, 19 to 24 points [35].

2.5. Statistical analysis

Data were extracted from eligible studies and arranged in a 2 × 2 table. The RR and their respective confidence intervals (95% CI) were calculated following either the fixed or the random-effects model, depending on the heterogeneity between the studies. The heterogeneity and inconsistency were assessed using Cochran's Q test and I^2 statistic [36]. When heterogeneity was confirmed ($p < 0.05$; $I^2 > 50\%$), the random-effects model was applied and when feasible, a subgroup analysis was conducted to create more homogenous groups. We did not generate a funnel plot because a minimum number of ten studies were considered for the elaboration of this graph and judgment of the risk of bias associated with missing data [37].

The kappa statistic was calculated to verify the interrater reliability [38] in the risk of bias assessment. Analyses were carried out with R version 4.0.0 and the 'meta' package version 4.13–0 [39].

2.6. Sensitivity analysis

Sensitivity analysis was performed restricting analysis to high-quality studies. A second sensitivity analysis was performed restricting the analysis to studies with third-trimester acetaminophen exposure only, as the NSAIDs are not recommended in the third trimester of pregnancy due to the risk of fetotoxicity [40,41]. Hence, exposure to this drug in the third trimester may lead to a different risk for adverse pregnancy outcomes compared to exposure in the first and second trimesters.

3. Results

3.1. Selected studies

The initial search returned a total of 1,111 records, of which 454 were duplicates. After screening titles and abstracts, 11 studies were analyzed regarding inclusion criteria and 5 were excluded. Subsequently, references of the included studies were manually searched to detect relevant articles, but none was identified. The reasons for excluding articles were that they did not meet the criteria for the study design that had been previously defined [11,42,43], or did not analyze acetaminophen separately [44,45] (Figure 1).

3.2. Study characteristics

Six records were eligible for inclusion in the systematic review and meta-analysis, consisting of 4 cohorts [21,46–48] and 2 case-control [22,49] studies. They were published from 1999 to 2020, with 2 from Canada, 2 from Denmark, 1 from Hungary, and 1 from Kenya (Table 1).

In total, 273,720 women were included in the studies of which 39,443 were exposed to acetaminophen during pregnancy. Three studies reported on acetaminophen exposure during all pregnancy trimesters [21,47,48], 1 study reported on exposure during the first trimester [49], 1 study reported on exposure only during the third trimester [46], and 1 study did not report the time of exposure [22].

Acetaminophen use during pregnancy was assessed differently in the studies: 2 studies evaluated this exposure through prescription [46,48], 3 through self-medication [21,47,49], and 1 study considered exposure to the drug as both prescription and self-medication [22]. The studies used Risk Ratio (RR) [21], Hazard Ratio (HR) [47], and Odds Ratio (OR) [22,46,48,49] as measures of association.

3.3. Quality of the included studies

In agreement with the NOS four studies were considered as high quality [21,46–48], of which two studies were 'eight stars' [46,48] and two studies were 'seven stars' [21,47]. Two studies were considered as moderated quality and scored 'five stars' [22,49] (Table 2).

According to the MINORS, four studies were classified as high quality [21,46–48], one study as moderate quality [49], and one study as low quality [22]. One study scored 22 points [48], two studies scored 21 points [21,47], one scored 20 points [46], one scored 17 points [49], and one scored 12 points [22] (Table 3).

A perfect agreement between the reviewer's quality assessment was obtained for both tools (kappa = 1.0).

3.4. Meta-analysis

3.4.1. Preterm birth

The association between acetaminophen use during pregnancy and preterm birth was assessed by 6 studies [21,22,46–49], 4 cohorts and 2 case-control studies. There was no significant increase in the risk of preterm birth in women who use acetaminophen during pregnancy (RR 0.97; 95% CI 0.59–1.58; $p < 0.01$; $I^2 = 96.0\%$) (Figure 2).

Considering the high heterogeneity of the studies ($p < 0.01$; $I^2 = 96.0\%$), an analysis by type of study was conducted. The analysis reveals no risk of preterm birth among cohort studies (RR 0.94; 95% CI 0.54–1.65) as well as among case-control (RR 0.98; 95% CI 0.10–9.32). A significant heterogeneity was present in this analysis ($p < 0.01$; $I^2 = 97.0\%$) (Figure 3).

