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Systematic Review

Low-Dose Aspirin for Preterm Birth Prevention in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis

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Abstract: Background/Objective: Preterm births disproportionately affect low- and middle-income countries (LMICs), where evidence-based interventions to improve birth outcomes are lacking. The objective of this study was to systematically review, collate, and synthesize data on low-dose aspirin's (LDA) effect on the incidence of preterm births in women from LMICs. **Materials and Methods:** This review included nine randomized controlled trials (RCTs) spanning thirteen LMICs, with 22,545 participants. The intervention group comprised 11,275 participants and the control group comprised 11,270 participants. The relative risk ratios and pooled intervention effects were calculated using Review Manager software, RevMan v5.4.1, with a random effects model. Low-dose aspirin's effects on five outcomes were analyzed: preterm birth, perinatal mortality, low birth weight, antepartum hemorrhage, and post-partum hemorrhage. The quality of the studies was assessed by the Cochrane risk-of-bias tool and overall quality of evidence, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Two independent authors participated in screening, data extraction, and quality assessment of the included studies. **Results:** Low-dose aspirin therapy significantly lowered the risks of preterm births (RR 0.91, 95% CI 0.84–0.98, $p = 0.02$) and perinatal mortality (RR 0.83, 95% CI 0.73–0.94, $p < 0.01$) in at-risk pregnant women from LMICs. Its effects on low birthweight and ante- and post-partum hemorrhages were less conclusive. **Conclusions:** Targeted LDA therapy should be considered to reduce preterm births in at-risk pregnant women from LMICs.

Keywords: preterm; aspirin; premature; low and middle income; LMICs

Academic Editor: Berthold Huppertz

Received: 19 December 2024
Revised: 27 February 2025
Accepted: 6 March 2025
Published: 27 March 2025

Citation: Ganpat, Y.; Campbell, F. Low-Dose Aspirin for Preterm Birth Prevention in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis. *Reprod. Med.* **2025**, *6*, 8. https://doi.org/10.3390/reprodmed6020008

1. Introduction

Preterm birth is the delivery of a neonate, either spontaneously or iatrogenically, before 37 completed weeks of gestation [1]. Based on the risk of morbidity and mortality, preterm births can be clinically subdivided into extremely preterm (<28 weeks), very preterm (28–32 weeks), and moderate to late preterm (32–37 weeks) [1]. The global preterm birth rate is estimated at 15 million live births per year, with 60% of preterm deliveries occurring in South Asia and Sub-Saharan Africa. These regions also account for 80% of the world's 1.1 million deaths due to preterm birth-related complications [2–4]. Comparatively, preterm infant mortality rates are lower in developed countries, but the long-term complications are well represented globally.

Infants born before 28 weeks and up to 32 weeks, i.e., extremely and very preterm infants, have a considerably higher risk of intracranial hemorrhage, respiratory distress syndrome, apnea of prematurity, patent ductus arteriosus, necrotizing enterocolitis, and

compromised immune systems, whereas near-term infants experience more perinatal and neonatal complications relative to full-term infants (38 to <42 weeks) [5,6]. Children born at <30 weeks of gestation are more prone to neurological conditions such as cerebral palsy, autism spectrum disorder, seizures, epilepsy, and learning disabilities. Consequently, education costs for children born at 23–27 weeks are triple those for children born at 28–33 weeks, and the differential is even greater when compared to the costs for all preterm children [7,8]. Even as adults, individuals born prematurely are more prone to developing type 2 diabetes, hypertension, and cardiovascular and cerebrovascular diseases [9]. A moderately increased risk of these illnesses (10–20%) would overwhelm economic and health systems in developing countries already grappling with a chronic disease epidemic [9].

Preventative strategies targeting the pathological basis of both spontaneous and iatrogenic preterm births will yield the greatest clinical and economical benefit for LMICs. The etiology of preterm birth is complex and multifactorial, but inflammatory processes at the feto–maternal interface are a significant contributor [10–12]. Aberrant inflammation releases cytokines and other immuno-modulators, which stimulate prostaglandin release, potently inducing uterine contractions [11,12]. This untimely inflammation can result from sterile or infectious pathways [10–12]. The former pathway can become activated by uteroplacental ischemia, which upregulates the production of free radicals and reactive oxygen species, thereby causing excessive apoptosis of trophoblast cells and endothelial dysfunction. Consequently, pre-eclampsia can develop, which itself increases risk for preterm delivery [13]. This uncontrolled inflammation is the basis for anti-inflammatory therapy with drugs such as aspirin [14–16]. Research from primarily developed countries showed that low-dose aspirin (LDA) prevented pre-eclampsia, thereby indirectly lowering preterm deliveries and associated complications [17]. Similarly, the ASPIRIN trial [18], which encompassed 7 LMIC settings, reported beneficial effects and low rates of maternal bleeding complications. Clinical benefits, safety, and affordability seem to support LDA's administration in poorer contexts where current preventative strategies are either very context specific (malaria prevention, nutritional supplementation) or resource intensive and ineffective (cervical cerclage, vaginal progesterone) [18,19]. Therefore, this study aimed to ascertain low-dose aspirin's effect on the incidence of preterm births in women from LMICs.

