Low-Dose Aspirin for Preventing Preeclampsia and Its Complications: A Meta-Analysis

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Low-dose aspirin (LDA) is thought to prevent preeclampsia in high-risk pregnancy, but it is not universally used out of concern for its efficacy and safety. The authors meta-analyzed 29 randomized controlled trials (RCTs) to evaluate LDA for preventing preeclampsia and its complications. LDA can reduce the incidence of preeclampsia (odds ratio [OR], 0.71; 95% confidence interval [CI], 0.57–0.87), severe preeclampsia (OR, 0.37; 95% CI, 0.23–0.61), preterm birth (OR, 0.81; 95% CI, 0.75–0.88), and intrauterine growth restriction (IUGR) (OR, 0.80; 95% CI, 0.71–0.90). LDA is more effective in reducing incidence of preeclampsia or IUGR if used before 16 gestational weeks than if used later. LDA increases the incidence of placental abruption (OR, 1.35; 95% CI, 1.05–1.73) but not other major complications. The available evidence suggests that LDA is effective in preventing preeclampsia, preterm birth, and IUGR in high-risk pregnancies without posing a major safety risk to mothers or fetuses. *J Clin Hypertens (Greenwich).* 2015:1–7.

Preeclampsia is the main cause of perinatal mortality and morbidity,[1] occurring in approximately 2% to 8% of all pregnancies around the world,[2] mostly in developing countries.[3] The etiology of preeclampsia remains unclear, although several hypotheses have been proposed. The most widely accepted are that the condition arises because of abnormal trophoblastic invasion of uterine vessels, immunological intolerance between maternal and fetoplacental tissues, or endothelial cell activation and dysfunction.[4]

Because low-dose aspirin (LDA) can maintain the balance between prostacyclin and thromboxane, it is thought to help prevent preeclampsia and related complications. Indeed, numerous studies have suggested that antiplatelet agents such as prophylactic LDA can prevent gestational hypertension and preeclampsia in patients with high-risk pregnancies,[5,6] and this approach is used in medical centers around the world. The World Health Organization recommends LDA (75 mg) before 20 weeks of pregnancy for women at high risk for preeclampsia,[1] the US Preventive Services Task Force recommends LDA (81 mg/d) after 12 gestational weeks in women at high risk for preeclampsia,[2] and national guidelines for the management of hypertension in pregnant women in Canada, the United Kingdom, and the United States also recommend prophylactic LDA.[7–10] Nevertheless, the global use of LDA remains patchy, perhaps in large part because of some controversy about its efficacy. Some studies have shown that LDA has no significant effect on risk of preeclampsia.[11]

To comprehensively assess the efficacy and safety of LDA, we applied the principles and methods of the Cochrane Collaboration to meta-analyze studies on prophylactic LDA to prevent preeclampsia and its complications in both mothers and fetuses. Our findings provide a strong evidence base in support of the use of LDA in patients with high-risk pregnancies.

METHODS

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search Strategy and Selection Criteria

We systematically searched the following literature databases to identify relevant randomized controlled trials (RCTs) published since database inception to April 1, 2014: Embase, PubMed, MEDLINE, American College of Physicians (ACP), the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Ovid, China Biomedicine (CBM), China National Knowledge Infrastructure (CNKI), Chinese Scientific and Technological Journal Database (VIP), and Wanfang Database. Searches were carried out using the following keywords: "aspirin," "ASA," "antiplatelet," "acetylsalicylic acid," "pregnancy complications," and "preeclampsia." Related conference papers, PhD dissertations, and systematic reviews were also searched manually for potentially relevant references.

Inclusion and Exclusion Criteria

Any RCT, published or unpublished, was eligible for inclusion if it compared LDA with either placebo or no treatment in women in early pregnancy at risk for

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preeclampsia. Quasi-random studies or cluster-randomized trials were excluded.

Women were considered at risk for preeclampsia if they presented with at least one of the following: (1) clinical high-risk factors, such as antiphospholipid syndrome, chronic renal disease, hypertension, diabetes mellitus, history of preeclampsia in past pregnancies, a family history of preeclampsia, multiple pregnancies, and systolic blood pressure (SBP) ≥130 mm Hg or diastolic blood pressure (DBP) ≥80 mm Hg in the first trimester[12–14]; (2) abnormal findings on uterine artery Doppler ultrasound indicating the presence of unilateral or bilateral diastolic notch, a high resistance index, or a high pulsatility index[15]; (3) a positive rollover test, defined as an increase of >15 mm Hg in DBP when the pregnant woman rolls from her left side onto her back[16]; or (4) a positive angiotensive sensitivity test, defined as an effective presser dose >10 ng/kg/min when DBP increases >20 mm Hg.[17]

All potentially eligible trials were reviewed independently by two authors (XTT, ZF). Discrepancies were resolved by discussion.