3.4.2. Low birth weight

Four studies evaluated the association between acetaminophen use during pregnancy and low birth weight [21,22,47,48]. The meta-analysis showed a 35.0% lower risk of low birth weight among acetaminophen users (RR 0.65; 95% CI 0.59–0.72; $p = 0.75$; $I^2 = 0.0\%$) (Figure 4).

3.4.3. Small for gestational age

Two studies estimated the association between acetaminophen exposure in pregnancy and small for gestational age [21,47]. In the meta-analysis, a 31.0% decrease in the risk of

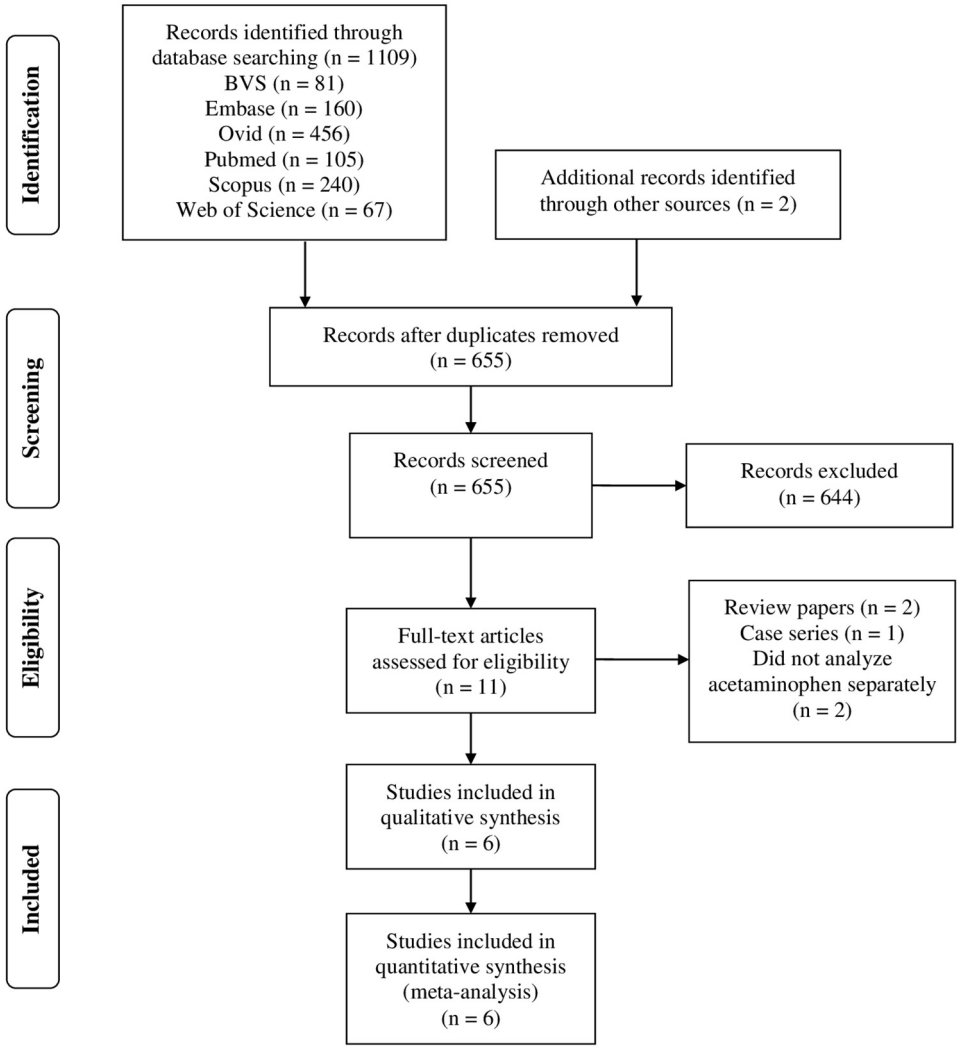

Figure 1. Flow chart of search results.

small for gestational age was observed among pregnant women who used acetaminophen (RR 0.69; 95% CI 0.50–0.97; p = 0.05; I^2 = 74.0%) (Figure 5).

