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 odds 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 significantly reduce the odds of superimposed pre-eclampsia in the RCTs (OR 0.83, 95% CI 0.55-1.25, PI 0.27-2.56, low quality evidence) or observational studies (OR 1.21, 95% CI 0.78-1.87, PI 0.07-20.80, very low quality evidence). Low-dose aspirin prophylaxis did not reduce the odds of preterm pre-eclampsia, and early aspirin initiation 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). The quality of the data is limited by heterogeneity and risk of bias, including loss to follow-up.
- What does this study add to what is already known? Low-dose aspirin in pregnancy does not significantly 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 odds of superimposed pre-eclampsia and poor perinatal outcomes.

2. Data sources

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

3. Study eligibility criteria

Cohort, case-control, and randomized controlled studies reporting women with chronic hypertension pregnant with a singleton were included. Eligible studies compared low-dose aspirin use during pregnancy 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 95% confidence and prediction intervals, and the quality of data was 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 significantly reduce the odds of superimposed pre-eclampsia in the RCTs (OR 0.83, 95% CI 0.55-1.25, PI 0.27-2.56, low quality evidence) or observational studies (OR 1.21, 95% CI 0.78-1.87, PI 0.07-20.80, very low quality evidence). Low-dose aspirin also did not reduce the odds of preterm pre-eclampsia (OR 1.17, 95% CI 0.74-1.86), and early aspirin initiation had no significant impact. There was no significant effect on 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

This meta-analysis was unable to demonstrate a significant change in the odds of superimposed pre-eclampsia, small for gestational age infants, or perinatal mortality with the use of low-dose aspirin in women with chronic hypertension. 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 the National Institute for Health and Care Excellence (NICE) guidance[6] and the Saving Babies' Lives care bundle[7] in the United Kingdom, 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; some meta-analyses reported that earlier aspirin initiation significantly improved the rates of pre-eclampsia compared to later aspirin initiation,[17,18] although other meta-analyses of individual patient data from women with risk factors for pre-eclampsia found no significant

differences.[19,20] Furthermore, there is evidence that earlier aspirin initiation is associated with increased effectiveness for the prevention of preterm birth and small for gestational age (SGA) babies.[21] There is also continued uncertainty about appropriate dosing leading to variation of the dose used in clinical trials from 60mg to 200mg daily.

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. Additionally, meta-analysis findings often represent pooled data from women with a variety of risk factors for pre-eclampsia, sometimes complicated by multiple high-risk comorbidities in the same woman; when women with chronic hypertension do receive their own subgroup analysis, this is often for the primary outcome of pre-eclampsia alone.

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 (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 would only be excluded if an adequate translation could not 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, and perinatal mortality (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[22] for RCTs which categorizes the risk of bias as low, some concerns, or high, and ROBINS-I[23] 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). Meta-analyses were performed using a random-effects model, given the observed heterogeneity between studies. The results of the pooled analysis were presented as forest plots and considered significant with a P value of <0.05.

Heterogeneity between estimates was represented with the I^2 statistic (greater than 40% suggests significant heterogeneity) and the 95% prediction interval for those analyses including three or more RCTs. The 95% prediction interval estimates where the true effects are to be expected for 95% of similar studies that might be conducted in the future.24 Heterogeneity of results was investigated by analyses differentiating between study methods, timing of commencement of aspirin, and the outcome of preterm pre-eclampsia. When RCTs and observational studies reported the same outcome, Chi-squared subgroup difference testing was utilised to assess the differences between their findings. Heterogeneity stemming from aspirin dose could not be assessed as three of the nine studies did not specify dose used; this is described in the discussion.

Fragility indices for the results of the meta-analyses of RCTs are also reported; these represent the minimum number of patients whose outcome status would have to change to turn a statistically significant result to a nonsignificant result (or vice versa).[25] Publication bias was not explored using funnel plot asymmetry tests as there were fewer than 10 studies included. All analyses were conducted with R statistical software version 4.2.1.[26]

The overall quality of the evidence pooled for each outcome was assessed using the GRADE approach,[27] utilizing GRADEPro software.[28] 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 in estimates of effect, imprecision of effect estimates, or potential publication bias.

This systematic review and meta-analysis was registered on PROSPERO (CRD42021285921, and functioning as a protocol) prior to screening of the search results.[29]

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 none were excluded from the analysis.