Data Collection

Data were collected from included studies to allow determination of the incidence of preeclampsia and its principal complications in mothers and fetuses, as defined in Williams Obstetrics (23rd edition).[4] These complications include severe preeclampsia, preterm delivery, postpartum hemorrhage, placental abruption, antepartum hemorrhage, cesarean birth, perinatal death, intrauterine growth restriction (IUGR), spontaneous abortion, neonatal intraventricular hemorrhage (NIH), low Apgar score (5-minute score <7), and transfer to the neonatal intensive care unit (NICU). Antepartum hemorrhage was defined to include events such as epistaxis, rectal bleeding, hematemesis, and ecchymoses, but not placental abruption. Given that many consider 16 gestational weeks as the cutoff after which prophylactic LDA becomes less effective,[8,18] we collected data on preeclampsia and complications before and after this time point to allow subgroup analyses.

Assessment of Risk of Bias in Included Studies

Two authors (XTT, ZF) independently assessed risk of bias in each included study using the criteria in the Cochrane Handbook for Systematic Reviews of Interventions.[19] Risk of bias was assessed for each of the following aspects of study execution and reporting: random sequence generation (selection bias), allocation concealment (selection bias), selective reporting (reporting bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and other bias.

Statistical Analysis

Data were analyzed using RevMan 5.0 (Cochrane Collaboration). Pooled data were meta-analyzed using either the Mantel-Haenszel fixed-effects model (if the heterogeneity indicator I^2<50%) or a random-effects model (if I^2>50%) to generate odds ratios (ORs) and associated 95% confidence intervals (95% CIs).

RESULTS

Search Results

A total of 1512 relevant articles were identified, of which 1483 were judged to be ineligible for inclusion because they were duplicate publications, were not RCTs, did not compare LDA with placebo or no treatment, or did not report adequate outcomes data (Figure). In the end, we included 29 RCTs involving 21,403 women (Table I).

Study Characteristics

Of the 29 RCTs included, 26 were published in English and three in Chinese. Two of the RCTs were published in 2013 or later. LDA was compared with placebo in 23 trials, with no treatment in five trials, or with vitamin E in one trial. All RCTs mentioned random allocation, with 26 describing randomization in detail; however, five trials did not report allocation concealment or blinding. All studies reported complete data on preeclampsia and related complications such that all were included in the meta-analysis of all outcomes (Table II).

All RCTs received a "good" rating for methodological quality, and all showed good compliance and follow-up completion. Low risk of selection bias was present, while the risk of other types of bias was unknown.

Prevention of Preeclampsia and Severe Preeclampsia

Meta-analysis showed that LDA significantly reduced the incidence of preeclampsia (OR, 0.71; 95% CI, 0.57–0.87) and severe preeclampsia (OR, 0.37; 95% CI, 0.23–0.61; Table II). Risk of preeclampsia with prophylactic LDA initiated before 16 gestational weeks was lower than the risk when therapy was initiated after 16 gestational weeks (Table III). How risk of severe preeclampsia compared before and after the 16-week cutoff is unclear, because limited sample size prevented us from performing this subgroup analysis.

Prevention of Maternal or Neonatal Complications

Meta-analysis showed that LDA decreased the incidence of IUGR (OR, 0.80; 95% CI, 0.71–0.90) and preterm birth (OR, 0.81; 95% CI, 0.75–0.88), while slightly increasing the incidence of placental abruption (OR, 1.35; 95% CI, 1.05–1.73; Table I). In contrast, LDA did not appear to exert any significant influence on the incidence of the following complications: spontaneous abortion (OR, 0.56; 95% CI, 0.30–1.07), postpartum hemorrhage (OR, 1.03; 95% CI, 0.94–1.12), cesarean birth (OR, 1.00; 95% CI, 0.93–1.07), perinatal death (OR, 0.91; 95% CI, 0.76–1.09), antepartum hemorrhage (OR, 1.14; 95% CI, 0.94–1.37), neonatal 5-minute