2. Materials and Methods

The review protocol was registered prospectively with the international prospective register of systematic reviews (PROSPERO; registration CRD42020212358) [20]. No amendments were made.

2.1. Information Sources and Search Strategies

The Ovid-Medline, Embase, and CENTRAL databases were searched for relevant RCTs published between 1947 and 13 July 2023. Combinations of the appropriate medical subject heading (MeSH) terms, keywords, and word variants for "pre-eclampsia", "preterm birth", and "aspirin" were utilized. The Boolean connectors "AND" and "OR" were used to connect search terms. The search and selection criteria were restricted to human and English language studies. All database searches were imported into Mendeley Reference Manager [21]. Conference abstracts, case reports, letters, and editorials were excluded. Reference lists of relevant articles were hand-searched for additional reports to supplement citation and gray literature searches. The detailed search strategy can be found in Table A1.

2.2. Eligibility Criteria and Data Extraction

Included RCTs had to: (a) recruit participants $\geq$ 18 years old with a clinically confirmed, viable pregnancy without fetal anomalies, (b) administer low-dose aspirin

(≤150 mg/daily) from time of randomization until 36 weeks and 7 days of gestation or delivery, and (c) be conducted in LMICs. The recommendation that aspirin should not be prescribed to minors informed our selection of a ≥18 years cut-off. Participants' baseline risk for pre-eclampsia was not a criterion to determine eligibility in the RCTs. RCTs that administered aspirin as a combination therapy or had aspirin-containing comparators were ineligible for selection.

Abstract screening was performed independently by two researchers. Full texts of potentially eligible studies were retrieved and independently assessed. Inconsistencies and disagreements were resolved through discussion. The researchers also extracted data on study characteristics i.e., author, year, location, study design, sample size, inclusion and exclusion criteria, and the following five outcomes: preterm births, low birthweight, perinatal deaths, antepartum hemorrhage, and post-partum hemorrhage.

2.3. Risk of Bias Assessment

Risk of bias was assessed independently by two authors using the Cochrane Risk of Bias tool according to the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias [22]. Each domain was evaluated as low, unclear, or high risk of bias. Publication bias for the primary outcome of interest (i.e., preterm birth) was assessed using a funnel plot.

2.4. Statistical Analysis

Data on the characteristics of intervention groups and reported outcomes were tabulated to decide which RCTs were eligible for synthesis. Review Manager (RevMan) 5.4.1 [23] software was used to calculate the overall pooled size effects using a random effects model to take into account heterogeneity. Between-study heterogeneity was quantified using the I^2 statistics, where 25%, 50%, and 75% corresponded to low, moderate, and high heterogeneity, respectively. Participants with varying baseline preterm birth risk factors were pooled to increase the overall sample size and, therefore, generate a more precise estimate of treatment effect. The meta-analyses results for the five outcomes of interest were reported as risk ratios (RRs) with corresponding 95% confidence intervals (CIs) and *p*-values. Forest plots graphically displayed these results. The certainty of evidence was rated using the Grading of Assessment, Development, Recommendations and Evaluation (GRADE) system [24].

3. Results

3.1. Search Process and Study Selection

Figure 1 illustrates the search and study selection processes. A total of 991 results were identified in database searches and an additional 9 results were identified through gray literature searching. Deduplication removed 617 records and the remaining 383 underwent title and abstract screening, following which 27 full-text articles were retrieved and screened against pre-specified inclusion criteria. Of these, 18 studies were excluded because they were conducted in high-income countries (n = 14), full-text articles were unavailable (n = 1), the publications were not in English (n = 2) or the study was subsequently retracted (n = 1). The remaining nine studies [18,25–32] were qualitatively synthesized and eight studies [18,25–29,31,32] were pooled for quantitative synthesis.

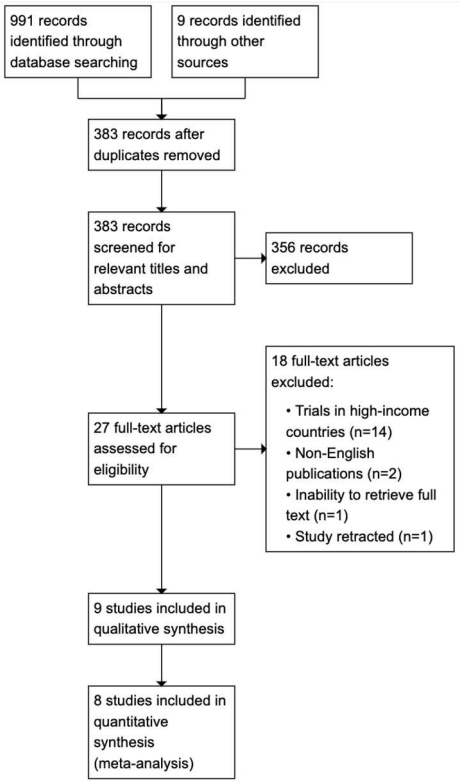

Figure 1. PRISMA flow diagram.