3.5. Sensitivity analysis

3.5.1. High-quality studies

In analysis restricted to high-quality studies, the association with preterm birth was not significant (RR 0.94; 95% CI 0.54–1.65; p < 0.01; I^2 = 97.0%). The risks of low birth weight (RR 0.65; 95% CI 0.59–0.72; p = 0.56; I^2 = 0.0%) and small for gestational age (RR 0.69; 95% CI 0.50–0.97; p = 0.05; I^2 = 74.0%) were significantly lower among acetaminophen users (Supplementary Material).

3.5.2. Third-trimester exposure

In analysis restricted to third trimester exposure to acetaminophen, exposure was not significantly associated with preterm birth (RR 0.72; 95% CI 0.20–2.59; p < 0.01; I^2 = 99.0%), low birth weight (RR 0.46; 95% CI 0.13–1.67; p < 0.01; I^2 = 95.0%), or small for gestational age (RR 0.38; 95% CI 0.08–1.87; p < 0.01; I^2 = 99.0%) (Supplementary Material).

4. Discussion

This systematic review and meta-analysis provide a quantitative estimate of the risk of adverse pregnancy outcomes after exposure to acetaminophen during pregnancy. We emphasize two main findings; first, it was observed that exposure to acetaminophen during pregnancy is associated with a significant reduction in the risk of low birth weight and small for gestational age, but not of preterm birth. These results were observed both in the primary analysis and in the sensitivity analysis restricted to high-quality studies. Second, we found that exposure to acetaminophen during the third trimester of pregnancy is not statistically significantly associated with preterm birth, low birth weight, and small for gestational age. However, it is important to highlight the low number of studies included in the analyses.

There was a great variation in the proportion of adverse pregnancy outcomes in the included studies. Preterm birth rates ranged from 3.4% (2.7% exposed; 6.5% unexposed) [47] to 19.1% (46.0% exposed; 18.5% unexposed) [49], low birth weight ranged from 2.1% (1.7% exposed; 2.7% unexposed) [47] to 5.8% (5.4% exposed; 6.1% unexposed) [21], and small for gestational age ranged from 9.2% (7.2% exposed; 11.8%

Table 1. Characteristics of the included studies.

Study	Year	Country	Study design	N	Acetaminophen use	Exposure time	Adjustment	Outcome
Arneja [21]	2020	Canada	Prospective cohort	Exposed: 726 Unexposed: 474	Self-medication	All trimesters	Maternal age; BMI at baseline; Maternal ethnicity; Education level; Fever during pregnancy; Comorbidities; Use of other pain medications; Smoking	PTB; LBW; SGA
Bérard [46]	2018	Canada	Prospective cohort	Exposed: 2,322 Unexposed: 154,204	Prescription	Third trimester	Maternal age; Receipt of social assistance; Area of residence (urban or rural); Maternal marital status; Education level; Autoimmune rheumatic diseases; Other prescribed medication use during pregnancy for the treatment of autoimmune diseases; Maternal chronic comorbidities during the 12 months before the pregnancy; Sex of the child	PTB
Czeizel [22]	2005	Hungary	Case-control	Exposed: 173 Unexposed: 37,978	Prescription and Self-medication	Not reported	Maternal age; Employment status; Anemia; Use of other medication; Birth order	PTB; LBW
Kaburi [49]	2014	Kenya	Case-control	Exposed: 14 Unexposed: 546	Self-medication	First trimester	Housing; Area of residence (urban or rural); Pre-eclampsia; Previous preterm labor; Smoking; Alcohol consumption; Use of other medication; Herbal use; Birth order	PTB
Rebordosa [47]	2009	Denmark	Prospective cohort	Exposed: 35,992 Unexposed: 27,841	Self-medication	All trimesters	Maternal age; Socio-economic status; Pre-pregnancy BMI; Cigarettes per day; Coffee intake; Birth order; Sex of the child	PTB; LBW; SGA
Thulstrup [48]	1999	Denmark	Prospective cohort	Exposed: 123 Unexposed: 13,327	Prescription	All trimesters	Maternal age; Smoking; Birth order	PTB; LBW

PTB: Preterm birth; LBW: Low birth weight; SGA: Small for gestational age.

Table 2. Quality assessment according to NOS.