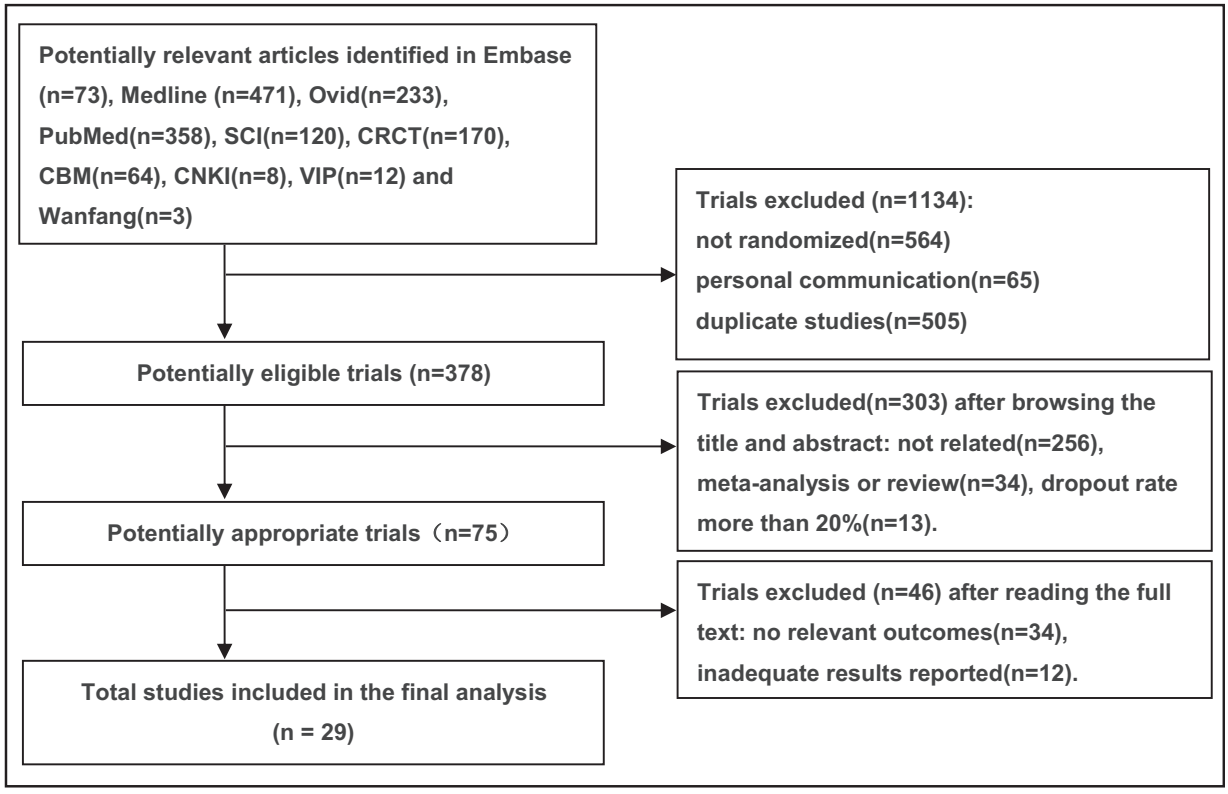

FIGURE. Flow diagram of literature searches and study selection.

Apgar score <7 (OR, 0.36; 95% CI, 0.08–1.57), NIH (OR, 0.77; 95% CI, 0.53–1.12), or transfer to the NICU (OR, 0.93; 95% CI, 0.71–1.23).

Risk of IUGR with prophylactic LDA initiated before 16 gestational weeks was lower than the risk when therapy was initiated after 16 gestational weeks (Table III). In contrast, whether LDA was initiated before or after 16 weeks did not affect its influence on the risk of preterm birth, perinatal death, or cesarean birth. We were unable to assess differential effects of prophylactic LDA initiated before or after 16 weeks on incidence of antepartum hemorrhage, NIH, neonatal Apgar score or transfer to the NICU. This is because only one RCT reported relevant data for antepartum hemorrhage, while none of the RCTs reported data for the other outcomes.

DISCUSSION

In 1979, Crandon and Isherwood first reported that taking aspirin may prevent preeclampsia in women,[20] and in 1985, Beaufils and colleagues[21] published the first RCT demonstrating the efficacy of LDA for preventing preeclampsia, fetal growth retardation, and fetal death. Since then, more than 55 RCTs and 23 systematic reviews and meta-analyses have been published on the ability of LDA to prevent preeclampsia and related complications. While many studies have shown significant clinical benefits,[2,5–9,18,22] others have not.[11–13,23–26] In order to comprehensively assess the available evidence for or against prophylactic LDA, we performed the present meta-analysis and showed strong evidence that the therapy is safe and effective.

Based on our pooled data, we calculated that LDA reduces the risk of preeclampsia in patients with high-risk pregnancies by 29%, the risk of preterm birth by 19%, and the risk of IUGR by 20%. A meta-analysis by Trivedi and colleagues involving 28,237 women in 19 RCTs, most of which were included here, reported a 21% reduction in the risk of preeclampsia due to LDA (relative risk, 0.79; 95% CI, 0.65–0.97).[27] A systematic review by Henderson and colleagues[2] concluded that LDA administered after the first trimester of pregnancy can reduce the risk of preeclampsia by at least 10%, IUGR by 20%, and preterm birth by approximately 14%. These findings strongly argue in favor of aspirin prophylaxis in early high-risk pregnancy to reduce risk of preeclampsia and related complications.