Synthesis of results

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, in separate analyses by methodology. Low-dose aspirin prophylaxis did not significantly reduce the odds of superimposed pre-eclampsia in the RCTs (OR 0.83, 95% CI 0.55-1.25, PI 0.27-2.56, low quality evidence, Figure 2) or observational studies (OR 1.21, 95% CI 0.78-1.87, PI 0.07-20.80, very low quality evidence, Figure 3). Even with point estimates of the OR either side of the null, there were no significant differences in the findings of the observational studies and RCTs (X2 statistic 1.47, p = 0.22). The quality of the evidence is limited by risk of bias in the majority of the studies, heterogeneity (I2 >40%), and imprecision (Figure 4). The heterogeneity is reflected in the prediction interval, which is much wider for the observational studies than the RCTs. The data from the RCTs is associated with a fragility index of 11, suggesting that it would take 11 outcome status changes to turn this statistically insignificant result into a significant one, which is unfortunately smaller than the number of patients lost to follow-up within included studies.

Four RCTs and one observational study reported that aspirin was commenced before 20 weeks' gestation. The pooled results from the RCTs with early aspirin initiation did not demonstrate a significant reduction in pre-eclampsia rates (OR 0.74, 95% CI 0.47-1.16, I2 52%, PI 0.14-4.05, low quality evidence, Figure 5). The observational study did not report a statistically different OR for superimposed pre-eclampsia to the RCTs (X2 statistic 1.93, p = 0.16).

Three RCTs reported preterm pre-eclampsia, including 383 women on aspirin and 354 women on control. The pooled data also found no significant effect of low-dose aspirin (OR

1.17, 95% CI 0.74-1.86, I2 0%, low quality evidence, Figure 6) with a wide prediction interval (0.06-23.39); the evidence was assessed to be of low quality due to the implementation of post-hoc secondary analyses of data and the few numbers of events (Figure 4).

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, 95% CI 0.45-0.89; I2=0%, Figure 7). 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 4). The fragility index of five is much smaller than the number of patients lost to follow-up in the included studies.

Three RCTs reported small for gestational age neonates, with an associated odds ratio of 0.96 (95% CI 0.65-1.40, PI 0.08-11.53, moderate quality evidence) in women with chronic hypertension and aspirin compared to hypertensive women without aspirin during pregnancy (Figure 8). Data from the observational study which reported small for gestational age outcome did not report a statistically significant OR for superimposed pre-eclampsia to the RCTs (X2 statistic 2.50, p = 0.11).

Perinatal mortality, including stillbirth and neonatal deaths, was reported by two RCTS including 28/362 (7.7%) cases in the treatment group and in 28/352 (8.0%) cases in the placebo group (OR 0.88, 95% CI 0.36-2.14, Figure 9). This was assessed to be very low quality evidence due to risk of bias, heterogeneity (I2=54%), and imprecision (Figure 4).

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. Data pooled from six randomized controlled trials identified a reduction in the odds of superimposed pre-eclampsia of 17% (OR 0.83, 95% CI 0.55-1.25, low quality evidence), and although this reduction did not reach statistical significance, the data suggests that the intervention is more likely to confer benefits than not. This interpretation is limited as the fragility index of 11 is lower than the number of women lost to follow-up in the included studies; there is a theoretical risk that the outcomes of those lost to follow-up could have resulted in the findings of the analysis changing significantly.

The three retrospective cohort studies of very low quality suggest that low-dose aspirin may be associated with an increased odds of superimposed pre-eclampsia in women with chronic hypertension (OR 1.21, 95% CI 0.78-1.87), although the prediction interval is wide and therefore there is much uncertainty regarding what similar future studies may find. Overall, uncertainty around the relationship between low-dose aspirin and the development of superimposed pre-eclampsia was large and further high-quality data is required; discussion of the limitations of these analyses is found below.

Similarly, this lack of significant 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 from two RCTs that there was a significant 37% reduction in the odds of preterm birth in the cohort receiving aspirin prophylaxis (OR 0.63, 95% CI 0.45-0.89). As above, unfortunately the fragility index of 5 is lower than the number of women lost to follow-up in the included studies.

