Research Article

Role of Aspirin in Early Pregnancy to Reduce Preterm Births- A Systematic Review

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Abstract

Background: Preterm birth is a key contributor of neonatal morbidity and mortality and a considerable threat is posed to maternal and child health. To counter the threat, many different interventions have been used including aspirin intervention during early pregnancy. Aspirin, because of its anti-inflammatory and anti-platelet properties has been found to be efficient in reducing preterm birth rate if given during early pregnancy. In this systematic review we intend to appraise the role of aspirin in low dose in reducing the rate of premature delivery while administered during early pregnancy.

Objective: To determine whether the rate of spontaneous preterm births is reduced by administering aspirin in low dose during early pregnancy.

Methods: A comprehensive literature search from 3 databases (PubMed, Google Scholar and PakMediNet) was conducted yielding 16 final articles. Our inclusion criteria was limited to studies published from January 2013 to January 2023 and about the use of aspirin in prevent preterm birth in early pregnancy. To ensure transparency in the systematic review, we strictly followed PRISMA guidelines. Finally, we extracted the results of aspirin interventions from these studies and assembled and analyzed the final results.

Results: Out of the 362 studies from initial studies, 16 articles were finalized for the systematic review, which included 10 Randomized controlled trials studies. We studied effect of aspirin in preventing preterm birth while administered during early pregnancy based on some primary outcomes i.e. reduction in preterm birth; and secondary outcomes i.e. pre-eclampsia, post-partum hemorrhage, birth weight, gestational age and hospital length of stay. Of the 16 research articles, 13 (81%) showed a considerable decrease in preterm birth rate while only 3 (19%) studies showed no remarkable decline in preterm birth rate. In analysis of secondary outcomes, pre-eclampsia showed reduction in 8 studies while one study showed increase and one showed no effect on pre-eclampsia. Reduction in post-partum hemorrhage was shown in 4 studies while one study showed its increase. One study showed increase while 2 showed no effect on birth weight. 3 studies showed that there was no effect of aspirin on gestational age. One study showed reduction in hospital length of stay of mother upon aspirin intervention during early pregnancy.

Conclusion: This systematic review emphasis the role of aspirin in preventing preterm birth while administered during early pregnancy. As evident from majority of included studies, there is a decreasing trend in preterm births with aspirin used during early pregnancy. Researchers and obstetric healthcare workers can recognize and utilize this promising role of aspirin in preventing spontaneous preterm births during early pregnancy.

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Introduction

Preterm birth, defined as the birth of a baby before 37 weeks of gestation, is one of the leading causes of neonatal morbidity and mortality. The term includes both spontaneous deliveries and medically indicated (iatrogenic) premature births due to preeclampsia, fetal growth retardation, infection, endocrine, or immunological disorders.[1]

Preterm birth also leads to enduring long-term disability in survivors, with a disproportionate strain on both social and healthcare services, especially in low and middle-income countries. Around 15 million preterm births occur annually, accounting for about 5% to 10% of all pregnancies[2] with a

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mortality rate of approximately 1 million children annually.[3]

Preventing preterm deliveries is one of the most challenging problems for obstetricians, and many different preventative strategies, including low-dose aspirin therapy, are adopted.[4] Low-dose of aspirin is used as a potential preventive measure against preterm birth if initiated in early pregnancy.

According to the National Institute for Health and Care Excellence, low-dose aspirin (75–150 mg) prophylaxis should be started early in pregnancy, before 16 weeks, or even at 12 weeks of gestation[6], and should continue until delivery.[5]

Low-dose aspirin has been proven effective in reducing iatrogenic preterm birth by lowering the risk of preeclampsia, intrauterine growth restriction, and placental insufficiency, as well as spontaneous preterm birth by reducing uterine contractility and inflammation via inhibition of cyclooxygenase enzymes activity[7].

The low dose of aspirin has been studied for the prevention of preterm birth caused mainly by preeclampsia and fetal growth restriction. In a study conducted in Iran, 86 patients were included for the study and the increase in diastolic and systolic blood pressures was recorded during pregnancy in two groups, one administered with low-dose aspirin and the other with placebo. The increase in systolic blood pressure was by 8.25 ± 14.83 and 19.06 ± 18.33 mmHg in the aspirin and placebo groups, respectively. A similar increase was observed in diastolic blood pressure by 6.12 ± 11.46 and 13.48 ± 13.95 mmHg in aspirin and placebo groups, respectively.[8] This provides evidence of the effect of a small dose of aspirin in reducing one of the major causative factors of preterm birth in early pregnancy, preeclampsia.