In the present study, subgroup analysis comparing the effects of prophylactic LDA therapy initiated at ≤16 or >16 gestational weeks showed that initiating therapy before 16 weeks reduced the risk of preeclampsia or IUGR to a greater extent than starting the therapy after 16 weeks. Similarly, a meta-analysis by Roberge and colleagues[18] involving 27,222 women in 42 RCTs, only some of which were included here, found that starting

TABLE I. Characteristics of Selected Trials

Study	Gestational Age at Entry, wk	Follow-Up Completion, %	Patients, No.	Entry Criteria	Treatment Arms	Main Outcomes
Schiff 1989[16]	28–29	94.2	69	1	Aspirin 100 mg vs placebo	PE; IUGR; placental abruption; preterm birth; cesarean section; intraventricular hemorrhage; neonatal Apgar score; transfer to NICU
Fan 2005[29]	18–20	100	100	1	Aspirin 100 mg vs vitamin E 0.4 g/d	PE; IUGR; placental abruption; preterm birth; cesarean section; PPH
Schröcksnadel 1992[30]	28–32	100	41	1	Aspirin 80 mg vs placebo	PE; preterm birth; cesarean section; PPH; perinatal death; severe PE; neonatal Apgar scores; transfer to NICU
Ebrashy 2005[31]	14–16	100	139	2	Aspirin 75 mg vs no treatment	PE; cesarean section; IUGR; perinatal death; severe PE
Harrington 2000[32]	17–23	97.2	216	2	Aspirin 100 mg vs no treatment	PE; placental abruption; perinatal death; cesarean section; neonatal Apgar scores; transfer to NICU
Vainio 2002[33]	12–14	95.6	90	2	Acetylsalicylic acid 0.5 mg/kg/d vs placebo	PE; IUGR; cesarean section; PPH
Morris 1996[34]	18	100	102	2	Aspirin 100 mg vs placebo	PE; severe PE; preterm birth; other antepartum hemorrhage
Bower 1996[35]	24	95.2	63	2	Aspirin 60 mg vs placebo	PE; severe PE; IUGR
Liao 2001[36]	mid- and late pregnancy	100	47	2	Aspirin 60 mg vs placebo	PE; eclampsia
Speer 2004[37]	22–24	98.9	554	2	Aspirin 150 mg vs placebo	PE; placental abruption; preterm birth; PPH; perinatal death; transfer to NICU
Subtil 2003[38]	14–20	99.4	3294	2	Aspirin 100 mg vs placebo	PE; PPH; antepartum hemorrhage; transfer to NICU; placental abruption; severe PE; spontaneous abortion; cesarean section; perinatal death; NIH
McCowan 1999[39]	24–36	100	65	2	Aspirin 100 mg vs placebo	PE; perinatal death; cesarean section; transfer to NICU; NIH
Villa 2013[22]	12–13+6	80	152	2	Aspirin 100 mg vs placebo	PE; cesarean section; severe PE
McParland 1990[40]	20	100	100	2	Aspirin 75 mg vs placebo	PE; preterm birth; perinatal death
Yu 2003[41]	22–24	98.9	560	2	Aspirin 150 mg vs placebo	PE; preterm birth; placental abruption; perinatal death; transfer to NICU
CLASP 1994[12]	12–32	99.4	9364	3	Aspirin 60 mg vs placebo	PE; IUGR; perinatal death; antepartum hemorrhage; NIH; transfer to NICU
ECPPA 1996[13]	12–32	96.1	1009	3	Aspirin 60 mg vs placebo	PE; preterm birth; IUGR; perinatal death; NIH; antepartum hemorrhage
Chiaffarino 2004[42]	<14	87.5	40	3	Aspirin 100 mg vs no treatment	PE; spontaneous abortion; IUGR
Beaufils 1985[21]	NR	91.2	102	3	Dipyridamole 300 mg and aspirin 150 mg vs no treatment	PE; spontaneous abortion; IUGR; perinatal death; PPH
Viinikka 1993[43]	15	94.7	208	3	Aspirin 50 mg vs placebo	PE; PPH; transfer to NICU; cesarean section; perinatal death
Byaruhanga 1998[44]	20–28	92	250	3	Aspirin 75 mg vs placebo	PE; PPH; IUGR; perinatal death; preterm birth; transfer to NICU
Ayala 2013[14]	12–16	100	350	3	Aspirin 100 mg vs placebo	

TABLE I. Characteristics of Selected Trials (Continued)