Study	Selection	Comparability	Outcome	Total score
Arneja [21]	***	**	**	7
Bérard [46]	****	*	***	8
Czeizel [22]	***	*	*	5
Kaburi [49]	**	*	**	5
Rebordosa [47]	****	*	**	7
Thulstrup [48]	****	*	***	8

unexposed) [47] to 13.3% (12.2% exposed; 14.1% unexposed) [21]. Therefore, our findings should be cautiously interpreted once these incidences may not reflect the current rates of adverse pregnancy outcomes worldwide. Additionally, there was an expressive variation in the rates of acetaminophen use among pregnant women between the studies, ranging from 0.5% [22] to 61.0% [21], approximately.

In our meta-analyses, we observed a high heterogeneity between the studies that persists after subgroup and sensitivity analysis. This could be justified by several factors like differences in study designs; introduction of selection bias in some studies; differences in the doses, frequency of use, and time of exposure to acetaminophen; and differences in some population characteristics, like age and education level.

We also observed opposite effects between some studies regarding preterm birth. Studies with women exposed to acetaminophen during pregnancy from America [21,46] and Africa [49] presented a higher risk of preterm birth while those from Europe [22,47,48] presented a reduced risk of preterm birth, which may be explained by the different prevalence of this adverse birth outcome between these continents [50]. In addition, the different ways to obtain information about acetaminophen exposure during pregnancy in the case-control studies [22,49] may also have contributed to this difference, since Kaburi et al [49] obtained this information only through self-report at the time of childbirth, which may overestimate acetaminophen use.

Most studies adjusted their analyzes for maternal age [21,46–49] and birth order [22,47]. Although the articles included in this review adjusted for several confounding factors, they were not able to control their analysis for the principal confounders described in the literature. Only one study adjusted it analyzes for ethnicity [21], one for the socioeconomic status [47], one for pre-gestational BMI [47], one for preeclampsia [49], one for alcohol consumption [49], and none for exposure to drugs of abuse.

In Arneja et al study [21], approximately 74.0% of pregnant women were white. This high proportion may have contributed to reducing the risks of adverse pregnancy outcomes among women exposed to acetaminophen since black ethnicity has been reported as a factor positively associated with outcomes as preterm birth [51] and low birth weight [52].

The majority of pregnant women included in Rebordosa et al study [47] had a high socioeconomic level (66.7%), which

Table 3. Quality assessment according to MINORS.

Study	Arneja [21]	Bérard [46]	Czeizel [22]	Kaburi [49]	Rebordosa [47]	Thulstrup [48]
A clearly stated aim	2	2	0	2	2	2
Inclusion of consecutive patients	2	2	0	1	2	2
Prospective collection of data	2	2	0	2	2	2
Endpoints appropriate to the aim of the study	2	2	0	2	2	2
Unbiased assessment of the study endpoint	2	2	1	2	2	2
Follow-up period appropriate to the aim of the study	2	2	2	1	2	2
Loss to follow up less than 5%	1	0	1	0	1	2
Prospective calculation of the study size	0	0	0	2	2	0
An adequate control group	2	2	2	2	2	2
Contemporary groups	2	2	2	2	2	2
Baseline equivalence of groups	2	2	2	0	2	2
Adequate statistical analyses	2	2	2	1	2	2
Total score	21	20	12	17	21	22

Items are scored as follows: not reported (0); reported but inadequate (1); reported and adequate (2).

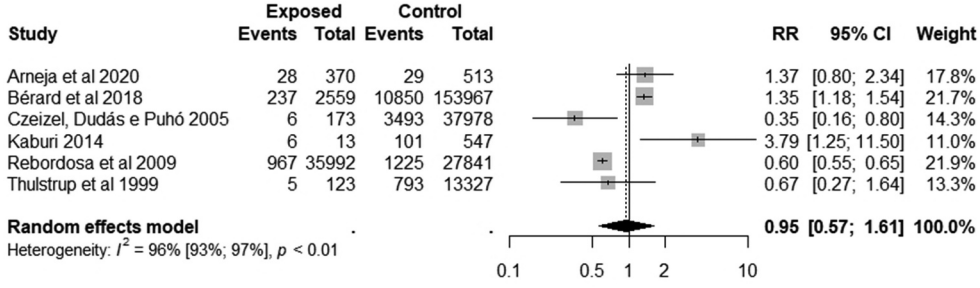

Figure 2. Association between acetaminophen use during pregnancy and preterm birth.

possibly had an impact on reducing the risk of adverse pregnancy outcomes. Despite the differences in the socioeconomic status classification in the literature and the limitations of the studies, lower socioeconomic status is a factor associated with adverse pregnancy outcomes [53,54].

