TITLE: Low-dose aspirin for the prevention of superimposed pre-eclampsia in women with chronic hypertension: a systematic review and meta-analysis.

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CONDENSATION:

Low-dose aspirin use in pregnancy for women with chronic hypertension does not reduce the risk of pre-eclampsia, but does improve preterm birth rates.

SHORT TITLE: Low-dose aspirin for prevention of pre-eclampsia in chronic hypertension: a meta-analysis.

AJOG AT A GLANCE

- Why was this study conducted? Prophylactic low-dose aspirin is recommended in pregnancies at high-risk of pre-eclampsia. There is conflicting evidence of its efficacy in pregnancies of women with chronic hypertension.
- What are the key findings? Among women with chronic hypertension, low-dose aspirin prophylaxis did not reduce the odds of pre-eclampsia (OR 0.91, 95% CI 0.64-1.29) or preterm pre-eclampsia (OR 1.05, 95% CI 0.67-1.65), and commencing aspirin prior to 20 weeks' gestation also had no significant impact. There was no significant reduction in the odds of small-for-gestational age neonates or perinatal mortality, however there was a significant reduction in preterm birth (OR 0.63, 95% CI 0.45-0.89).
- What does this study add to what is already known? Low-dose aspirin in pregnancy does not reduce the risk of pre-eclampsia for women with chronic hypertension, but does reduce the risk of preterm birth.

ABSTRACT

1. Objective

This systematic review and meta-analysis investigates whether the use of low-dose aspirin during pregnancy by women with chronic hypertension reduces the risk of superimposed pre-eclampsia and poor perinatal outcomes.

2. Data sources

In September 2021 the following sources were searched: EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform, and the EU Clinical Trials Register. Only human studies were included; there were no time or language restrictions.

3. Study eligibility criteria

Studies reporting women with chronic hypertension pregnant with a singleton pregnancy were included. Only cohort, case-control, and randomized controlled trials were included. Eligible interventions were low-dose aspirin use during pregnancy, not restricted to a specific dose, duration, or timing of use during pregnancy. Eligible studies compared the intervention to a control arm.

4. Study appraisal and synthesis methods

Risk of bias was assessed using the ROB2 and ROBINS-I tools. A meta-analysis was performed using a random-effects model, estimating odds ratios (OR) and their 95% confidence interval, and the quality of pooled data assessed with the GRADE approach. Heterogeneity was investigated in regards to study methodology, timing of commencement of aspirin, and the outcome of preterm pre-eclampsia.

5. Results

Nine studies (three retrospective cohort studies and six randomized trials) including 2150 women with chronic hypertension were included. Low-dose aspirin prophylaxis did not reduce the odds of pre-eclampsia (OR 0.91, 95% CI 0.64-1.29, low or very low quality evidence) or preterm pre-eclampsia (OR 1.05, 95% CI 0.67-1.65, low quality evidence), and commencing aspirin prior to 20 weeks' gestation also had no significant impact. There was no significant reduction in the odds of small for gestational age neonates or perinatal mortality, however there was a significant reduction in preterm birth (OR 0.63, 95% CI 0.45-0.89, moderate quality evidence). The quality of the evidence is limited by heterogeneity and risk of bias.

6. Conclusions

In women with chronic hypertension, use of low-dose aspirin during pregnancy does not reduce or increase the risk of pre-eclampsia, small for gestational age neonates or perinatal mortality. However, significant reduction in preterm birth justifies the continued use of aspirin prophylaxis. This work was prospectively registered on PROSPERO (CRD42021285921).