Study	Gestational Age at Entry, wk	Follow-Up Completion, %	Patients, No.	Entry Criteria	Treatment Arms	Main Outcomes
						PE; preterm birth; IUGR; cesarean section; PPH; perinatal death; antepartum hemorrhage
Grab 2000[45]	≤20	100	43	3	Aspirin 100 mg vs placebo	PE
Parazzini 1993[46]	16–32	94	1106	3	Aspirin 50 mg vs no treatment	PE; IUGR; cesarean section; spontaneous abortion; perinatal death; transfer to NICU
Sibai 1998[47]	13–26	98.6	774	3	Aspirin vs placebo	PE; placental abruption; perinatal death; NIH; transfer to NICU
Zhao 2012[48]	13–16	98	242	3	Aspirin 75 mg vs placebo	PE; IUGR; cesarean section; spontaneous abortion; placental abruption; severe PE
Caritis 1998[49]	13–26	98.6	2539	3	Aspirin 60 mg vs placebo	PE; PPH; preterm birth; placental abruption; NIH
Wallenburg 1986[50]	28	95.7	46	4	Aspirin 60 mg vs placebo	PE; cesarean section
Kyle 1995[51]	28	100	80	4	Aspirin 60 mg vs placebo	PE; perinatal death; cesarean section

Abbreviations: IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit; NIH, neonatal intraventricular hemorrhage; NR, not reported; PE, preeclampsia; PPH: postpartum hemorrhage. Entry criteria: 1, positive rollover test; 2, abnormal uterine artery Doppler ultrasound; 3, clinical high-risk conditions; 4, positive angiotensive sensitivity test.

TABLE II. Effect of Low-Dose Aspirin on the Incidence of PE and Its Complications in High-Risk Women

		Events, No.		Statistical Heterogeneity			Meta-Analysis	
Outcome	Trials, No.	Aspirin	Placebo	χ^2	*P* Value	I^2, %	OR (95% CI)	*P* Value
PE	29	951/10,748	1134/10,655	68.93	<.0001	59	0.71 (0.57–0.87)	.001
Severe PE	6	23/1938	56/1929	5.61	.35	11	0.37 (0.23–0.61)	<.0001
Preterm birth	15	1263/7629	1492/7623	25.75	.03	46	0.81 (0.75–0.88)	<.00001
IUGR	14	519/7741	639/7782	20.52	.08	37	0.80 (0.71–0.90)	.0003
Placental abruption	10	146/9217	109/9228	5.34	.80	0	1.35 (1.05–1.73)	.02
Antepartum hemorrhage	5	252/6997	224/7008	4.53	.34	12	1.14 (0.94–1.37)	.17
Spontaneous abortion	4	15/2333	26/2255	4.88	.18	39	0.56 (0.30–1.07)	.08
Apgar score <7 at 5 minutes	3	2/163	6/154	0.01	.91	0	0.36 (0.08–1.57)	.17
Perinatal death	19	230/10176	250/10126	16.04	.52	0	0.91 (0.76–1.09)	.31
NIH	7	47/8456	67/8860	8.05	.15	38	0.77 (0.53–1.12)	.17
Transfer to NICU	12	1453/8227	1575/8510	49.69	<.00001	80	0.93 (0.71–1.23)	.63
Cesarean section	16	2424/8110	2388/8013	18.40	.24	18	1.00 (0.93–1.07)	.97
PPH	8	1362/8638	1335/8652	4.24	.75	0	1.03 (0.94–1.12)	.57

Abbreviations: CI, confidence interval; IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit; NIH, neonatal intraventricular hemorrhage; OR, odds ratio; PE, preeclampsia; PPH: postpartum hemorrhage.

LDA at ≤16 weeks' gestation led to greater reduction in perinatal death, preeclampsia, fetal growth restriction, and preterm birth. These data support the 16-week cutoff often used to decide whether prophylactic LDA will be effective.[8] This cutoff may reflect the fact that trophoblastic invasion of uterine spiral arteries normally begins at around 8 to 10 weeks and is mostly complete by 16 to 18 weeks, although it can continue until 22 weeks.[28]

Despite the strong evidence of clinical benefit from LDA, our meta-analysis also suggests that it may slightly increase the risk of placental abruption by 35%. Nevertheless, we found no evidence that prophylactic LDA significantly affects risk of other complications affecting the mother or fetus, including postpartum hemorrhage, spontaneous abortion, cesarean birth, neonatal hemorrhage, low Apgar score, or NICU transfer. To our knowledge, this is the first meta-analysis to provide evidence that LDA may increase the risk of placental abruption. Henderson and colleagues[2] noted the potential for increased risk but were unable to demonstrate it definitively because of limited statistical