Around 68.0% of the women in the study by Rebordosa et al [47] were eutrophic, which may have led to a decrease in the risk of the outcomes analyzed among the study participants. According to a systematic review and meta-analysis with 60 observational studies, pre-gestational body mass index (BMI) influences the development of adverse pregnancy outcomes. This research showed that babies born to underweight women are more likely to be preterm birth (OR 1.30; 95% CI 1.13–1.49) and small for gestational age (OR 1.67; 95% CI 1.49–1.87). Besides, they also concluded that underweight and obese mothers are more likely to have low birth weight [55].

Rebordosa et al suggest that the use of acetaminophen during pregnancy causes pre-eclampsia by reducing the synthesis of prostacyclin and subsequent effects on hypertension [47]. Case-control studies conducted in Iran and Tanzania have shown that the risk of preterm birth is 2.6 to 5.8 times higher among women with pre-eclampsia, respectively [56,57]. Moreover, a prospective cohort of 63,833 women from the Danish National Birth Cohort who gave birth to a single child born alive, found an association between acetaminophen use during pregnancy and pre-eclampsia [25]. The authors observed that women who used acetaminophen during the third trimester of pregnancy had an increased risk of pre-eclampsia (RR 1.40, 95% CI 1.24–1.58).

Kaburi et al described higher alcohol consumption by women who had preterm birth (10.3% versus 5.1%; p = 0.043) [49]. Thus, it is assumed that this difference may lead to an increase in preterm birth risk among pregnant women exposed to acetaminophen, considering that the literature shows an increase in the occurrence of adverse pregnancy outcomes among women who consume alcohol during pregnancy [58–60].

Systematic review and meta-analyses demonstrate a significant increase in the risk of preterm birth, low birth weight, and small for gestational age among pregnant women who use drugs of abuse [61–63]. Thus, the lack of control for this confounding factor can impact the associations observed in the studies.

Furthermore, we were unable to assess the effect of acetaminophen use depending on the dose and frequency of use, since none of the included studies provided information regarding exposure dose and only one study provided information on the frequency of use [21].

In our primary analysis, we found an unaltered risk of preterm birth and a reduced risk of low birth weight and small for gestational age in women exposed to acetaminophen during pregnancy. The biological plausibility of these results is not fully described in the literature. Studies have shown that acetaminophen crosses the placenta after the administration of therapeutic doses [10,64], and its fetal concentration reaches levels very close to the mother's one [10]. This medication can reduce the production of prostacyclin during pregnancy, resulting in tocolytic activity [23]. Thus, acetaminophen can impact newborns' birth weight from

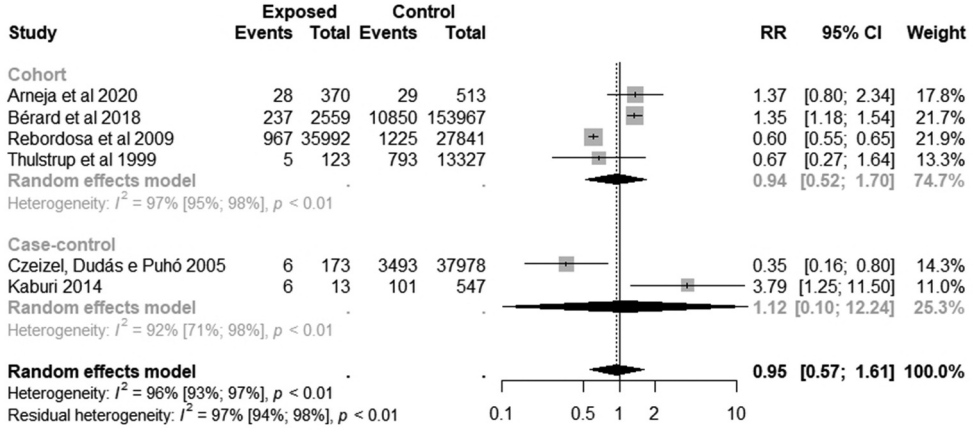

Figure 3. Association between Acetaminophen use during pregnancy and preterm birth by study type.

