

The Analysis Study of Low Dose Aspirin for Prevention of Superimposed Preeclampsia in Women with Chronic Hypertension: A Comprehensive Systematic Review

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ABSTRACT

Background: Chronic hypertension (cHTN) is the greatest risk factor for the development of preeclampsia. Low-dose aspirin has been used as a therapy for preeclampsia prevention. This study aims to show effectiveness of low dose aspirin for prevention of superimposed preeclampsia in women with chronic hypertension. **Methods:** By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. Several different online reference sources, like Pubmed and ScienceDirect, were used to do this. **Results:** We compiled a total of 16 papers, 9 of which came from PubMed and 7 of which came from ScienceDirect. We excluded 1 review article, 1 duplicate article, 4 articles having ineligible subject, 3 articles having ineligible intervention, and 2 articles having ineligible outcomes data. In the end, we included five research that met the criteria. **Conclusion:** Low dose aspirin may reduce the incidence of superimposed preeclampsia in pregnant women with cHTN. However, a further investigations is still needed to determine the effectiveness.

Keyword: low dose aspirin, prophylactic aspirin, pregnancy, chronic hypertension, preeclampsia, superimposed preeclampsia

INTRODUCTION

Preterm birth, caesarean delivery, foetal growth limitation, perinatal mortality, preeclampsia, acute renal failure, pulmonary edema, and maternal stroke or death are among the adverse outcomes linked to chronic hypertension (cHTN).¹ Out of all maternal features and medical history, cHTN is the greatest risk factor for the development of preeclampsia (PE), complicating 1% to 2% of pregnancies.² Superimposed preeclampsia occurs when women with cHTN develop preeclampsia. It is characterised by either newly developed proteinuria or markedly elevated preexisting proteinuria, as well as deteriorating or uncontrollably elevated hypertension.³ Superimposed PE occurs in about 20% of women with cHTN, and after adjustment for confounding factors, the risk of preterm superimposed PE is 5 to 6 times higher in women with cHTN than in those without.²

Low-dose aspirin has been used as a therapy for preeclampsia

prevention. It began in the 1980s.⁴ Aspirin is currently the most widely used drug in the prevention of cardiovascular complications and cancer diseases.⁵ Aspirin, first synthesized in 1897, was used to relieve pain, fever, and inflammation. Its mechanism of action was elucidated by John Vane in 1971. Aspirin-induced inhibition of prostaglandin (PG) synthesis in human platelets was reported in a paper by Smith and Willis. However, the antiplatelet effect of aspirin was unclear due to the influence of classical PGs on platelet aggregation. The unique molecular mechanism of aspirin inactivating cyclooxygenase (COX) activity was identified by Philip Majerus in St. Louis.⁶

The biological mechanisms, underlying LDA-mediated benefits against PE, remains elusive. The most recognized of these mechanisms is associated with the anticoagulant effect of aspirin, due to increased thromboxane and decreased prostacyclin production in preeclamptic women's placentas.

Clinical trials showed promise, but meta-analysis studies showed aspirin was most effective when started <16 weeks of gestation and at doses >100 mg/day.^{4,5} The purpose of this systematic review is to determine the effectiveness of low dose aspirin for prevention of superimposed preeclampsia in women with chronic hypertension.

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this systematic review, we compare and contrast we compare and contrast therapeutic use of low dose aspirin for prevention of superimposed preeclampsia in women with chronic hypertension. It is possible to

accomplish this by researching or investigating the effectiveness of low dose aspirin to prevent superimposed preeclampsia in women with chronic hypertension. In addition, we also investigate neonatal outcomes, including preterm birth and miscarriage, stillbirth, or neonatal death in women with chronic hypertension taking low dose aspirin. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine effectiveness of low dose aspirin for prevention of superimposed preeclampsia. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published within the last 10 years. Examples of studies that are not permitted include editorials, submissions that do not have a DOI,

review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "low dose aspirin"; "prophylactic aspirin", "pregnancy", "chronic hypertension"; "preeclampsia"; and "superimposed preeclampsia" as keywords. The search for studies to be included in the systematic review was carried out from October, 26th 2023 using the PubMed and ScienceDirect databases by inputting the words: "low"[All Fields] AND "dose"[All Fields] AND "aspirin"[MeSH Terms] OR "aspirin"[All Fields] OR "aspirins"[All Fields] OR "aspirin s"[All Fields] OR "aspirine"[All Fields] OR "prophylactic"[All Fields] OR "prophylactically"[All Fields] OR "prophylactics"[All Fields]) AND "pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancy s"[All Fields] AND "chronic"[All Fields] OR "chronical"[All Fields] OR

"chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields]) AND "hypertense"[All Fields] OR "hypertension"[MeSH Terms] OR "hypertension"[All Fields] OR "hypertension s"[All Fields] OR "hypertensions"[All Fields] OR "hypertensive"[All Fields] OR "hypertensive s"[All Fields] OR "hypertensives"[All Fields])) AND ("preeclampsia"[MeSH Terms] OR "pre eclampsia"[All Fields] OR "preeclampsia"[All Fields] OR "superimpose"[All Fields] OR "superimposed"[All Fields] OR "superimposes"[All Fields] OR "superimposing"[All Fields] AND ("preeclampsia"[MeSH Terms] OR "pre eclampsia"[All Fields] OR "preeclampsia"[All Fields] AND (y_10[Filter]) AND (clinicaltrial[Filter]) AND (english[Filter]) used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to

determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

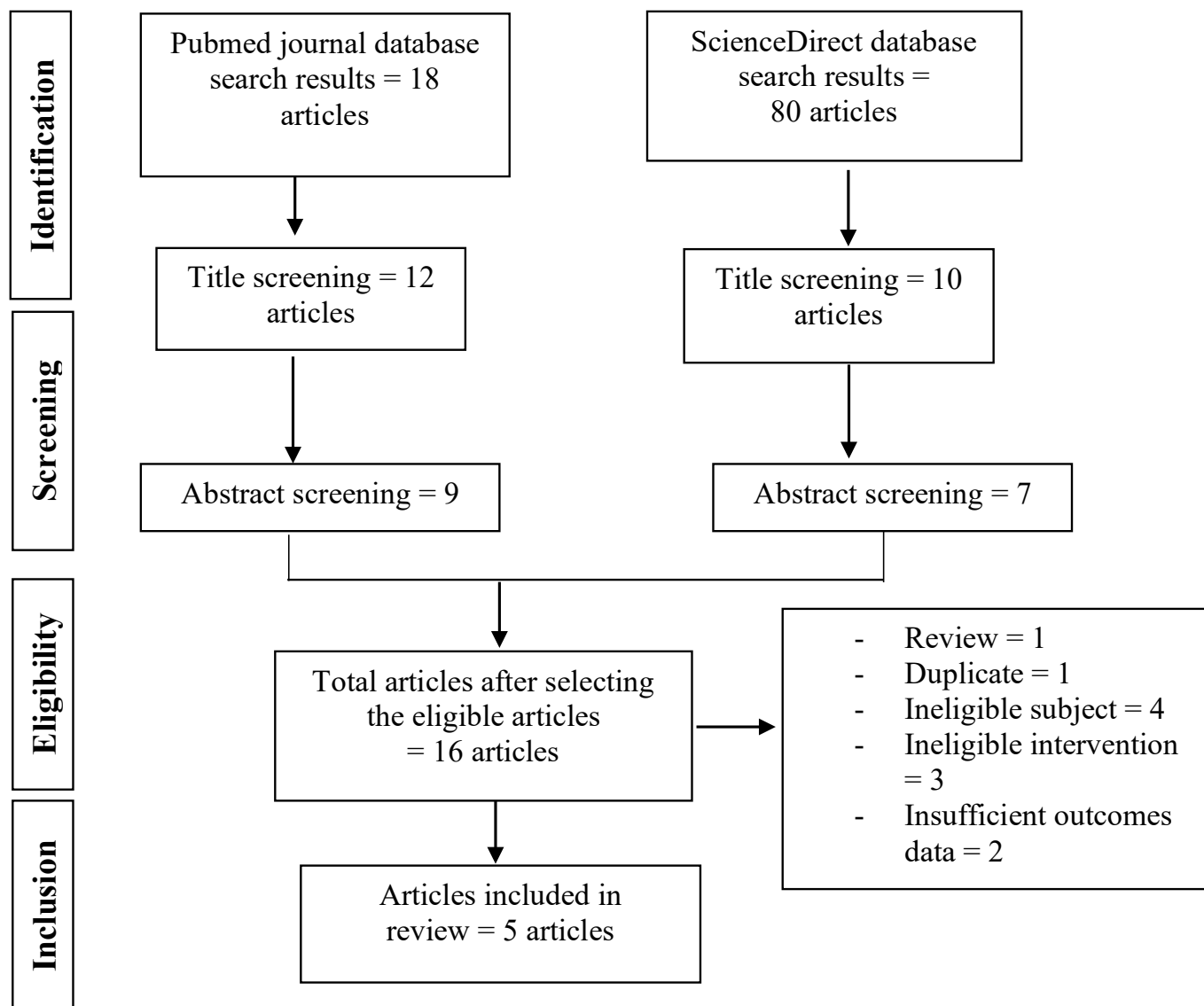


Figure 1. Article search flowchart

RESULT

In the PubMed database, the results of our search brought up 18 articles, whereas the results of our search on ScienceDirect brought up 80 articles. The results of the search conducted by title screening yielded a total 12 articles for PubMed and 10 articles for ScienceDirect. We compiled a total of 16 papers, 9 of which came from PubMed and 7 of which came from ScienceDirect. We excluded 1 review article, 1 duplicate article, 4 articles having ineligible subject, 3 articles having ineligible intervention, and 2 articles having ineligible outcomes data. In the end, we included five research that met the criteria.

Maternal outcomes

- **Incidence of superimposed preeclampsia**

Lin, et al. (2021)⁷ found that in participants with chronic hypertension, the incidence of preeclampsia showed no significant difference between the aspirin group (24.1% [58/241]) and the control group (23.0% [46/200]). Overall, in this study, 16.9% (152/898) of the participants developed preeclampsia.

The incidence of preeclampsia was 16.8% (78/464) in the aspirin group and 17.1% (74/434) in the control group (RR, 0.986; 95% CI, 0.738 - 1.317; P = .924).