Comparison with existing literature

Large meta-analyses of pooled data from women with a variety of risk factors for pre-eclampsia, such as the recent United States Preventive Services Taskforce report[21] and Cochrane review,[30] have found that low-dose aspirin prophylaxis reduces the risk of pre-eclampsia and other perinatal outcomes. The results of this meta-analysis contradicts these previous reviews, however our findings are supported by data from women with chronic hypertension: a meta-analysis of individual patient data of high-risk women from the PARIS Collaborative Group 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, although in the total cohort of women with a variety of risk factors there was a significant reduction in the relative risk.[19] These differences in results may be explained by the heterogeneity in the populations investigated.

In regards to the timing of the initiation of aspirin, we found that pooled data from the five studies where aspirin was commenced before 20 weeks' gestation also did not demonstrate a significant reduction in the odds of developing superimposed pre-eclampsia, which is consistent with previous work which has shown no significant difference in pre-eclampsia

risk with earlier versus later initiation among women with risk factors for pre-eclampsia,[20, 21] although there is also evidence to the contrary.[17, 18]

Our finding that aspirin prophylaxis significantly reduced the odds of preterm birth is echoed by an individual participant data meta-analysis of women with risk factors for pre-eclampsia, which found a significant reduction in risk of preterm birth before 37 weeks gestation with aspirin and/ or dipyridamole (RR 0.93, 95% CI 0.86-0.996). Interestingly, when considering only the women with chronic hypertension (1266 on antiplatelets and 1252 on control), there was a more pronounced effect estimate of a 27% reduction in the risk of spontaneous preterm birth before 37 weeks gestation (RR 0.73; 95% CI 0.53-0.999).[31] However, this analysis found no significant reduction in preterm birth before 34 weeks or before 28 weeks in women with chronic hypertension, whereas there was a significant reduction in the risk of preterm birth before 34 weeks gestation for the wider, more diverse, cohort (RR 0.86, 95% CI 0.76-0.99).[31] These findings suggest that low-dose aspirin prophylaxis may be more efficacious in the prevention of late preterm birth in women with chronic hypertension than for those with other risk factors for pre-eclampsia, although the test of interaction between treatment group and chronic hypertension history was not significant, and the effect has not been shown for moderate to very preterm birth. Given the hypothesis that placental vascular pathology causes moderate to late PTB, and that very PTB is associated more with infection-inflammation,[31] it may be theorized that aspirin works well in the prevention of late preterm birth in women with chronic hypertension due to action on placental vascular pathology to which chronic hypertension more greatly predisposes than other pre-eclampsia risk factor groups, although this requires further investigation.

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, including subgroup data from the well-known Network of Maternal-Fetal Medicine Units[15] and ASPRE[16] trials. We were able to investigate 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. This is reflected in the prediction intervals which suggest that similar future studies may find true effects across a wide range of possibilities, including beneficial but also harmful effects. This heterogeneity 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 superimposed pre-eclampsia, SGA birth, and preterm gestation). In regards to the main outcome of superimposed pre-eclampsia, although studies utilised different definitions, some of which may have underestimated the incidence of superimposed pre-eclampsia, they all fell within the International Society for the Study of Hypertension in Pregnancy definition[2] described in this review's protocol.[29] The studies were found to have low risk of bias in the measurement of the outcome as there was no evidence that the measurement differed between intervention groups, was influenced by knowledge of intervention status, or that there were systematic errors in measurement of the outcome related to intervention received. Three of the nine studies (all of which reported on women with a variety of risk factors) described

only a definition for pre-eclampsia, and not one for superimposed pre-eclampsia in women with chronic hypertension. Future systematic reviews may seek to impose stricter eligibility criteria to limit heterogeneity, and prospective studies including only women with chronic hypertension may improve the identification of superimposed pre-eclampsia.

Some risk of bias was present in seven of the nine studies included. While these biases did not reach a critical level, there are particular concerns regarding the reported loss to follow-up in multiple RCTs and the relatively low fragility indices, suggesting that those lost to follow-up may have been able to sway the results of the analyses. Additionally, there may have been inadequate controlling for confounding factors in the retrospective studies, the use of post-hoc secondary analyses of data confer a lack of transparency for selection of reported results, and unspecified dosing of aspirin suggests possible deviation from intervention.