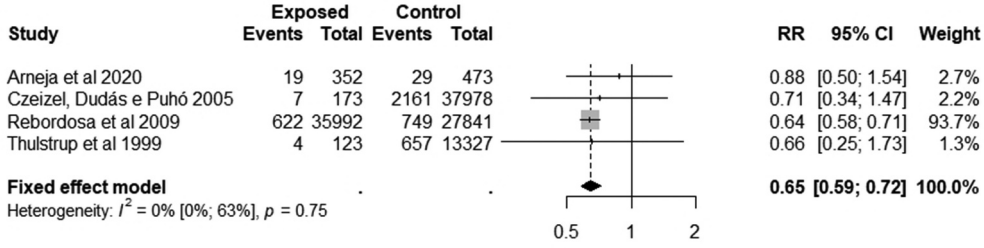

Figure 4. Association between acetaminophen use during pregnancy and low birth weight.

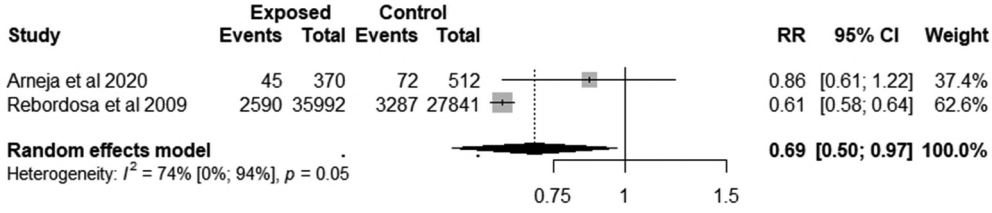

Figure 5. Association between acetaminophen use during pregnancy and small for gestational age.

mothers exposed to it, reducing the risk of low birth weight and small for gestational age.

Additionally, acetaminophen may impair maternal and fetal liver function due to its hepatotoxicity. Once the fetus's liver is responsible for hematopoiesis, injuries in this organ can reduce stem cells in the blood and affect the fetus's growth and development [26].

In the first sensitivity analysis, we analyzed data only from high-quality studies and the results of this analysis were similar to those of our primary analysis. In the second sensitivity analysis, we analyze data from studies that included exposure to acetaminophen only during the third trimester, due to the risk of fetal toxicity of NSAIDs in this period of pregnancy [40,41], and no increased risk of preterm birth, low birth weight, or small for gestational age was observed; in fact, we observed a non-significantly decreased risk of the outcomes in this analysis. Therefore, based on the existing data, it is not possible to conclude a lower risk of any of the outcomes in pregnant women exposed to acetaminophen during the third trimester of pregnancy.

Although research on the safety and potential risks of using acetaminophen during pregnancy regarding adverse pregnancy outcomes presents conflicting results, this drug is widely used during pregnancy, being the first-choice analgesic for use during pregnancy [65].

Most of the studies included in this meta-analysis did not report an increased risk for any of the outcomes [21,22,47,48]. However, the lack of evidence of a significant increase in the risk of adverse pregnancy outcomes does not necessarily mean that acetaminophen is a safe or risk-free medication during pregnancy.

4.1. Strengths and limitations

This systematic review and meta-analysis present strengths and limitations. This is a comprehensive assessment of the

evidence, incorporating all available published studies about acetaminophen use in pregnancy and adverse pregnancy outcomes. Strengths also include the use of two different risk of bias assessment tools (Newcastle-Ottawa Scale and MINORS), the use of random-effects meta-analysis to deal with the heterogeneity when needed, and the conduction of sensitivity analysis to assess the risks of the outcomes considering only high-quality studies and third-trimester exposure.

An important limitation is the possibility of type I errors and chance findings due to the low number of studies included. Although meta-analyses of small numbers of studies present valid results, they have limitations that can impact their findings [66]. Another limitation is the possibility of recall bias regarding acetaminophen use in case-control studies and selection bias in some of the included studies.

Furthermore, some of the original studies assumed in the data analysis that the exposure to acetaminophen was consistent throughout pregnancy even when this exposure was measured only once [22,46,49].

Another limitation is the different ways to obtain information on the use of acetaminophen, underestimating or overestimating the exposure. The articles included in this research obtained this information through questionnaires application [21,22,47,49], data from national systems of medicines prescription [46,48], and medical records [22]. The use of questionnaires to obtain information on the exposure, as it depends on the participants' recall and self-report, favors the recall bias in the studies. Additionally, data that consider acetaminophen use only through prescription may underestimate the exposure, since acetaminophen is widely consumed during pregnancy through self-medication [67,68].