Moore, et al. (2015)⁸ showed that there was a significant benefit of aspirin in women with CHTN (18.28% vs 31.18%, P = 0.041). The overall rate of preeclampsia was 25%. This study suggested that there was no significant difference in our primary outcome of preeclampsia at any time in pregnancy between the aspirin and placebo groups (22.26% vs 27.52%, P = 0.164).

Muldoon, et al. (2023)⁹ showed that the highest risk for preeclampsia was seen among those with twin pregnancies (ARR:4.10, 95% CI:2.15–7.82), a history of preeclampsia (ARR:2.75, 95% CI:1.62–4.67), and chronic hypertension (ARR:2.18, 95% CI:1.28–3.72). This study also found the highest incidence of preterm preeclampsia was documented among 35 (58.33%) with a history of preeclampsia, 22 (36.67%) with chronic hypertension. There were 660 (28.63%) pregnant individuals taking

aspirin and included in this analysis. There were 548 (83.03%) taking low-dose aspirin and 112 (16.97%) taking high-dose aspirin. There were 132 cases of term preeclampsia (20.00%) and 60 cases of preterm preeclampsia (9.09%).

Tolcher, et al. (2020)¹⁰ included 2539 women; 1273 were assigned to the aspirin group and 1266 to the placebo group for the HRA study, including women with pregestational insulin-treated diabetes mellitus, chronic hypertension, multiple gestations, or a history of preeclampsia in a previous pregnancy were enrolled between 13 and 26 weeks' gestation and randomized to 60 mg aspirin daily or placebo. Of the cohort, 1426 were non-Hispanic black (56.2%), 832 were non-Hispanic white (32.8%), 269 were Hispanic (10.6%), and 12 were categorized as other (0.5%), and there was no difference between ethnicity and race when comparing the aspirin and placebo groups ($P = .546$). This study showed that stratification by ethnicity and race did not reveal a decreased incidence of preeclampsia when

comparing aspirin and placebo for any of the subgroups ($P > .05$).