KEY WORDS: Aspirin, antiplatelet, chronic hypertension, essential hypertension, pregnancy, pre-eclampsia, preterm birth, small for gestational age, perinatal morbidity

MAIN TEXT

INTRODUCTION

Pre-eclampsia is a complex medical syndrome of uncertain etiology, affecting around 5% of pregnancies worldwide[1] and responsible for over 500,000 fetal and neonatal deaths and over 70,000 maternal deaths each year.[2] Previous research has identified chronic hypertension, which is present in up to 5% of pregnant women,[3] as a major risk factor for the development of pre-eclampsia.[4,5] National guidelines, specifically NICE guidance[6] and the Saving Babies' Lives care bundle[7] in the UK, recommend that women with chronic hypertension receive low dose aspirin prophylaxis from 12 weeks' gestation until delivery to reduce the risk of complications due to placental dysfunction, such as pre-eclampsia and preterm birth. Aspirin modulates platelet function and inflammation, and is used in an attempt to prevent or mitigate progress of pathological processes that lead to the development of pre-eclampsia.

Early studies reported the use of aspirin was associated with a significant decrease in the incidence of pre-eclampsia,[8-11] however this was found to be less evident in larger trials performed subsequently.[12-14] Women deemed to be at high risk of developing pre-eclampsia were then specifically investigated, with trials again producing conflicting results.[15,16] Heterogeneity in dosing and timing of aspirin between studies clouded the picture; for example, meta-analyses reported that aspirin started at or before 16 weeks' gestation significantly improved the rates of pre-eclampsia and neonatal morbidity whereas aspirin started after 16 weeks did not have a significant benefit.[17,18] There is also continued

uncertainty about the dosing leading to variation of the dose used in clinical trials from 60mg to 200mg daily. Furthermore, there is a paucity of evidence for the clinical value of aspirin prophylaxis in women with chronic hypertension, typically because of inadequately powered studies or reliance on secondary analysis in large trials.

Objectives

This systematic review and meta-analysis aimed to investigate whether the use of low-dose aspirin during pregnancy by women with chronic hypertension reduces the risk of superimposed pre-eclampsia. Additionally, the impact of aspirin on perinatal outcomes (small for gestational age (SGA), preterm birth, and perinatal mortality) was investigated.

METHODS

Eligibility criteria

Studies reporting women pregnant with a singleton pregnancy with chronic hypertension were included. Chronic hypertension was defined as: a pre-existing diagnosis of chronic hypertension; women on antihypertensive medications prior to pregnancy; or who had recorded blood pressure >140/90 on two occasions prior to 20 weeks gestation. Chronic hypertension may coexist with other illnesses such as diabetes, antiphospholipid syndrome, and renal disease, and studies including women with these conditions were not excluded from our review and analysis. Cohort, case-control, and randomized controlled trials (RCTs) were included. Case series, case reports, and conference abstracts or posters were excluded. The eligible interventions were low-dose aspirin use during pregnancy, not restricted to a specific dose, duration of treatment, or timing of use during pregnancy.

Eligible studies compared the intervention group to a control arm (women receiving a placebo or not receiving aspirin during pregnancy).

Data sources and search strategy

This review was performed using the NICE Healthcare Databases Advanced Search platform to search EMBASE and MEDLINE, alongside a search of the Cochrane Central Register of Controlled Trials, to identify relevant published studies. To identify ongoing and unfinished studies, the following resources were searched: ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform, and the EU Clinical Trials Register. Additionally, reference lists from key studies and other relevant systematic reviews (including those found via a search of PROSPERO) were reviewed.

Key search terms were chronic (or essential) hypertension, pregnancy-induced (or maternal) hypertension, pre-eclampsia, and aspirin (or antiplatelet); MeSH terms, keywords and variations on the terms were used. The search strategy was reviewed by a librarian independent of the research team. Only human studies were included, and there were no time or language restrictions. Relevant studies published in non-English languages will only be excluded if an adequate translation cannot be produced. The search was performed in September 2021.

Study selection and data extraction

Search results' titles and abstracts were screened independently by two researchers (ER and VG). Articles thought to potentially address the research question were retrieved and assessed for inclusion eligibility independently by the two researchers. Disagreements were resolved by discussion including the third author (BT). In cases of multiple reports on the

same cohort's data, the article with the most information presented relevant to our research question was included.