According to another study done on nulliparous women, in which 2543 women were included and divided into two groups, with low-dose of aspirin, and with placebo with similar baseline characteristics for both groups. The rate of preterm births was 1.03% in the low-dose aspirin group while it was 2.34% in the placebo group.[9] Unless there is also a recognized risk factor for preterm babies, the answer to the question of the use of aspirin in preventing spontaneous preterm births remains uncertain. The significance of this study is in providing valuable insights into the effectiveness of low-dose of aspirin as a preventive measure against preterm birth. So the aim of this systematic review is to produce sufficient evidence on the role of aspirin in preventing preterm birth in early pregnancy. The findings of this systematic review may have important implications for clinical practice, improving public health policy, enhancing maternal and infant health outcomes, and developing guidelines for aspirin use to prevent preterm birth in early pregnancy. Such a review can also guide future research in this important area of maternal and neonatal health.

Methods

Study Design:

In this study, we did a systematic and comprehensive analysis of relevant literature from different databases on how the administration of low-dose aspirin during early pregnancy prevents preterm birth. To ensure transparency in this systemic review we adhered strictly to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.

Search Strategy:

In this literature review, we included articles published during the past 10 years i.e. from January 2013 to January 2023. We used different databases such as Google Scholar, PubMed, and PakMediNet to study the effect of aspirin in small dose administered in the early days of pregnancy prevents preterm birth. In each of these databases following keywords and MeSH Terms were used: "Aspirin AND Early Pregnancy", "Aspirin AND Preterm Birth", "Aspirin AND Early Pregnancy AND Preterm Birth", "Aspirin AND Early Pregnancy OR Preterm Birth", "Aspirin AND Preterm Birth OR Early Pregnancy".

Study Eligibility Criteria

Inclusion Criteria:

Studies involving the use of low-dose aspirin, early pregnancy administration of aspirin, only human participants, the prevention of preterm birth, publications from January 2013 to January 2023, articles in the English language only, and full-text articles available electronically, were included in the review.

Exclusion Criteria:

Studies involving the use of drugs other than aspirin, languages other than English, not focusing on the prevention of preterm birth, animal participants, adverse effects of aspirin on pregnancy, and studies not conducted during early pregnancy were excluded.

Study Selection:

We divided all the articles that were retrieved from different databases using the above-mentioned key terms, among all the authors. Each author did the initial screening based on the title and abstracts of the selected articles. After this initial screening, the selected articles were distributed among the authors for thorough reading and application of inclusion and exclusion criteria as mentioned earlier, for the ultimate selection of articles that were to be included in this study.

Data Extraction and Synthesis:

After the final selection of articles, we extracted data from them keeping in view the study features like the impact of aspirin in small dose on different underlying etiologies of preterm birth (i.e. preeclampsia, intrauterine growth restriction, and placental insufficiency, etc.) and different methods by which effect of small dose of aspirin in avoiding risk of preterm birth was measured (i.e. gestational age, preterm labor, rupturing of the membrane, postpartum hemorrhage, mode of birth, etc.). Two authors independently cross-checked the extracted data to prevent any discrepancies. Finally, the extracted data was narratively assembled using Microsoft Excel software.

Results

As illustrated in Fig.1, we searched three databases, Google Scholar, PubMed, and PakMediNet, and yielded a total of 362 articles. We removed 82 duplicates and 65 articles published before January 2013 leaving us with 215 arcticles. On further screening by reading titles and abstracts, we eliminated 182 irrelevant articles. Of the remaining 33 arcticles, a full text of 4 were not found. Upon full-length surfing of the remaining 29 articles, we applied our inclusion-exclusion criteria and selected 16 final articles for our systematic review. Prisma flow chart, showing our selection strategy is given below in Fig.1.