3.2. Study Characteristics

The nine [18,25–32] studies included in this systematic review were all RCTs. The Hoffman trial [18] was multi-national, enrolling participants from India, Pakistan, The Democratic Republic of Congo, Zambia, Kenya, and Guatemala. The eligible studies dated from 1996 to 2020 and included a total of 22,545 participants, of whom 11,275 were allocated to intervention groups and 11,270 to control groups. Sample sizes ranged from 65 to 11,558. Participants were recruited from obstetric clinics who, incidentally, each had at least one pre-eclamptic risk factor (chronic hypertension, gestational hypertension, type 1 or 2 diabetes, high uterine artery pulsatility index, primiparity, nulliparity, multifetal gestation, renal disease, age $\geq$ 35 years, history of preeclampsia or intrauterine growth restriction, and family history of preeclampsia). Daily aspirin ranging from 25 mg to 100 mg was self-administered from the time of randomization until 36 weeks and 7 days of gestation or delivery. In six trials [18,25–27,31,32], the controls received a placebo regimen, whereas no comparator was given in three trials [28–30]. The primary outcome of interest, i.e., preterm birth < 37 completed weeks of gestation, was reported in all nine [18,25–32] trials, while three [18,27,30] trials reported on low birthweight < 1500 g, five [18,26,27,30,32] trials on perinatal mortality, five [18,25,27,31,32] trials on antepartum hemorrhage, and six [18,25–27,31,32] trials on post-partum hemorrhage. The detailed characteristics of the included studies are displayed in Table A2.

3.3. Risk of Bias Within Studies

Eight [18,25–29,31,32] trials adequately reported on random sequence generation and five [18,25–27,29] trials on allocation concealment. There was high risk of bias in the Bakhti [30] study from inadequate blinding of participants and personnel. Blinding of outcome assessment was adequate in five [18,25–27,30] trials while six [18,25,26,28–30] trials were free of attrition bias. All nine [18,25–32] trials were free of selective reporting and other biases. The risks of bias are displayed in Figures A1 and A2.

3.4. Results of Individual Studies

Risk ratios (RRs) and associated confidence intervals were calculated from the incidence data to measure the effect of the intervention (i.e., low dose aspirin) on the five (5) outcomes of interest: pre-term birth, low birth weight, perinatal mortality, and antepartum and post-partum hemorrhage. Calculations were performed in RevMan 5.4.1 [23]. Table A3 shows a summary of the individual study results.

3.5. Results of Synthesis

3.5.1. Primary Outcome

- Preterm birth

Eight [18,25–29,31,32] studies, with 22,381 participants, were included in the pooled analysis. The Bakhti [30] study was excluded from the analyses for high risk of performance bias. Aspirin-treated women had a 9% reduced risk of delivering prematurely (RR 0.91; 95% CI 0.84 to 0.98; $p = 0.02$). Heterogeneity was low, $I^2 = 0\%$. The results are presented in Figure 2.

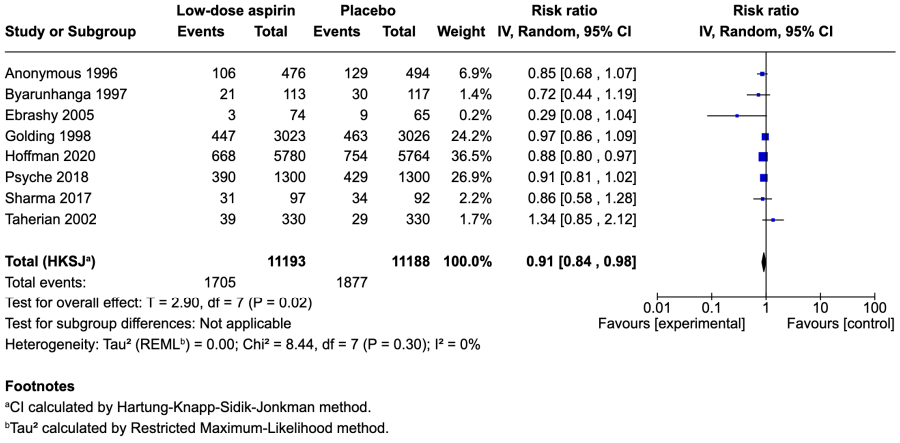

Figure 2. Forest plot comparing low-dose aspirin and placebo for preterm birth prevention in at-risk women [18,25–29,31,32].

3.5.2. Secondary Outcomes

The relative risks of each secondary outcome following low-dose aspirin therapy versus placebo are presented in Table 1.

Table 1. Relative risks of secondary outcomes following low-dose aspirin versus placebo.

Secondary Outcomes	Trials (n)	Participants (n)	Random Effect, Relative Risk (95% CI)	*p*-Value	I^2 (%)
Low birthweight	2	17,301	0.93 (0.87 to 1.00)	0.04	0
Perinatal mortality	4	20,427	0.83 (0.73 to 0.94)	<0.01	0
Antepartum hemorrhage	5	21,315	0.92 (0.66 to 1.27)	0.51	19
Post-partum hemorrhage	6	21,873	1.20 (0.89 to 1.61)	0.18	47

- Low birthweight

Two studies [18,27], with 17,301 participants, reported the incidence of low birthweight and pooling indicated no clear difference in effect (RR 0.93; CI 0.87 to 1.00; $p = 0.04$) between aspirin- and placebo-treated women. No heterogeneity was detected ($I^2 = 0$).