Xiang, et al. (2020)¹¹ showed that there were substantial disparities in extreme maternal hypertension, and pre-eclampsia between the treatment group (low-dose aspirin (LDA) and labetalol) and the control group. In LDA group, 30.5% or 40 women developed superimposed PE, labetalol group 30% or 38 women, and placebo group 48/1% or 61 women (chi square test 15.10, p value < 0.001).

Neonatal outcomes

- **Preterm birth**

Lin, et al. (2021)⁷ showed that there was no significant difference in the incidence of neonatal or fetal outcomes, including preterm baby between the aspirin and control groups (LDA group: 79 (17%); control group 79 (18.2%); RR 0.935 (0.705 - 1.241), $P = .644$). Xiang, et al. (2020)¹¹ showed that in LDA group, the proportion of preterm birth was considerably lower than in the control group (LDA group: 24 (18.3%); control group: 39 (30.9%); $p < 0.05$). Tolcher, et al. (2020)¹⁰

showed that there were no significant differences in other measured outcomes including preterm birth (aspirin group: 502 (39.434%); placebo group: 532 (42.022%); RR 0.94 (0.86 - 1.03); p value = .26). In Hispanic (38.636% vs 46.715%), non-Hispanic white (40.943% vs 45.455%, non-Hispanic black (38.851% vs 39.281%).

- **Stillbirth or neonatal death**

Lin, et al. (2021)⁷ showed that there was no significant difference in the incidence of neonatal or fetal outcomes, including fetal or neonatal mortality between the aspirin and control groups (LDA group: 50 (10.8); control group: 55 (12.7); RR 0.850 (0.593 - 1.218)). Tolcher, et al. (2020)¹⁰ showed that the risk of stillbirth was significantly increased among non-Hispanic black women

who received aspirin compared with non-Hispanic black women who received placebo in the high-risk aspirin study (1.4% vs 0.4%; p value = .048). Moreover, there were no significant differences in other measured outcomes including stillbirth, or neonatal death. Overall, in LDA group, stillbirth incidence is 1.650% (21), while in control group 2.528% (32); RR 0.65 (0.38 - 1.13). In LDA group, neonatal death incidence is 1.650% (21), while in control group 1.817% (23); RR 0.91 (0.51 - 1.63). Xiang, et al. (2020)¹¹ showed that there were no substantial differences in the incident of neonatal mortality among different groups (p>0.05), LDA group 3 (2.5%), labetalol group 10 (7.5%), and placebo 6 (5%) with chi square test 4.53 and p value 0.15.

Table 1. The literature include in this study

Author	Origin	Method	Sample Size	Dose	Duration	Result
Lin, 2021 ⁷	China	RCT	441 women with cHTN	100 mg	From (12-20) - 34 week	This findings showed that aspirin at a dosage of 100 mg per day did not reduce the incidence of preeclampsia in pregnant women with high risk factors in China, including chronic hypertension and did not adversely affect the mothers or neonates.
Moore, 2015 ⁸	USA	Secondary analysis of RCT	186 women with cHTN	60 mg	From recruitment - delivery	This result demonstrated that LDA reduced the risk of late-onset preeclampsia in high-risk women when initiated early in pregnancy. To optimize pregnancy outcome in women at increased risk for preeclampsia (particularly those with CHTN), this findings support initiation of LDA prior to 17 weeks' gestation.