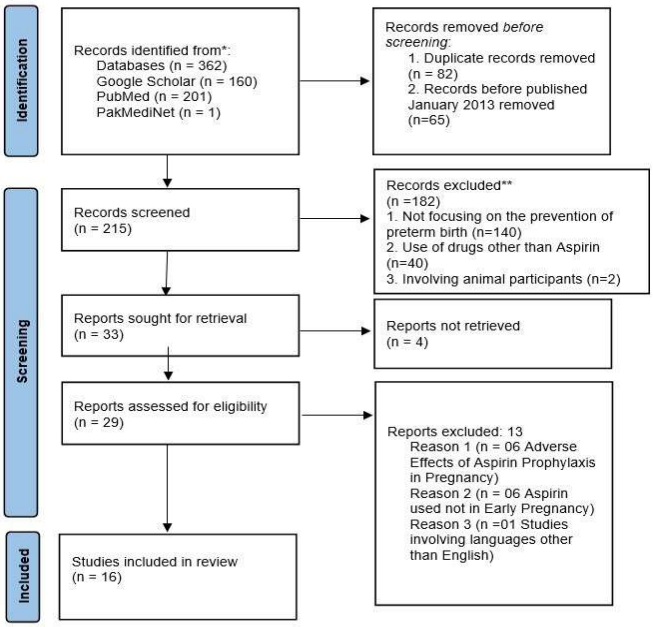

Figure 1: *PRISMA 2020 Flow Diagram showing selection of Studies*

Study characteristics:

We finalized 16 studies for our systematic review by strictly following PRISMA guidelines to ensure transparency in our final studies. Out of 16 selected studies; 10 are randomized control trials, 4 are prospective and retrospective cohort studies and 2 are review studies. Out of these, 3 tudies were conducted in the USA, 3 in the Netherlands, 2 in Iran, 1 in Canada, 1 in Sweden, and 1 in Australia, and 4 were based on data from multiple countries. Participants included in these studies ranged from as small as 90 participants to a number of 269303 participants.

Table 1: *Data Extracted from selected studies.*

Sr. #	Study type	Authors	Region	Effect of aspirin on Preterm birth rate (Primary outcome)	Effect of aspirin on Secondary outcomes like Gestational age at birth, Birth weight, Pre-eclampsia, postpartum hemorrhage, hospital length of stay, mode of birth
1	RCT 2020	Nazanin Abdi et al.[8]	Iran	No significant difference between two groups	No significance difference in gestatioinal age and birth weight. A statistically significant reduction was observed in rate of PE in the aspirin group compared to the placebo group
2	Post-hoc, Cohort/Prospective,cost-effectiveness study 2023	Jackie K Patterson et al[10]	Congo, Guatemala, Kenya, Pakistan, Zambia	Low-dose aspirin treatment for the prevention of preterm birth is a cost-effective intervention low-income and middle-income countries.	
3	RCT 2015	Robert M. Silver, M.D et al[7]	USA	Non-significant reduction in the risk of preterm birth in low-dose aspirin group	No significant effect on Pre-eclampsia.