- Perinatal mortality

Four [18,26,27,32] studies, with 20,427 participants, reported the incidence of perinatal mortality and showed a 17% reduced risk (RR 0.83; 95% CI 0.73 to 0.94; $p < 0.01$) with aspirin treatment. No heterogeneity was detected ($I^2 = 0\%$).

- Antepartum hemorrhage

Five studies [18,25,27,31,32], involving 21,315 participants, reported the incidence of antepartum hemorrhage. Pooling showed no difference in effect with low-dose aspirin therapy compared to placebo (RR 0.92; 95% CI 0.66 to 1.27; $p = 0.51$). There was low heterogeneity ($I^2 = 20\%$).

- Postpartum hemorrhage

Seven studies [18,25–27,31,32], with 21,873 participants, reported the incidence of postpartum hemorrhage. Pooling indicated no difference in effect between the aspirin-treated and placebo cohorts (RR 1.20; 95% CI 0.89 to 1.61; $p = 0.18$). Low heterogeneity ($I^2 = 47\%$).

3.6. Publication Bias and Quality of Evidence

The funnel plot in Figure 3 appeared asymmetrical, implying that publication bias could have influenced LDA's effect on preterm birth.

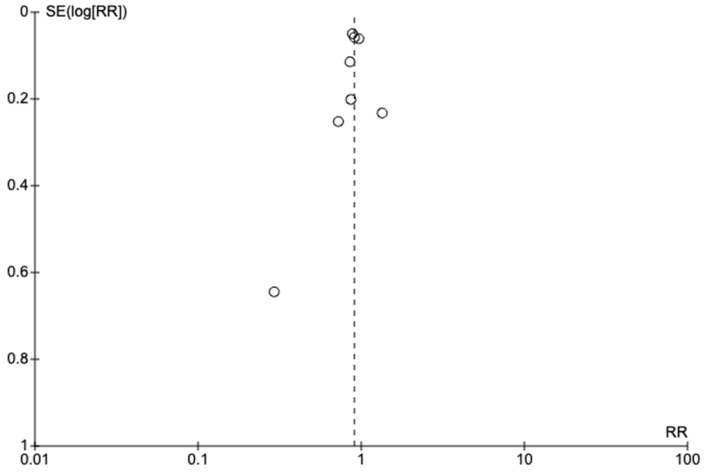

Figure 3. Funnel plot of studies on low-dose aspirin versus placebo for preterm birth prevention in at-risk women.

Using the GRADE [24] approach, the certainty of evidence on preterm birth was rated as low. Preterm birth was downgraded because the pre-eclamptic risk factor profile varied among women; hence some risk factors might have been more responsive to LDA therapy than others. The presence of publication bias also contributed to this downgrade. Evidence on the secondary outcomes was rated as follows: "high" for perinatal mortality, "low" for antepartum and postpartum hemorrhage, and "moderate" for low birthweight. The grade assessment is presented in Table A4.

4. Discussion

This systematic review and meta-analysis assessed the effectiveness of LDA in preventing preterm births in LMIC contexts. There were differences across studies in clinical characteristics (baseline pre-eclampsia risk factors), demographic profiles, LDA dosages, and comparators, as well as treatment duration. All participants had at least one risk factor for pre-eclampsia. The main findings of our meta-analyses are: (1) LDA reduced

the risk of preterm births (RR 0.91; 95% CI 0.84 to 0.98; $p = 0.02$); (2) LDA reduced the risk of perinatal mortality (RR 0.83; 95% CI 0.73 to 0.94; $p < 0.01$); and (3) the effects on birth weight, antepartum hemorrhage, and post-partum hemorrhage were inconclusive.

Our findings support targeted LDA administration in LMICs, where the burden of prematurity and prematurity-related deaths are disproportionately higher. Notwithstanding, there is no indication that LDA prophylaxis has been scaled up or indeed incorporated in high-risk antenatal care in these areas. This opposes current guidelines in high-income countries where prophylactic aspirin is recommended in at-risk women by both the National Institute for Health and Care Excellence (NICE) and the American College of Obstetricians and Gynecologists (ACOG), following extensive screening [33–35]. Such screening is likely unavailable in poorer contexts because of unskilled staff and minimal to no antenatal screening technologies such as ultrasonography. The absence of these facilities in LMICs does not, however, invalidate current screening techniques and should therefore not deter pre-eclampsia screening and LDA administration, not least because screening algorithms developed in high-income countries might be unsuitable for low-income areas, where unique risk factors for preterm births (e.g., malaria infection and human immunodeficiency virus) exist [36]. In fact, the International Federation of Gynecology and Obstetrics (FIGO) has pragmatically recommended that, where resources are limited, "contingency screening" for preterm pre-eclampsia can be considered [36]. In LMICs, this will most likely involve a thorough patient history, eliciting factors such as maternal age, racial origin, parity, medical conditions, and prior and family history of pre-eclampsia.