Data on study characteristics, participant characteristics, methodologies, outcomes measured, and results were manually extracted from each study by one researcher and checked by a second. Results presented for the following outcomes were extracted and tabulated for inclusion in the meta-analysis: superimposed pre-eclampsia, preterm pre-eclampsia, preterm birth, small for gestational age, stillbirth, and neonatal mortality.

Assessment of risk of bias

Risk of bias was assessed by one researcher, and discussed with a second, utilizing Cochrane tools: ROB 2[19] for RCTs which categorizes the risk of bias as low, some concerns, or high, and ROBINS-I[20] for non-randomized interventional studies which categorizes the risk of bias as low, moderate, serious or critical. ROB 2 involves assessment of: confounding, selection of participants, intervention classification, deviations from intervention, missing data, measurement of outcomes, and selective reporting. ROBINS-I involves assessment of: randomisation, deviations from intervention, missing outcome data, measurement of outcome, and selective reporting. The impact on the results of studies found to have the highest level of risk of bias was to be reviewed with a sensitivity analysis.

Data synthesis and assessment of quality of evidence

The outcomes of the studies were estimated with the odds ratio (OR) and its 95% confidence interval (95% CI). A meta-analysis was performed using a random-effects model. The significance of the combined OR was calculated using the Mantel-Haenszel statistical method and determined by the Z test and the p-value. The results of the pooled analysis

were presented as forest plots and considered significant with a P value of <0.05 and a Z-value of >2. I^2 statistic was reported as an estimate of the proportion of the total variability between estimates that can be due to heterogeneity and was calculated using the test statistic Q. An I^2 statistic of great than 40% suggests significant heterogeneity. Publication bias was not explored using funnel plot asymmetry tests as there were fewer than 10 studies included. Heterogeneity of results was investigated by analyses differentiating between study methods, timing of commencement of aspirin, and the outcome of preterm pre-eclampsia. The data were analyzed using Review Manager (RevMan) 5.3 software.[21] The overall quality of the evidence pooled for each outcome was assessed using the GRADE approach,[22] utilizing GRADEPro software.[23] Evidence from RCTs was downgraded from "high quality" and evidence from observational studies was downgraded from "low quality" by one or two levels depending on severity of risk of bias, indirectness of evidence, inconsistency, imprecision of effect estimates, or potential publication bias. These assessments are presented in the Summary of Findings table alongside the principle outcomes of interest: superimposed pre-eclampsia, preterm pre-eclampsia, preterm birth, and perinatal mortality.

This systematic review and meta-analysis was registered on PROSPERO (CRD42021285921, and functioning as a protocol) prior to screening of the search results.[24]

RESULTS

Study selection

Following systematic searches of databases and reference lists, we identified 1819 unique records, of which 1674 were excluded after title and abstract screening. A further 129

records were excluded following full text review and seven full-text articles were not retrieved, resulting in nine articles for inclusion in the meta-analysis (Figure 1).

Study characteristics

Of the nine included studies, six were RCTs, and three were retrospective cohort studies (Table 1). There was a wide geographical distribution of study populations. Four studies included only participants with chronic hypertension, while the other six included women with different risk factors for pre-eclampsia. The sample sizes of women with chronic hypertension ranged from 37 to 473 women. The three retrospective cohort studies compared aspirin to no prophylaxis, as did one of the randomized trials, otherwise a placebo was utilized. All studies used low-dose or “prophylactic” aspirin, with doses ranging from 60mg to 150mg once daily, although three studies did not specify the dose. In five studies the aspirin was commenced prior to 20 weeks gestation.

Secondary outcomes were reported in five of the nine studies, although there was variation in outcome definition. Studies reported preterm pre-eclampsia as either before 34 weeks, before 37 weeks, or before 37 weeks with delivery. Additionally, studies reported small for gestational age or intrauterine growth restriction as birth weight below 3rd, 5th, or 10th centiles.