Muldoon, 2023 ⁹	Canada	Secondary analysis of RCT	194 women with cHTN	75 - 81	Before 16 weeks' gestation	This study concluded that even while taking aspirin, 20% of pregnant individuals at high risk still went on to develop preeclampsia.
Tolcher, 2020 ¹⁰	USA	Secondary analysis of RCT	1273 women with high risk	60 mg	From 13 - 26 week	This findings showed that low dose aspirin did not decrease incidence of preeclampsia in high risk patients, including chronic hypertension.
Xiang, 2020 ¹¹	China	RCT	393 women with cHTN	NA	From 12 - 36 week	This findings showed that the use of low dose aspirin or control group are correlated with a lower incidence of SGA, neonatal hypotension, and neonatal hyperbilirubinemia relative to labetalol. This findings suggested treatment during pregnancy with mild to moderate chronic high blood pressure may help minimize mothers' and children's incidence.

DISCUSSION

The purpose of this research was to review studies published after January of 2013 and up to October of 2023 that investigated the effectiveness of low dose aspirin for prevention of superimposed preeclampsia in women with chronic hypertension. Three of five identified studies reported that low dose aspirin did not reduce the incidence of preeclampsia significantly in pregnant women in high risk patients, including chronic hypertension. However, two of identified studies suggested that low dose aspirin shows some benefits in minimizing mothers' and children's incidence when initiated early in pregnancy, including superimposed preeclampsia, preterm birth, and stillbirth, or neonatal death.

Superimposed pre-eclampsia (SPE) is a condition that develops in pregnant women with chronic hypertension when, after 20 weeks, there is a rise in blood pressure control and proteinuria, or when there is laboratory or clinical evidence of organ damage, including thrombocytopenia, kidney or hepatic failure, pulmonary edema, or

seizures. It impacts 13% to 50% of pregnancies⁴ and is linked to problems such placental abruption, preterm, fetal death, fetal growth restriction (FGR), hemolysis, high liver enzymes, low platelets (HELLP syndrome), and maternal death.¹²

Preeclampsia is more common in patients with chronic diseases such as CHTN, diabetes, lupus, renal disease, and antiphospholipid syndrome. This is probably because these conditions can cause inflammation, which can affect the endometrium and the uterine and ovarian vasculature prior to pregnancy, changing the course of implantation and placentation in the first trimester. There are two waves to the trophoblastic invasion: the decidual invasion of spiral arteries occurs in the first wave between 8 and 10 weeks, and the second wave invades myometrial segments between 16 and 18 weeks.³

Offering low-dose aspirin for the prevention of preeclampsia to individuals at risk for preeclampsia is thus the consensus recommendation of ACOG, SMFM, and the USPSTF.¹³ There are several

potential mechanisms that have been suggested: (1) enhancement of the placentation process, which is corroborated by the finding that a more significant reduction in the risk of preeclampsia is associated with early therapy initiation; (2) inhibition of platelet aggregation and its antithrombotic effect, which results in a decrease in placental infarct levels; and (3) anti-inflammatory effects and endothelial stabilization.¹⁴

Timing in aspirin initiation needs to be factored in when evaluating low-dose aspirin efficacy in preeclampsia prevention.³ For patients who are at risk, it is advised that they start taking low-dose aspirin, as recommended by ACOG and SMFM, at 81 mg per day between weeks 12 and 28 of pregnancy (ideally before 16 weeks), and to continue taking it every day until delivery or the end of the pregnancy.^{19,37} Reasonable evidence suggests that aspirin doses greater than 100 mg could be suitable substitutes for 81 mg.¹³

Multiple meta-analyses have been conducted; some suggest that low-dose aspirin can decrease the

incidence of perinatal death. Low-dose aspirin has an excellent safety profile in pregnancy, with no increased risk of adverse fetal or neonatal effects.^{3,13} Preterm birth is associated with increased rates of disability and infant death, with higher costs of healthcare both in the neonatal period and in the long term, and important personal consequences for families. The use of aspirin in pregnancies at high risk for preeclampsia has been found to significantly lower rates of preterm birth before 32 weeks, with associated significantly reduced length of neonatal intensive care unit (NICU) stay in the aspirin group (although rates of NICU admission were not affected).¹⁵

CONCLUSION

Low dose aspirin may reduce the incidence of superimposed preeclampsia in pregnant women with cHTN. However, a further investigations is still needed to determine the effectiveness.

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