TABLE III. Differential Effects of Low-Dose Aspirin on Risk of PE or Related Complications Depending on Whether the Therapy Was Initiated Before or After 16 Gestational Weeks

Outcome	Trials, No.	Patients, No.	Events, No.		Meta-Analysis		I^2, %	Subgroup Analysis
			Aspirin	Placebo	OR (95% CI)	*P* Value		*P* Value
PE	21	4406	11.1	17.1	0.57 (0.40–0.80)	.001	61	
≤16	7	1165	14.2	28.3	0.37 (0.27–0.50)	<.00001	44	.05
>16	14	3241	10.0	13.0	0.77 (0.62–0.97)	.02	45	
IUGR	10	1540	11.7	20.4	0.50 (0.38–0.67)	<.00001	0	
≤16	6	1044	10.5	20.8	0.4 (0.30–0.61)	<.00001	0	.003
>16	4	496	14.4	19.8	0.67 (0.41–1.08)	.10	0	
Preterm birth	12	2470	15.9	23.3	0.62 (0.50–0.76)	<.00001	42	
≤16	3	726	8.7	21.5	0.32 (0.20–0.51)	<.00001	0	.08
>16	9	1744	18.9	24.1	0.74 (0.58–0.93)	.01	6	
Perinatal death	14	3785	2.6	3.4	0.76 (0.53–1.10)	.15	0	
≤16	3	784	1.3	1.8	0.73 (0.24–2.21)	.58	12	.15
>16	11	3001	3.0	3.8	0.76 (0.52–1.13)	.18	0	
Cesarean section	13	2570	35.4	32.7	1.12 (0.94–1.32)	.20	26	
≤16	4	693	21.2	24.4	0.84 (0.59–1.20)	.33	0	.83
>16	9	1877	40.5	35.9	1.21 (1.00–1.47)	.05	29	

Abbreviations: CI, confidence interval; IUGR, intrauterine growth restriction; OR, odds ratio; PE, preeclampsia. The following complications were not meta-analyzed because of limited numbers of randomized controlled trials (RCTs) reporting the relevant outcomes data: postpartum hemorrhage=only one RCT; spontaneous abortion=two RCTs; severe preeclampsia=two RCTs; antepartum hemorrhage=one RCT; transfer to neonatal intensive care unit=one RCT; and placental abruption, neonatal intraventricular hemorrhage, or neonatal Apgar score=no RCTs.

power and significant heterogeneity in the data on preeclampsia incidence.

Study Strengths and Limitations

More than 12 meta-analyses and systematic reviews have been published since 1990 on LDA, and many of them were based on relatively small studies. The present meta-analysis included 29 high-quality RCTs involving 21,403 women; three of these studies were from China (389 women), which has never been included in meta-analyses as far as we know. Our meta-analysis examined a broad scope of outcomes for both the mother and fetus and was able to provide well-powered meta-analyses for all those outcomes. On the other hand, too few studies in our review reported outcomes data for LDA initiated earlier than 16 weeks, making it impossible for us to compare the effects of early or late LDA on risk of many complications.

Our meta-analysis was also limited by heterogeneity in the data, likely reflecting the range of countries (6), LDA initiation times (13–32 gestational weeks), and aspirin doses (50–150 mg/d) in the included studies. Nevertheless, I^2 for most outcomes was <50%, allowing us to use fixed-effect meta-analysis.

CONCLUSIONS

Prophylactic LDA, especially when initiated before 16 gestational weeks, is effective at preventing preeclampsia, severe preeclampsia, preterm birth, and IUGR in patients with high-risk pregnancies. LDA does not significantly affect the risk of major preeclampsia-related complications affecting mother and fetus, with the exception of a slight increase in risk of placental abruption. Our meta-analysis provides the most rigorous assessment to date of the literature on LDA safety and efficacy to prevent preeclampsia and its complications. It also highlights the need for large, well-conducted RCTs directly comparing LDA initiated before or after 16 gestational weeks.

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References

1. WHO. *Recommendations for Prevention and Treatment of Pre-Eclampsia and Eclampsia*. Geneva: World Health Organization; 2011.
2. Henderson JT, Whitlock EP, O'Conner E, et al. Low-dose aspirin for the prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2014;160:695–703.
3. Rosenfield A, Maine D. Maternal mortality – a neglected tragedy. Where is the M in MCH? *Lancet*. 1985;2:83–85.
4. Cunningham F, Leveno K, Bloom S, et al. *Pregnancy Hypertension. Pathophysiology, Prediction and Prevention*. Williams Obstetrics [M]. 23rd ed. New York, NY: McGraw-Hill, 2010:357–816.
5. Duley L, Henderson-Smart DJ, Meher S, et al. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev*. 2007;18:CD004659.
6. Askie LM, Duley L, Henderson-Smart DJ, et al. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet*. 2007;369:1791–1798.
7. Roberts JM, August PA, Bakris G, et al. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol*. 2013;122:1122–1131.
8. Magee LA, Helewa M, Moutquin JM, et al. Hypertension Guideline Committee; STIRRHS Scholars. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *J Obstet Gynaecol Can*. 2008;30(3 Suppl):S1–S48.