Risk of bias of included studies

Seven of the nine studies included were found to have a source of risk of bias (Table 2). However, none of the studies were found to have “critical” risk (for cohort studies) or “high” risk (for randomized trials) and therefore were not excluded from the analysis.

Synthesis of results

Primary outcome: A total of 1078 women affected by chronic hypertension on aspirin were compared to 1072 women with chronic hypertension on placebo (or no aspirin) during pregnancy. There was no significant difference in the prevalence of superimposed preeclampsia between the aspirin (25.4%, 274/1078) and the comparison group (22.9%, 246/1072) (OR 0.91, 95% CI 0.64-1.29, I2 50%), and no significant differences in findings between the observational studies and RCTs (Figure 2). For the outcome of superimposed pre-eclampsia, the RCTs presented low quality evidence and the observational studies very low quality evidence, due to risk of bias in the majority of the studies, heterogeneity (I2 statistic >40%), and imprecision (Figure 3).

Secondary outcomes:

In five studies, aspirin was commenced before 20 weeks' gestation and their pooled results did not demonstrate a significant reduction in pre-eclampsia rates (Figure 4; OR 0.69, 95% CI 0.43-1.11, I2 52%). Regarding preterm pre-eclampsia, sub-group analysis of 383 women on aspirin and 354 women on control from three RCTs also found no significant effect (Figure 5; OR 1.17, 95% CI 0.74-1.86, I2 0%); the evidence was assessed to be of low quality in part due to the implementation of post-hoc secondary analyses of data (Figure 3).

Aspirin significantly reduced the odds of preterm birth. Two RCTs including 360 women on aspirin and 350 women on control reported the number of preterm births with respect to aspirin and control groups (22.2% versus 31.1%; OR 0.63 (Figure 6; 95% CI 0.45-0.89; I2=0%). This was assessed to be moderate quality evidence as one of the two studies had risk of bias, specifically in regards to lack of information on concealment of randomization, intervention allocation, and aspirin dose (Figure 3).

Pooled results of four studies reporting small for gestational age (SGA) neonates reported an overall odds ratio of 1.06 (95% CI 0.74–1.53; I2=1%) in women with chronic hypertension and aspirin compared to hypertensive women without aspirin during pregnancy (Figure 7). Perinatal mortality, including stillbirth and neonatal deaths, occurred in 28/362 (7.7%) cases in the treatment group and in 28/352 (8.0%) cases in the placebo group (Figure 8; OR 0.88, 95% CI 0.36-2.14, I2=54%). This was assessed to be very low quality evidence due to risk of bias, heterogeneity, and imprecision (Figure 3).

COMMENT

Principal findings

In this meta-analysis, we address an important clinical question: whether low-dose aspirin in pregnancy reduces the risk of pre-eclampsia and neonatal morbidity in women with chronic hypertension. We identified nine studies including 2150 women with chronic hypertension that met our inclusion criteria, of which none were judged to be at the highest risk of bias. We found that low-dose aspirin prophylaxis did not reduce the odds of pre-eclampsia amongst women with chronic hypertension, although the evidence was of low or very low quality. This lack of effect persisted even when considering only preterm pre-eclampsia as the outcome or where aspirin was commenced prior to 20 weeks' gestation. There was also no significant reduction in the odds of small for gestational age neonates or perinatal mortality. However, there is moderate quality evidence that there was a significant 37% reduction in the odds of preterm birth in the cohort receiving aspirin prophylaxis.

Comparison with existing literature

The results of this meta-analysis is supported by previous research, including a meta-analysis of individual patient data of high-risk women, which found that in women with chronic hypertension (1678 on antiplatelets and 1625 on control), there was no significant risk reduction for pre-eclampsia (RR 0.97; 95% CI 0.84-1.12) following administration of aspirin or dipyridamole.[25] Similarly, a preterm birth individual participant data meta-analysis of women with chronic hypertension (1266 on antiplatelets and 1252 on control) found that aspirin and/or dipyridamole conferred a 25% reduction in the risk of spontaneous preterm birth before 37 weeks gestation (RR 0.73; 95% CI 0.53-0.999).[26]

Strengths and limitations

Strengths of this meta-analysis include a large total population size of 2150 pregnant women with chronic hypertension from many different ethnic backgrounds. We were able to analyze the relationship between aspirin use, including timing of initiation of aspirin, and a number of different maternal and neonatal outcomes.