In LMICs, skepticism and hesitancy to LDA prophylaxis may arise because health systems, especially those lacking neonatal intensive care units (NICUs), are incapable of managing potential drug complications. While NICUs are essential in dealing with possible, but rare, complications, such as gastroschisis and premature closure of the ductus arteriosus, with high-dose aspirin administration, they become less of a requirement with lower aspirin doses of up to 150 mg/day [35–39]. Furthermore, if the unavailability of NICUs precludes LDA therapy, should it not also hinder prescription of other, potentially more unsafe drugs? Glucocorticoids, for example, are endorsed by the WHO for women in LMICs who are at risk of delivering prematurely, although higher rates of neonatal hypoglycemia and no significant improvements in the rates of jaundice requiring phototherapy, early-onset neonatal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal deaths were reported in a dexamethasone-treated cohort [39]. In other words, the drawbacks do not likely outweigh the benefit of the drug, and so consideration of the risk-to-benefit ratio should be accorded high clinical importance, regardless of resource context. Furthermore, expanding access to highly efficacious medications, such as aspirin, for women living in rural areas with limited education and only minimum maternal and preterm newborn care increases health equity.

Given solid evidence that low-dose aspirin reduces hypertensive disorders and related complications in pregnancy, providing aspirin prophylaxis seems practical, yet certain key questions remain unanswered. First, an optimal dose needs to be established. For preeclampsia prophylaxis, dosages ranging from 75 mg to 160 mg daily have been studied [40], with a systematic review by Van Doorn et al. [41] reporting that aspirin doses < 150 mg/day may not sufficiently reduce the risk of preterm preeclampsia, while 150 mg/day can considerably reduce preterm pre-eclampsia by about 62%. This relates to the dose–response effect of aspirin, whereby dosages < 100 mg/day irreversibly but selectively inhibits COX-1, resulting in decreased platelet synthesis of thromboxane-A2 without affecting vascular wall production of prostacyclin [41,42], while higher doses provide dual inhibition of COX-1 and COX-2 to effectively block all prostaglandin production as well as COX-2-enhanced sensitivity to angiotensin II, activation of the immune system,

and oxidative stress [42]. In sum, higher doses might better restore angiogenic balance and improve vascular function in high-risk women. Yet, Choi and colleague provided an opposing report of lowered pre-eclampsia risk if LDA was initiated before 20 weeks of gestation, regardless of the dose [43]. Second, future research should ascertain the suitability of LDA prophylaxis in low-income settings facing unique challenges such as limited to non-existent antenatal, intra-partum, and postnatal care. Third, whether non-targeted administration of LDA would be beneficial remains unclear. Findings from a recent systematic review by Man et al. [44] showed that aspirin therapy in nulliparous, low-risk pregnant women did not significantly reduce the risk of pre-eclampsia or pregnancy-induced hypertension, but the risk of preterm birth <34 weeks was halved (RR 0.50, 95% CI 0.26 to 0.96, $p = 0.04$) in the aspirin-treated cohort. Since these results could have been influenced by the quality of the pooled RCTs, where the majority were deemed to be at high risk of bias, high-quality studies are required, especially in poorer contexts where adequate screening is lacking and non-targeted aspirin therapy might be more appropriate [44].

The strengths of our review included using the 150 mg cut-off for LDA to capture as many eligible RCTs for a more comprehensive review and analysis, a rigorous methodology ensuring that only high-quality RCTs were included, an extensive search strategy covering three clinical databases and involving an extended study period, as well as the use of the random effects model to pool data. Further, this is the first systematic review to collate and synthesize evidence on LDA and preterm births from exclusively LMIC contexts. This review therefore provides insights on the importance of LDA treatment in poorer countries.

The limitations of our review include a risk of selection bias as only English language trials were included. Moreover, certain risk factors for preterm birth, such as socio-demographics and disease profiles, differ by geographical region, but despite our extensive search strategy, we were unable to find any relevant European studies for our review. To illustrate, type 1 diabetes, an autoimmune disease which, according to the American College of Obstetricians and Gynecologists, puts a woman at high risk of pre-eclampsia, is most prevalent in Europe, while infections such as malaria, Zika virus, and HIV, which can also trigger an overactive immune response, leading to placental inflammation and preeclampsia, have a predilection for tropical and subtropical areas of Africa, the Americas, Southern Asia, and the Western Pacific [35,45,46]. Such regional variations in disease distribution are important. Although immune dysregulation, which is the target of LDA, can arise from an initial autoimmune or infectious insult, Bauserman et al. [47] showed that LDA's effect on adverse pregnancy outcomes might be modified based on regional etiological profiles—while malaria did not alter the effects of LDA on preterm birth, it decreased the benefit of LDA on perinatal mortality. The results of the present study should, therefore, be interpreted in the context of local risk factors that might modify the effectiveness of certain treatment strategies, by potentiating, reducing, or eliminating the desired effect. Across studies, variations in baseline risk for pre-eclampsia, the dosage of aspirin (ranged from 25 mg to 100 mg daily) administered, and the duration of therapy (ranged from 4 week to 31 weeks) could have impacted the effect of LDA on our outcomes of interest, despite using a random effects analysis model. Publication bias was detected in studies reporting on the incidence of preterm birth with LDA therapy, meaning that smaller negative trials were likely not published.