All the included studies obtained information on the outcomes from hospital or health care records, which contributes to reducing the recall bias. However, most studies did not explain the criterion adopted for the definition of the gestational age, except for one study carried out between 1998 and 2009 that validated this measure through ultrasounds [46].

5. Conclusions

Considering the limitations previously stated, the findings of our meta-analysis suggest that acetaminophen use during pregnancy does not increase the risk of preterm birth, low birth weight, and small for gestational age. However, the available information in the literature is limited and further studies considering exposure dose and the frequency of use of acetaminophen are needed to clarify the influence of acetaminophen use during pregnancy on adverse pregnancy outcomes. Future studies should also control for the most important confounding factors that may impact outcomes, such as ethnicity, socioeconomic status, pre-gestational BMI, pre-eclampsia, alcohol consumption, and use of drugs of abuse. Moreover, new studies using real-world data or evidence could lead to more qualified evidence and help to address the role of acetaminophen on adverse pregnancy outcomes.

6. Expert opinion

Medication use during pregnancy is a very common practice, especially through self-medication, that has increased in the last few years. Nonetheless, this high pattern of consumption can be harmful to both the mother and the fetus.

Acetaminophen is one of the most used drugs by pregnant women, been the only analgesic and antipyretic recommended for use during pregnancy.

Some birth cohort studies have shown consistent associations of prenatal exposure to acetaminophen with adverse childhood outcomes, including asthma [17], ADHD [18], and autism [19]. However, there is no clear consensus about the effects of acetaminophen on child development since these associations have been contested once they may be subject to biases and confounding factors [69].

A hypothesis discussed among experts is that the development of childhood disorders associated with prenatal exposure to acetaminophen may be mediated by adverse pregnancy outcomes [20,21]. However, there is a lack in the literature regarding the consequences of its use on preterm birth, low birth weight, and small for gestational age.

The present systematic review and meta-analysis evaluated the effect of acetaminophen on preterm birth, low birth weight, and small for gestational age and indicates that this drug may represent a safe medication in pregnant women. Nevertheless, there is still a low number of studies about this theme that can impact our findings. The low number of studies reporting associations of prenatal acetaminophen exposure with adverse pregnancy outcomes may be a consequence of inaccurate exposure assessment. Most of the studies selected for review are based on mothers' reports of acetaminophen use during pregnancy, through the application of questionnaires. Consequently, adverse pregnancy outcomes could have influenced maternal responses to interviews during pregnancy; when the results are suboptimal, women may be more likely to remember any potential explanatory behavior. Self-assessment of reported exposure may also result in misclassification bias. An analytical strategy that could eliminate the possibility of misclassification bias would be to measure prenatal exposure to acetaminophen in a biological sample rather than relying on maternal self-report. Measuring chemicals in meconium, the first stool of newborn babies, can be an effective and noninvasive method to assess cumulative prenatal exposures. In this systematic review, none of the studies have used this technique.

Furthermore, the studies available in the literature so far presents several limitations as not controlling to important confounding factors that can impact the outcomes analyzed. Also, the majority of manuscripts did not evaluate the exposure dose and frequency of acetaminophen use and their effects on adverse pregnancy outcomes. Another important point that may have impacted our results is the low prevalence of the outcomes found in the selected studies.

Therefore, although we did not observe a significant increase in the risk of adverse pregnancy outcomes analyzed in our study, acetaminophen should not be presumed as

a risk-free medication during pregnancy and its use must consider the patient's clinical needs, the adequate doses, and the appropriate treatment duration; more work is needed to rule out confounding by indication and to assess generalizability before a change in clinical practice is recommended.

To better assess the causality between prenatal exposure to acetaminophen and its effects on adverse pregnancy outcomes, it is necessary to better understand its biological mechanisms. This is an important step to serve as potential targets in future intervention studies.

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Author contributions

C.T. Castro and D.B. Santos conceived the study. C.T. Castro and D.B. Santos contributed to the study design, data analysis, and data interpretation. C.T. Castro and R.S. Gama contributed to the study selection, data extraction, and interpretation of data. C.T. Castro, D.B. Santos, M. Pereira, M.G. Oliveira, T.S. Dal-Pizzol, and M.L. Barreto were involved in drafting the manuscript and revised it critically. All authors read and approved the final manuscript.

Declaration of interests

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