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. The use of aspirin in pregnancies at high risk for pre-eclampsia has been found to 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).[32]

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 provider-initiated 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.

We have shown that when considering women with chronic hypertension separately to a pooled cohort of women with different risk factors for pre-eclampsia, aspirin may not be as effective for the prevention of superimposed pre-eclampsia as previous meta-analyses suggest, but may be more effective for the prevention of late preterm birth compared to other pre-eclampsia risk factor groups. Given the 25% risk of pre-eclampsia in women with chronic hypertension[5] and the increasing frequency of cardiovascular disease in pregnancy,[33] a prospective study to investigate the impact of aspirin use for women with chronic hypertension on perinatal and maternal outcomes is justified and may answer some of the questions raised in this paper.

Conclusions

This meta-analysis was unable to demonstrate a significant change in the odds of superimposed pre-eclampsia, small for gestational age infants, or perinatal mortality with the use of low-dose aspirin 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. Given the mixed quality of the source data and the limitations of the meta-analyses, further work with women with chronic hypertension is required to clarify the value of aspirin prophylaxis.

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TABLE 1 - Characteristics of included studies

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[34] 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[35] 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[36] 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[37] 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[38] 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[39] New Zealand	Single center Retrospecti ve cohort, 1991-1993.	155 pregnanci es 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 commenc ed at < 20 weeks	No aspirin	*Superimposed pre-eclampsia, perinatal loss, *SGA (BW <5th centile), PTB (before 37 and 32 weeks), abruption.
Moore 2015[40] USA	Secondary analysis of Caritis 1998,[15] 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 recruitme nt 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[41] UK, Spain, Italy, Belgium, Greece, Israel	multicenter, double-blind, RCT. (Secondary analysis of ASPRE)[16]	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[42] 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

TABLE 2 - Risk of bias assessments

Retrospective Cohort Studies	**Confounding**	**Selection of participants**	**Intervention classification**	**Deviations from intervention**	**Missing data**	**Measurement of outcomes**	**Selective reporting**	**Overall**	**Comments**
Boriboonhirusarn 2017[34]	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[37]	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[39]	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[35]		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[36]		Low	Low	Low	Low	Low	Low	Follow-up forms obtained for 96% of randomized women (476 allocated to aspirin, 494 to placebo)
Lin 2021[38]		Low	Low	Low	Low	Low	Low	Study protocol reviewed. Registered with clinicaltrials.gov: NCT02797249, with

								recruitment commencing following registration.
Moore 2015[40]		Low	Low	Low	Low	Some concerns	Some concerns	Secondary analysis of Caritis 1998.[15]
Poon 2017[41]		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[42]		Some concerns	Low	Low	Low	Low	Some concerns	No information on concealment of randomisation and intervention allocation. "Low dose aspirin" - dose undefined.

TABLE 3 - Summary of meta-analyses of the effect of low-dose aspirin on maternal and neonatal outcomes in women with chronic hypertension

Outcome	**Studies (number of patients)**	**OR (95% confidence interval)**	**95% Prediction interval**	**Fragility index**
Superimposed pre-eclampsia	Six RCTs (1,484)	0.83 (0.55-1.25)	0.27-2.56	11

Superimposed pre-eclampsia	Three Cohort (666)	1.21 (0.78-1.87)	0.07-20.80	NA
Superimposed pre-eclampsia given early aspirin initiation	Four RCTs (992)	0.74 (0.47-1.16)	0.14-4.05	6
Preterm pre-eclampsia	Three RCTs (737)	1.17 (0.74-1.86)	0.06-23.39	10
Preterm birth	Two RCTs (710)	0.63 (0.45-0.89)	NA	5
Small for gestational age	Three RCTs (900)	0.96 (0.65-1.40)	0.08-11.53	18
Perinatal mortality	Two RCTs (714)	0.88 (0.36-2.14)	NA	14

FIGURE LEGENDS

1. Flow diagram
2. Superimposed pre-eclampsia (RCTs)
3. Superimposed pre-eclampsia (cohorts)
4. Summary of findings, including GRADE assessments

5. Pre-eclampsia outcome when aspirin initiated before 20 weeks (RCTs)
6. Preterm pre-eclampsia (RCTs)
7. Preterm birth (RCTs)
8. Small for gestational age (RCTs)
9. Perinatal mortality (RCTs)