5. Conclusions

Low-dose aspirin significantly decreased the incidences of preterm birth and perinatal mortality in at-risk women from LMICs. There were no conclusive differences in the risks of low birthweight and antepartum and post-partum hemorrhages following LDA therapy versus placebo or no treatment. Based on our findings and the established safety of LDA, it

seems reasonable that clinicians working in LMICs should consider administering LDA to at-risk women based on local pre-eclampsia etiological profiles.

Author Contributions: Study concept and design, Y.G. and F.C.; acquisition of data, Y.G.; statistical analysis, Y.G.; interpretation of data, Y.G.; drafting of the manuscript, Y.G. and F.C.; critical revision of the manuscript for important intellectual content, Y.G. and F.C. All authors have read and agreed to the published version of the manuscript.

Funding: No funding was received for conducting this study.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are available upon request from the principal author.

Conflicts of Interest: The authors declare that they have no conflicts of interest.

Appendix A

Table A1. Search strategies.

EMBASE via Ovid–last searched 13 July 2023 @ 13:40 hrs.		
Number	Searches	Results
1	exp acetylsalicylic acid/	209,695
2	aspirin.tw.	115,744
3	asa.tw.	47,971
4	acetylsalicylic acid.tw.	12,253
5	acetylsalicylate.tw	705
6	antiplatelet agent.tw.	2457
7	1 or 2 or 3 or 4 or 5 or 6	260,739
8	exp premature labor/co, dm, dt, pc, th [complication, disease management, drug therapy, prevention therapy]	7899
9	prematur*.tw.	189,215
10	preterm birth.tw.	24,283
11	preterm delivery.tw.	14,798
12	(early labour or early labor).tw.	729
13	early delivery.tw.	909
14	8 or 9 or 10 or 11 or 12 or 13	223,264
15	randomized controlled trials/	181,727
16	random$.mp.	1,769,188
17	controlled clinical trials/	10,828
18	15 or 16 or 17	1,774,717
19	7 and 14 and 18	473
20	limit 19 to (human and english language)	434

Table A1. *Cont.*

MEDLINE via Ovid–last searched 3 July 2023 @ 12:28 hrs.		
1	exp Premature Birth	13,934
2	Premature birth.tw.	2801
3	Exp Obstetric Labor, Premature/	26,461
4	(premature labour or premature labor).tw.	2824
5	Prematur*.tw.	130,587
6	exp Infant, Premature/	56,053
7	premature delivery.tw.	2415
8	preterm birth.tw.	13,975
9	(early labour or early labor).tw.	503
10	early delivery.tw.	536
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	183,708
12	exp Aspirin/	44,985
13	aspirin.tw.	43,625
14	acetylsalicylic acid.tw.	8308
15	antiplatelet therapy.tw.	9167
16	ASA.tw.	22,425
17	12 or 13 or 14 or 15 or 16	87,918
18	Randomized Controlled Trials/	135,465
19	Randomized Controlled Trial.pt.	511,314
20	controlled clinical trial.pt.	93,789
21	18 or 19 or 20	729,828
22	11 and 17 and 21	192
23	limit 22 to (english language and humans)	183
CENTRAL via Cochrane Library—last searched 8 July 2023 @ 18:37 hrs.		
1.	MESH descriptor: [Aspirin] explode all trees	
2.	(aspirin): ti,ab,kw OR (ASA): ti,ab,kw OR (low dose aspirin); ti,ab,kw	
3.	#1 OR #2	
4.	MeSH descriptor: [premature Birth] explode all trees	
5.	(preterm birth): ti,ab,kw OR (preterm delivery) ti,ab,kw OR (prematurity): ti,ab,kw	
6.	#4 OR #5	
7.	#3 AND #6	
8.	Limit #7 to Trials	
9.	Result = 374	

Table A2. Characteristics of included studies.