9. Krause T, Lovibond K, Caulfield M, et al. Guideline Development Group. Management of hypertension: summary of NICE guidance. *BMJ*. 2011;25:343–349.
10. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. *Blood Press*. 2014;23:3–16.
11. Rossi AC, Mullin PM. Prevention of pre-eclampsia with low-dose aspirin or vitamins C and E in women at high or low risk: a systematic review with meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2011;158:9–16.
12. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. *Lancet*. 1994; 343:619–629.
13. ECPPA: randomised trial of low dose aspirin for the prevention of maternal and fetal complications in high riskpregnant women. ECPPA (Estudo Colaborativo para Prevenção da Pré-eclampsia com Aspirina) CollaborativeGroup. *Br J Obstet Gynaecol*. 1996; 103:39–47.
14. Ayala DE, Ucieda R, Hermida RC. Chronotherapy with low-dose aspirin for prevention of complications in pregnancy. *Chronobiol Int*. 2013;30:260–279.
15. Albaiges G, Missfelder-Lobos H, Lees C, et al. One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. *Obstet Gynecol*. 2000;96:559–564.
16. Schiff E, Peleg E, Goldenberg M, et al. The use of aspirin to prevent pregnancy-induced hypertension and lower the ratio of thromboxane A2 to prostacyclin in relatively high risk pregnancies. *N Engl J Med*. 1989;321:351–356.
17. Gant NF, Daley GL, Chand S, et al. A study of angiotensin II pressor response throughout primigraved pregnancy. *J Clin Invest*. 1973;52:2682–2689.
18. Roberge S, Nicolaides KH, Demers S, et al. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis. *Ultrasound Obstet Gynecol*. 2013;41:491–499.
19. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
20. Crandon AJ, Isherwood DM. Effect of aspirin on incidence of pre-eclampsia. *Lancet*. 1979;1:1356.
21. Beaufils M, Uzan S, Donsimoni R, et al. Prevention of pre-eclampsia by early antiplatelet therapy. *Lancet*. 1985;1:840–842.
22. Villa PM, Kajantie E, Räikkönen K, et al. Aspirin in the prevention of pre-eclampsia in high-risk women: randomised placebo-controlled PREDO Trial and a meta-analysis of randomized trials. *BJOG*. 2013;120:64–74.
23. Meher S, Alfirevic Z. Aspirin for pre-eclampsia: beware of subgroup meta-analysis. *Ultrasound Obstet Gynecol*. 2013;41:479–485.
24. Golding J. A randomised trial of low dose aspirin for primiparae in pregnancy. The Jamaica Low Dose Aspirin Study Group. *Br J Obstet Gynaecol*. 1998;105:293–299.
25. Rotchell YE, Cruickshank JK, Gay MP, et al. Barbados Low Dose Aspirin Study in Pregnancy (BLASP): a randomised trial for the prevention of pre-eclampsia and its complications. *Br J Obstet Gynaecol*. 1998;105:286–292.
26. Groeneveld E, Lambers MJ, Lambalk CB, et al. Preconceptional low-dose aspirin for the prevention of hypertensive pregnancy complications and preterm delivery after IVF: a meta-analysis with individual patient data. *Hum Reprod*. 2013;28:1480–1488.
27. Trivedi NA. A meta-analysis of low-dose aspirin for prevention of preeclampsia. *J Postgrad Med*. 2011;57:91–95.
28. Pijnenborg R, Dixon G, Robertson WB, et al. Trophoblastic invasion of human deciduasFrom 8 to 18 weeks of pregnancy. *Placenta*. 1980;1:3–19.
29. Fan CF, Song M. A small dose of aspirin for prevention of preeclampsia. *Chinese Journal of Birth Health and Heredity*. 2005;13:68–69.
30. Schröcksnadel H, Sitte B, Alge A, et al. Low-dose aspirin in primigravidae with positive roll-over test. *Gynecol Obstet Invest*. 1992;34:146–150.
31. Ebrashy A, Ibrahim M, Marzook A, et al. Usefulness of aspirin therapy in high-risk pregnant women with abnormal uterine artery Doppler ultrasound at 14–16 weeks pregnancy: randomized controlled clinical trial. *Croat Med J*. 2005;46:826–831.
32. Harrington K, Kurdi W, Aquilina J, et al. A prospective management study of slow-release aspirin in the palliation of uteroplacental insufficiency predicted by uterine artery Doppler at 20 weeks. *Ultrasound Obstet Gynecol*. 2000;15:13–18.