4	Review article 2020	Julie A Quinlivan[11]	Australia	Aspirin reduces the rate of preterm birth by reducing hypertensive disorders associated with pregnancy.	Aspirin reduces the risk of hypertensive disorders associated with pregnancy i.e. Pre-eclampsia
5	RCT 2018	Maria Andrikopoulou, et al[9]	USA	Low dose aspirin therapy reduces preterm birth rate in nulliparous women.	
6	RCT 2016	AA Allshouse et al.[12]	USA	Decrease preterm birth especially sPTB, PPROM PTB	It reduce the incidence of pre-eclampsia
7	RCT 2019	Landman, A. J. E. M. C et al.[13]	Netherland	Decrease the incidence of preterm birth	It decreases the incidence of pre-eclampsia between 8 to 16 weeks. It also decreases postpartum hemorrhage.
8	RCT 2018	Anadeijda J E M C Landman et al.[14]	Netherland	It decreases the preterm birth ratio when therapy starts between 13 and 25 weeks	
9	Swedish register-b ased cohort study 2023	Ellen Kupka, et al.[15]	Sweden	Low-dose aspirin use was associated with a reduced risk for preterm birth	
10	RCT 2023	Laura A Magee, et al.[16]	Kenya, Pakistan, Zambia, DR Congo, India, and Guatemala	Aspirin significantly reduced the incidence of any preterm birth (including birth at <34) by 1.5%.	It decreases early-onset pre-eclampsia. The use of aspirin was associated with slightly increased risks of postpartum Hemorrhage.
11	RCT 2022	Anadeijda J. E. M. C. Landman et al.[17]	Netherlands	Preterm birth <37 weeks occurred in 41 (21.2%) women in the aspirin group and 49 (25.4%) in the placebo group , i e. reduces rate of PTB	Median gestational age at birth was 38+1 weeks in both the aspirin and placebo Groups. Mean birth weight was slightly lower in the aspirin group compared to the placebo Group. Postpartum hemorrhage >500mL occurred in 26.0% of women in the aspirin group and 27.1% in the placebo group. Postpartum hemorrhage >1000mL occurred in 9.4% of women in the aspirin group and 6.9% in the placebo group.
12	RCT 2020	Matthew K. Hoffman, et al.[18]	Multi-country (Democratic Republic of Congo, Guatemala, India, Kenya, Pakistan, Zambia)	The incidence of preterm delivery (before 37 weeks) is less in the women receiving aspirin (11.6%) as compared to women in the placebo group (13.1%).	No difference in occurrence of foetal growth abnormalities Including birth weight. There was no significant difference between the incidence of overall hypertensive disorders of pregnancy in women randomised to aspirin (6.1%) and those who received placebo (5.6%).
13	Narrative Review 2020	Richard Berger et al.[19]	Various Countries	Aspirin (60-150 mg/day) started between 13 and 26 weeks of pregnancy reduces the risk of spontaneous preterm birth before 34 weeks of gestation in women at high risk of preterm birth.	The efficacy of aspirin in preventing preeclampsia Issignificantly dependent on when Aspirin therapy is started and therefore preeclampsia-induced changes will be reduced only if aspirin administration is started very early. There is no increase in bleeding complications following the administration of low-dose aspirin in pregnancy.

14	Perspective /Commentary 2022	Hodgetts Morton V et al.[20]		A small reduction in recurrent preterm birth was observed in women taking low-dose aspirin, but this was not statistically significant.	Low-dose aspirin taken from early pregnancy is beneficial for reducing the incidence of preeclampsia.
15	retrospective population-based cohort study 2013	Joel G. Ray et al.[21]	Canada	aspirin reduces rates of provider-initiated preterm birth by 53 % associated with preeclampsia and intrauterine growth restriction	Aspirin reduces the rate of provider-initiated preterm birth associated with preeclampsia by 21.3%. Aspirin reduces the rate of provider-initiated preterm birth associated with intrauterine growth restriction by 14.6%. Aspirin reduces the maternal and neonate length of hospital stay.
16	RCT 2022	Kasraeian et al.[22]	Iran	Both doses of aspirin were effective in reducing the risk of preterm birth	

Data Extraction Table:

This systematic review presents the effects of Aspirin usage during early pregnancy to reduce preterm births. Along with the reduction in preterm births which is the primary outcome measure of this review, the results also showed the effect of aspirin on other pregnancy-related conditions that were included as secondary outcomes.

Reduction in Preterm-Births:

Out of 16 studies included in this systematic review, 13 studies (81%) showed a positive primary outcome measure i.e. reduction in preterm births. While in the remaining 3 studies (19%), there was no significant effect of aspirin observed in the reduction of preterm births as shown in Fig 2.

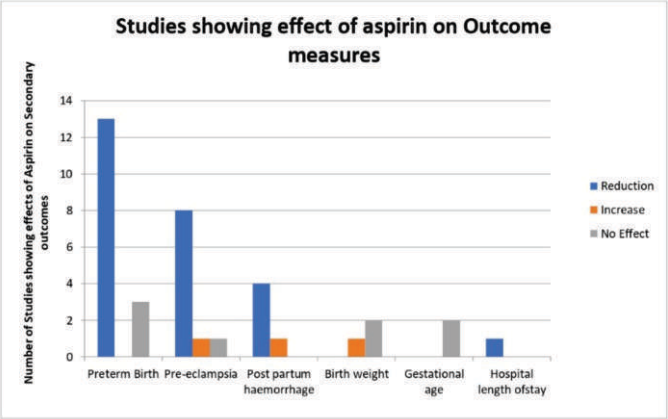

Figure 2: *Studies Showing effect of Aspirin on Outcome measures*

AA Allshouse, et al. (2016), and Landman, A. J. E. M. C (2019) noticed that low-dose aspirin use was associated with a decrease in the incidence of preterm births.[12,13] Thomas E. Merchant, Mary Ellen, et al. (2020) showed that Aspirin significantly reduced the incidence of any preterm birth by 1.5%.[16]