Author (Year)	Country	Study Design	Participant Assignment		Population	Intervention	Comparator	Outcomes Reported
			LDA	Placebo				
Anonymous (1996) [25]	Brazil	RCT	498	511	Women between 12 and 32 weeks of gestation with chronic HTN, primigravidity, DM, renal disease, history of PEC or IUGR	60 mg ASA daily until delivery	Placebo	Proteinuric PEC, preterm delivery, IUGR, stillbirths and neonatal deaths, BW, delivery type. Bleeding, fetal loss
Byaruhanga et al. (1997) [26]	Zimbabwe	RCT	125	125	Women between 20 and 28 weeks of gestation, previous history of PIH, PEC or eclampsia, chronic HTN	75 mg ASA daily until 38 weeks of gestation	Placebo	Pre-eclampsia, pregnancy duration, BW and perinatal deaths, type of delivery, outcome of pregnancy, post-dates, blood loss
Golding (1998) [27]	Jamaica	RCT	3023	3026	Primiparae between 12 and 32 weeks of gestation	60 mg ASA until delivery	Placebo	Proteinuria, proteinuric PEC, eclampsia, edema at delivery, onset of labor, type of delivery, GA at delivery, BW, perinatal death, 5-min APGAR, baby admitted to SCBU, maternal bleeding, wheezing or asthma, stomach pains, skin rash
Taherian et al. (2002) [28]	Iran	RCT	330	330	Nulliparity, single gestation, first prenatal visit before 20 weeks of gestation, BP < 130/80, no proteinuria on urine dipstick	75 mg ASA daily until delivery	No treatment	PEC, BP, BW, IUGR, preterm delivery, fetal and newborn morbidity (anomaly, RDS, sepsis, jaundice, death)
Ebrashy et al. (2005) [29]	Egypt	RCT	74	65	Women between 14 and 16 weeks of gestation, high risk for PEC or IUGR	75 mg ASA daily until 37 weeks of gestation	No treatment	PEC, IUGR, preterm delivery, 1-min and 5-min APGAR, maternal and neonatal bleeding
Bakhti et al. (2011) [30]	Algeria	RCT	82	82	Primigravid women consulting before 10th week of amenorrhea without previous vasculo-renal pathology	100 mg ASA until 36 weeks of gestation	No treatment	Gravidic hypertensive disorders, BW, gestational age at delivery, prematurity, perinatal mortality
Sharma et al. (2017) [31]	India	RCT	34	31	Women between 12 and 20 weeks of gestation, age > 34 years, chronic HTN, twins gestation, gestational diabetes, previous PEC, high uterine artery pulsatility index	75 mg ASA until 34 weeks of gestation	Placebo	PEC, PPH, abruption placentae, preterm delivery, IUGR
Psyche et al. (2018) [32]	India	RCT	1300	1300	Women between 13 and 24 weeks of gestation with high-risk of PEC (pregestational insulin-treated DM, chronic HTN, multifetal gestations, history of PEC)	75 mg ASA until delivery	Placebo	PEC, PPH, abruptio placentae, preterm delivery, SGA, perinatal death, neonatal IVH
Hoffman et al. (2020) [18]	Congo, Zambia, India etc.	RCT	5787	5771	Nulliparous pregnant women between 18 and 40 years, gestational age between 6 weeks + 0 days and 13 weeks + 6 days by USG.	81 mg ASA daily until delivery or 36 weeks + 7 days of gestation	Placebo	Preterm birth, maternal morbidities (hypertensive disorders, PPH, APH etc.), fetal morbidities (SGA, perinatal mortality, BW etc.)

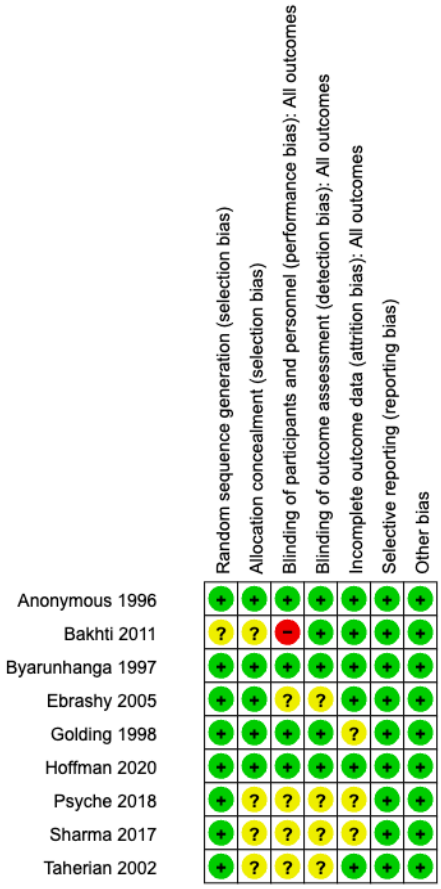

Figure A1. Risk of bias assessment: review author's judgement on each risk of bias domain for each individual study [18,25–32].

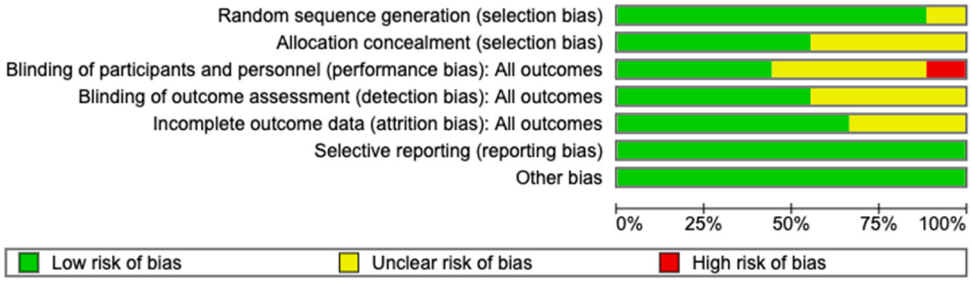

Figure A2. Risk of bias assessment: review author's judgement on each risk of bias domain presented as percentages across studies.

Table A3. Results of individual studies.