33. Vainio M, Kujansuu E, Iso-Mustajärvi M, et al. Low dose acetylsalicylic acid in prevention of pregnancy-induced hypertension and intrauterine growth retardation in women with bilateral uterine artery notches. *BJOG*. 2002;109:161–167.
34. Morris JM, Fay RA, Ellwood DA, et al. A randomized controlled trial of aspirin in patients with abnormal uterine artery blood flow. *Obstet Gynecol*. 1996;87:74–78.
35. Bower SJ, Harrington KF, Schuchter K, et al. Prediction of pre-eclampsia by abnormal uterine Doppler ultrasound and modification by aspirin. *Br J Obstet Gynaecol*. 1996;103:625–629.
36. Liao MS, Tang XL. Study of prediction of color Doppler ultrasound and prevention of low-dose aspirin for preeclampsia. *Chinese J Ultrasound Med*. 2001;17:307–308.
37. Speer P, Roberts JM. Aspirin did not prevent pre-eclampsia in women with abnormal uterine artery Doppler results. *Evid Obst Gynecol*. 2004;6:1–4.
38. Subtil D, Goeusse P, Puech F, et al. Aspirin (100 mg) used for prevention of pre-eclampsia in nulliparous women: the Essai Régional Aspirine Mère-Enfant study (Part 1). *BJOG*. 2003;110:475–484.
39. McCowan LM, Harding J, Roberts A, et al. Administration of low-dose aspirin to mothers with small for gestational age fetuses and abnormal umbilical Doppler studies to increase birthweight: a randomised double-blind controlled trial. *Br J Obstet Gynaecol*. 1999;106:647–651.
40. McParland P, Pearce JM, Chamberlain GV. Doppler ultrasound and aspirin in recognition and prevention of pregnancy-induced hypertension. *Lancet*. 1990;335:1552–1555.
41. Yu CK, Papageorghiou AT, Parra M, et al. Fetal Medicine Foundation Second Trimester Screening Group. Randomized controlled trial using low-dose aspirin in the prevention of pre-eclampsia in women with abnormal uterine artery Doppler at 23 weeks' gestation. *Ultrasound Obstet Gynecol*. 2003;22:233–239.
42. Chiaffarino F, Parazzini F, Paladini D, et al. A small randomised trial of low-dose aspirin in women at high risk of pre-eclampsia. *Eur J Obstet Gynecol Reprod Biol*. 2004;112:142–144.
43. Viinikka L, Hartikainen-Sorri AL, Lumme R, et al. Low dose aspirin in hypertensive pregnant women: effect on pregnancy outcome and prostacyclin-thromboxanebalance in mother and newborn. *Br J Obstet Gynaecol*. 1993;100:809–815.
44. Byaruhanga RN, Chipato T, Rusakaniko S. A randomized controlled trial of low-dose aspirin in women at risk from pre-eclampsia. *Int J Gynaecol Obstet*. 1998;60:129–135.
45. Grab D, Paulus WE, Erdmann M, et al. Effects of low-dose aspirin on uterine and fetal blood flow during pregnancy: results of a randomized, placebo-controlled, double-blind trial. *Ultrasound Obstet Gynecol*. 2000;15:19–27.
46. Parazzini F, Benedetto C, Frusca T, et al. Low-dose aspirin in prevention and treatment of intra-uterine growth retardation and pregnancy-induced hypertension. *Lancet*. 1993;341:396–400.
47. Sibai BM, Lindheimer M, Hauth J, et al. Risk factors for preeclampsia, abruptio placentae, and adverse neonatal outcomes among women with chronic hypertension. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med*. 1998;339:667–671.
48. Zhao YM, Xiao LP, Guo LM, et al. Low-dose aspirin oral before bedtime can prevent high risk pregnant women for preeclampsia. *Reprod Contrac*. 2012;32:355–359.
49. Caritis S, Sibai B, Hauth J, et al. Low-dose aspirin to prevent preeclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med*. 1998;338:701–705.
50. Wallenburg HC, Dekker GA, Makovitz JW, et al. Low-dose aspirin prevents pregnancy-induced hypertension and pre-eclampsia in angiotensin-sensitive primigravidae. *Lancet*. 1986;1:1–3.
51. Kyle PM, Buckley D, Kissane J, et al. The angiotensin sensitivity test and low-dose aspirin are ineffective methods to predict and prevent hypertensive disorders in nulliparous pregnancy. *Am J Obstet Gynecol*. 1995;173(3 Pt 1):865–872.