Julie A. Quinlivan (2020) concluded that the use of Aspirin during early pregnancy reduces the rate of preterm birth by reducing hypertensive disorders associated with pregnancy[11]. Also, a reduction of 53% was observed in preterm births associated with preeclampsia and intrauterine growth restriction.[21]

According to Maria Andrikopoulou, et al. (2018), a low dose of aspirin therapy reduces the pre-term birth rate in nulliparous women[9]. When compared with the placebo group, the incidence of preterm delivery is less in the women receiving aspirin (11.6%) as compared to women in the placebo group (13.1%)[18]. Due to all these positive outcomes, Low-dose aspirin treatment has proven to be a cost-effective intervention for the prevention of preterm birth in low-income and middle-income countries.[10]

On the other hand, some Randomized Controlled Trials showed that there was a non-significant reduction in the risk of preterm birth in the Aspirin Intervention group as compared to the placebo group.[7,8]

Secondary Outcomes:

As illustrated in Fig 2, the use of Aspirin during early pregnancy also showed significant secondary outcomes like changes in Pre-eclampsia, postpartum hemorrhage, Birth weight, Gestational age at birth, and hospital length of stay.

Pre-eclampsia was the most common secondary outcome and was observed in ten studies. Eight studies showed that aspirin use in early pregnancy reduces the chance of developing pre-eclampsia while one study showed that aspirin slightly promotes pre-eclampsia.[18] One study concluded that aspirin doesn't affect the chance of developing pre-eclampsia.[7]

In the case of postpartum hemorrhage, four studies favor

its reduction while one study showed an increase in hemorrhage with the use of aspirin during early pregnancy.[16] For birth weight, one study favors the decrease[17] and two studies showed no change.[8,18] Only 2 studies showed the impact of aspirin use on Gestational age at birth and concluded no change, while one of the 16 studies supports the positive effect of aspirin in reducing the hospital length of stay.[21]

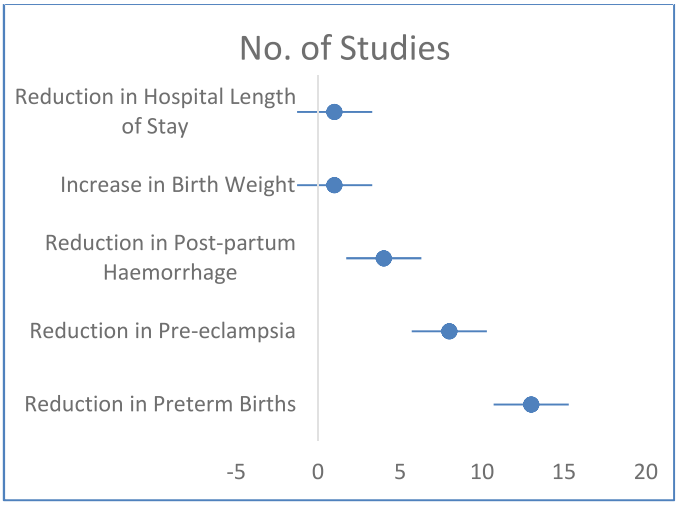

Figure 3: *Forest Plot*

Discussion

Preterm birth (before 37 weeks of pregnancy) is a significant health problem associated with harmful outcomes for both mother and infant.

Despite numerous interventions and strategies, the incidence of preterm births continues to rise, making it one of the major causes of neonatal morbidity and mortality worldwide[23].