Study ID	PREGNANCY OUTCOMES														
	Pre-Term birth			Low-Birth weight			Perinatal Mortality			Antepartum Hemorrhage			Post-Partum Hemorrhage		
	IG +(n)	CG +(n)	RR [95% CI; p]	IG +(n)	CG +(n)	RR [95% CI; p]	IG +(n)	CG +(n)	RR [95% CI; p]	IG +(n)	CG +(n)	RR [95% CI; p]	IG +(n)	CG +(n)	RR [95% CI; p]
Anonymous 1996 [25]	106 (476)	129 (494)	0.85 [0.68–1.07; 0.16]	NR	NR	-	NR	NR	-	11 (476)	15 (494)	0.76 [0.35–1.64; 0.49]	3 (476)	6 (494)	0.52 [0.13–2.06; 0.35]
Bakhti 2011 [30]	34 (84)	75 (84)	0.45 [0.35–0.59; 0.00] *	0 (84)	1 (84)	0.33 [0.01–8.07; 0.50]	0 (84)	7 (84)	0.07 [0.00–1.15; 0.06]	NR	NR	-	NR	NR	-
Byaruhanga 1997 [26]	21 (113)	30 (117)	0.72 [0.44–1.19; 0.20]	NR	NR	-	5 (114)	13 (122)	0.41 [0.15–1.12; 0.08]	NR	NR	-	11 (113)	10 (117)	1.04 [0.46–2.35; 0.92]
Ebrashy 2005 [29]	3 (74)	9 (65)	0.29 [0.08–1.04; 0.06]	NR	NR	-	NR	NR	-	NR	NR	-	NR	NR	-
Golding 1998 [27]	447 (3023)	463 (3026)	0.97 [0.86–1.09; 0.58]	303 (3023)	325 (3026)	0.93 [0.80–1.08; 0.36]	86 (3023)	103 (3026)	0.84 [0.63–1.10; 0.21]	75 (3023)	67 (3026)	1.12 [0.81–1.55; 0.49]	213 (3023)	135 (3026)	1.58 [1.28–1.95; 0.00] *
Hoffman 2020 [18]	668 (5780)	754 (5764)	0.89 [0.80–0.99; 0.02] *	1078 (5628)	1153 (5624)	0.93 [0.87–1.01; 0.07]	264 (5779)	309 (5763)	0.86 [0.73–1.00; 0.05]	26 (5761)	25 (5746)	1.03 [0.60–1.79; 0.90]	54 (5928)	43 (5907)	1.25 [0.84–1.86; 0.27]
Psyche 2018 [32]	390 (1300)	429 (1300)	0.91 [0.81–1.01; 0.10]	NR	NR	-	39 (1300)	52 (1300)	0.75 [0.50–1.13; 0.17]	26 (1300)	39 (1300)	0.67 [0.41–1.09; 0.11]	104 (1300)	104 (1300)	1.00 [0.78–1.30; 1.00]
Sharma 2017 [31]	31 (97)	34 (92)	0.86 [0.58–1.28; 0.47]	NR	NR	-	NR	NR	-	1 (97)	2 (92)	0.47 [0.04–5.14; 0.54]	4 (97)	5 (92)	0.76 [0.21–2.74; 0.67]
Taherian 2002 [28]	39 (330)	29 (330)	1.34 [0.85–2.12; 0.20]	NR	NR	-	NR	NR	-	NR	NR	-	NR	NR	-

Abbreviations: IG: intervention group; CG: control group; RR: risk ratio; +: women with outcome of interest; n: number of women in each group; NR: not reported; *: statistically significant results.

Table A4. GRADE assessment.

Summary of Findings:						
Low-dose aspirin compared to placebo for preterm birth prevention						
Patient or population: preterm birth prevention Setting: LMICs Intervention: Low-dose aspirin Comparison: placebo						
Outcomes	Anticipated absolute effects * (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Low-dose aspirin				
Preterm birth	168 per 1000	151 per 1000 (138 to 164)	RR 0.90 (0.82 to 0.98)	22,381 (8 RCTs)	⊕⊕◯◯ Low [a,b,c]	
Low birthweight	171 per 1000	159 per 1000 (149 to 171)	RR 0.93 (0.87 to 1.00)	17,301 (2 RCTs)	⊕⊕⊕◯ Moderate [d]	
Perinatal mortality	47 per 1000	39 per 1000 (34 to 44)	RR 0.83 (0.73 to 0.94)	20,427 (4 RCTs)	⊕⊕⊕⊕ High	
Antepartum hemorrhage	14 per 1000	13 per 1000 (10 to 16)	RR 0.91 (0.70 to 1.18)	21,315 (5 RCTs)	⊕⊕◯◯ Low [e]	
Post-partum hemorrhage	28 per 1000	29 per 1000 (21 to 40)	RR 1.05 (0.77 to 1.43)	21,873 (6 RCTs)	⊕⊕◯◯ Low [f,g]	
* The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio						
GRADE working group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.						

Explanations: a. Varying distribution of risk factors among women. b. Preterm birth was secondary outcome of interest. c. Small negative trials not published. d. The 95% confidence interval includes no effect. e. The 95% confidence interval included no effect and low total number of events. f. High level of heterogeneity. g. The 95% confidence interval includes no effect.

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