The quality of the evidence is significantly limited by the observed heterogeneity, which may be due to variations in definitions of population (for example use of different hypertension definitions and whether participants were required to be on treatment for hypertension), exposure (variable aspirin dose, including three studies which did not define the dose), and outcomes (such as variations in definitions of SGA birth and preterm gestation). Future systematic reviews may seek to impose stricter eligibility criteria to limit this heterogeneity. Additionally, some risk of bias was present in most of the studies included. While these biases did not reach a critical level, the potential impact of issues such as confounding in retrospective studies on the validity of results must be highlighted.

Clinical and research implications

Although low quality evidence suggests that aspirin had no significant effect on rates of pre-eclampsia among women with chronic hypertension, moderate quality evidence suggesting a reduction in preterm births has important consequences for clinical care. Preterm birth is associated with increased rates of disability and infant death, with higher costs of healthcare both in the neonatal period and longer term as well as important personal consequences for families. In accordance with our findings, a secondary analysis of the ASPRE trial identified that the use of aspirin in pregnancies at high risk for pre-eclampsia found significantly lower rates of preterm birth before 32 weeks with associated significantly reduced length of NICU stay in the aspirin group (although rates of NICU admission were not affected).[27]

Further research on the value of aspirin in pregnancy is required; as this is a meta-analysis we cannot exclude the possibility that there are some beneficial effects which are masked by the heterogeneity and evidence quality issues we have highlighted. Furthermore, as we did not differentiate between iatrogenic and spontaneous preterm birth, we are uncertain about the mechanism of aspirin action to reduce preterm birth. It is worth noting that rates of preterm pre-eclampsia and SGA were not affected by the use of aspirin, which may suggest aspirin impacts spontaneous preterm birth rather than preterm birth secondary to preterm pre-eclampsia and SGA. Given the 25% risk of pre-eclampsia in women with chronic hypertension[5] and the increasing frequency of cardiovascular disease in pregnancy,[28] a prospective study to investigate the impact of aspirin use for women with chronic hypertension on perinatal and maternal outcomes is probably justified and may answer some of the questions raised in this paper.

Conclusions

The findings from this systematic review and meta-analysis demonstrate that use of low-dose aspirin during pregnancy does not reduce or increase the risk of pre-eclampsia, SGA birth or perinatal mortality in women with chronic hypertension. However, the significant reduction in preterm birth may confer substantial personal, clinical and economic benefits, justifying the continued clinical use of aspirin prophylaxis in women with chronic hypertension.

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466 TABLE 1

Study	**Methods**	**Participants**	**Inclusion criteria**	**Exclusion criteria**	**Gestational age at entry**	**Intervention**	**Comparison**	**Outcomes** (*reported for women with chronic hypertension (cHTN) and stratified by aspirin exposure)
Boriboonhir-unsarn 2017[29] Thailand	Single center, Retrospective cohort 2011-2013	300 women with cHTN	cHTN (diagnosed before pregnancy, with or without treatment).	Women with pre-pregnancy diabetes, multiple gestation, documented fetal anomalies, incomplete data	NA	ASA prophylaxis (undefined)	No aspirin	*Superimposed preeclampsia, gestational age at delivery, small for gestational age, low birth weight, asphyxia, and NICU admission