In the medical world, there still remains a need for safe, effective, low-cost, and widely accessible strategies for reducing preterm birth rates. One of the proposed interventions is the use of low-dose of Aspirin (75–150 mg) in the early stages of the pregnancy. Due to its anti-contractile and anti-inflammatory properties, Aspirin has been suggested as a potential intervention for reducing preterm births.[9]

However, currently, there is limited and conflicting evidence to show whether low-dose aspirin is effective and safe to use during early pregnancy for this purpose or not. This lack of evidence has generated huge uncertainty and many questions like "Is Aspirin really helpful in reducing preterm births when used in early pregnancy?", "Are there any potential risks and benefits associated with Aspirin use in early pregnancy?" and more.

This systematic review aims to answer all these queries by evaluating the existing literature on the role of aspirin in early pregnancy to reduce pre-term labor and births. The results show that "The use of aspirin during pregnancy to reduce pre-term births" is supported by most of the studies (81%) included in this systematic review. While comparing with other similar studies, it was found that the results of most of the studies were in line with the results of this systematic review.

The study by Short et al.[24] (2021) concluded that the daily use of aspirin to reduce the chances of preterm births is a safe and well-tolerated intervention with minimum side effects. These findings are consistent with the results of the primary outcome i.e. rate of preterm births, of this systematic review.

In the meta-analysis of all the literature on this topic before 2003, Kozer et al.[25] (2003) statistically proved that there was a significant reduction in the risk of preterm births in the women receiving aspirin as compared to the placebo group. This proves that the aspirin therapy to reduce preterm births would have been effective even 20 years ago just like it is effective today as shown by the results of this systematic review.

Regarding the most important secondary outcome of this systematic review i.e. Preeclampsia, a study by Roberge et al.[26] (2012) showed that five trials on 556 women concluded that the low dose of aspirin reduces the risk of preterm preeclampsia. This conclusion is also in line with the results of our systematic review i.e. in 8 of 10 studies, the use of aspirin in early pregnancy reduces the chances of developing preeclampsia. From the results of this systematic review and comparisons with different trials and studies, it is obvious that the use of aspirin during early pregnancy greatly reduces the risks of preterm births and other pregnancy-related complications.

Although this review and its results show the benefits of aspirin therapy in early pregnancy, there is still a need to carry out more trials and studies on this topic. While conducting this review, we found that there are not many trials dealing with the effectiveness of aspirin use during early pregnancy, so we recommend that more studies should be directed to evaluate the long-term effects of aspirin on pregnant females. Moreover, by utilizing studies focusing on different blinding methods researchers can further work on this topic. However, based on existing literature until now, the review significantly supports the role of aspirin in early pregnancy to reduce the chances of preterm births.

The significance of this study is in providing valuable insights into the effectiveness of low-dose Aspirin as a preventive measure against preterm birth. Based on the results of this systematic review, aspirin therapy can be considered with more confidence in clinical practice, making health policy, improving interventions to reduce preterm labor and births, and keeping both the neonate and mother healthy.

Our systematic review is based on articles that were published from January 2013 to January 2023 so there is not much literature that can be reviewed. In addition to this, we only targeted articles with open access, thus resulting in the exclusion of many articles from the selected pool of studies. Due to the language barrier, we only assessed English literature, so it limited the comprehensiveness of our review. There might be a publication bias in studies selected for our review as the studies with statistically significant results are more likely to be published, thus showing over effectiveness of aspirin use.

Conclusion

The findings shown in this systematic review, provide significant evidence about the role of aspirin in avoiding premature births when administered during early pregnancy. A marked drop in rates of premature deliveries due to aspirin intervention was shown by most (81%) of the included studies. Moreover, aspirin usage demonstrated promising effects on secondary outcomes like pre-eclampsia, post-partum hemorrhage, birth weight, gestational age at birth, and hospital length of stay. Even though there were a few studies in which aspirin usage showed no statistically significant results, the overall curve of the results points towards the benefits of aspirin in reducing preterm birth. Low-dose aspirin in early pregnancy has important implications for clinical practice, improving maternal and infant health outcomes, public health policy, and developing guidelines.

Conflict of Interest: *None*

Authors Contribution: *None*

Authors Contribution:

MS: concept and design, acquisition of data

MSQ, MRS, NJ, MZN, NR, MSS: literature review, literature search and data extraction, data analysis and approval.

MSQ, MRS: Manuscript Writing, Final approval

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