Byaruhanga IJOG 1997[30] Zimbabwe	Single center RCT, double-blind 1994-1995	250 women at high risk, of which 37 had cHTN	Previous PIH/ PE/ eclampsia or cHTN	Contraindications to aspirin use; development of PE prior to entry in trial.	20-28 weeks	75mg aspirin up to 38 weeks	Placebo	*Pre-eclampsia, duration of pregnancy, perinatal mortality, birthweight
ECPPA 1996[31] Brazil	Multicenter RCT, double-blinded, ITT analysis, 1989-1993	1009 high-risk women, of which 473 had cHTN.	Women with Risk factors (e.g. chronic hypertension detected before or during pregnancy, primigravidity, diabetes, renal disease, a history or presence of	Women with contraindications to aspirin use, placenta praevia.	12-32 weeks	60mg aspirin OD (started at or after 12/40 until delivery)	Placebo	*Pre-eclampsia, *preterm delivery (<37/40), maximum maternal BP recorded after entry; crude birthweight (*IUGR = BW <3rd centile); *stillbirth (24/40+) and

			preeclampsia or IUGR)					neonatal death; maternal and fetal complications related to bleeding; blood transfusion
Lecarpentier 2013[32] France	Multicenter Retrospective cohort 2004- 2007	211 women with cHTN	cHTN (needing treatment before pregnancy)	Multiple pregnancies, secondary hypertension, proteinuria at less than 20 weeks' gestation, chronic	NA	Low dose aspirin (undefined)	No aspirin	*Superimposed pre-eclampsia, FGR (BW <5th centile), placental abruption, HELLP syndrome.

				hypertension but without any treatment at first prenatal visit, women transferred from other maternities, fetal malformations				
Lin 2021[33] China (Pre-proof)	Multicenter single-blind RCT 2016-2019.	990 high-risk women randomize	18-55 years, singleton pregnancy, live fetus at the gestational age of 12 to 20 weeks; high	Contraindications to aspirin use, autoimmune diseases; mental	< 20 weeks	100mg aspirin, initiated from 12 to	No aspirin	*Pre-eclampsia, *pre-eclampsia delivery before 34 weeks, *before 37 weeks, and

		d, of which 441 cHTN.	risk i.e. history of pre-eclampsia, diabetes (type 1 or 2), or chronic hypertension; or 2+ intermediate risk factors: obesity, advanced maternal age (≥35 years), family history of pre-eclampsia, or nulliparity	disorders; history of alcohol or drug abuse within 6 months; in-vitro fertilization (IVF); previous registration in another drug trial within the previous 3 months.		20 weeks until 34 weeks.		*at or after 37 weeks of gestation; gestational hypertension; HELLP syndrome; placental abruption; PPH, fetal distress, preterm birth; miscarriage, stillbirth, or neonatal death; fetal death with pre-eclampsia; perinatal death; fetal malformation; low birth weight; very low birth weight; SGA;

								apgar score and NICU admission.
McCowan 1996[34] New Zealand	Single center Retrospective cohort, 1991-1993.	155 pregnancies in women with cHTN	dBP >=90 before 20 weeks or pre-existing diagnosis of essential HTN and on antihypertensive medicines	Evidence of secondary causes of hypertension.	NA	75 mg aspirin commenced at < 20 weeks	No aspirin	*Superimposed pre-eclampsia, perinatal loss, *SGA (BW <5th centile), PTB (before 37 and 32 weeks), abruption.
Moore 2015[35] USA	Secondary analysis of Caritis 1998 - Multicenter double-	523 High-risk women, of which 186 cHTN.	Women with cHTN (on treatment or BP >=140/90 prior to pregnancy or prior to 20 weeks), diabetes, history of PE	Multifetal gestations, history of pre-eclampsia with current proteinuria	<17+0 weeks	60mg aspirin from recruitment until delivery	Placebo	*Superimposed pre-eclampsia at any gestation, *early pre-eclampsia (before 34/40), *late pre-eclampsia (34/40+),

	blind RCT 1991-1995							*SGA (BW <10th centile), *compositie early pre-eclampsia or SGA
Poon 2017[36] UK, Spain, Italy, Belgium, Greece, Israel	multicenter, double-blind, RCT. (Secondary analysis of ASPRE)	1776 women assigned, of which 110 cHTN.	18+ years, no serious mental illness or learning difficulties, singleton live pregnancy, no major abnormality demonstrated, estimated risk for preterm PE of >1 in 100 (including history of	(not specified)	At the 11-13 week visit.	Aspirin 150 mg, administered from 11-14 weeks until 36 weeks	Placebo	*Delivery with superimposed PE <37 weeks

			cHTN as reported by participants)					
Xiang 2020[37] China	Multicenter RCT, 2018-2019.	393 women with mild-mod cHTN	Mild - moderate cHTN (SBP 140-159, dBP 90-109) documented between 6-10 weeks gestation, without medication and target organ disease	Women with multiple embryos, prior proteinuria, and other conditions such as diabetes and asthma) as well as fetal defects during pregnancy	9 weeks (+/- 2 weeks)	LDA (undefined) From 12-36 weeks	Placebo	*Superimposed pre-eclampsia at any gestation, *SGA (BW <10th centile), *premature delivery (<37 weeks), *neonatal hypoglycemia, *neonatal *hyperbilirubinemia, *intrauterine fetal demise

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470 TABLE 2

Retrospective Cohort Studies	**Confounding**	**Selection of participants**	**Intervention classification**	**Deviations from intervention**	**Missing data**	**Measurement of outcomes**	**Selective reporting**	**Overall**	**Comments**
Boriboonhirusarn 2017[29]	Moderate	Low	Serious	Low	Low	Low	Moderate	Serious	Logistic regression adjusted for the confounders of age, parity, pre-pregnancy BMI, previous pre-eclampsia, (but not co-morbidities). Note - all participants same ethnicity. The intervention of “ASA prophylaxis” was undefined.

Lecarpentier 2013[32]	Serious	Low	Serious	Low	Low	Low	Moderate	Serious	Logistic regression to control for confounders included ethnicity, parity, prev pre-eclampsia (but not age, co-morbidities, or BMI). The intervention of “low dose aspirin” was undefined.
McCowan 1996[34]	Serious	Low	Low	Low	Low	Low	Moderate	Serious	Some potential confounders controlled for in relation to SGA outcome, but not described for pre-eclampsia.
Randomized Trials			**Randomisation**	**Deviations from interventi**	**Missing outcome data**	**Measurement of outcome**	**Selection of reported**	**Overall**	**Comments**

			on			**result**		
Byaruhanga 1997[30]		Low	Low	Some concerns	Low	Low	Some concerns	20 of the randomized subjects (8%) lost to follow-up (12 in aspirin group, 8 in placebo group).
ECPPA 1996[31]		Low	Low	Low	Low	Low	Low	Follow-up forms obtained for 96% of randomized women (476 allocated to aspirin, 494 to placebo)
Lin 2021[33]		Low	Low	Low	Low	Low	Low	Study protocol reviewed. Registered with clinicaltrials.gov:

								NCT02797249, with recruitment commencing following registration.
Moore 2015[35]		Low	Low	Low	Low	Some concerns	Some concerns	Secondary analysis of Caritis 1998.[38]
Poon 2017[36]		Low	Low	Low	Low	Some concerns	Some concerns	Subgroup analyses for obstetric history pre-specified but those for maternal characteristics/ medical history were post-hoc. Secondary analysis of ASPRE;[16] protocol reviewed. The ASPRE trial was registered with ISRCTN: ISRCTN13633058, with

								recruitment commencing following registration.
Xiang 2020[37]		Some concerns	Low	Low	Low	Low	Some concerns	No information on concealment of randomisation and intervention allocation. "Low dose aspirin" - dose undefined.

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473 FIGURE LEGENDS

474 1. Flow diagram

475 2. Pre-eclampsia by study design

476 3. Summary of findings, including GRADE assessments

477 4. Pre-eclampsia outcome when aspirin initiated before 20 weeks

478 5. Preterm pre-eclampsia

6. Preterm birth
7. Small for gestational age
8. Perinatal mortality