Does low-dose aspirin initiated before 11 weeks' gestation reduce the rate of preeclampsia?

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The authors report no conflict of interest.

Accepted as oral presentation at the 18th World Congress in Fetal Medicine 25-29 June 2019, Alicante, Spain.

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Word count abstract: 500

Word count main text: 3,757

Condensation: Aspirin given at <11 weeks' gestation in high risk women does not reduce the risk of preeclampsia and gestational hypertension but may reduce the risk of preterm delivery.

Short title: Early aspirin administration and preeclampsia

PROSPERO registration number: CRD42019125006

AJOG at a Glance:

Why was this study conducted?

- To perform a systematic review and meta-analysis to evaluate the effect of low-dose aspirin initiated at <11 weeks' gestation on the risk of preeclampsia, gestational hypertension, or any hypertensive disorder of pregnancy. Secondary outcomes included preterm delivery at <37 weeks' gestation and fetal growth restriction.

Key findings

- The administration of low-dose aspirin at <11 weeks' gestation in women with a history of recurrent pregnancy loss, women who had undergone *in vitro* fertilization or women with thrombophilia or antiphospholipid syndrome was associated with a non-significant decrease in the risk of preeclampsia, gestational hypertension, and any hypertensive disorder of pregnancy.
- Early low-dose aspirin reduced the risk of preterm delivery but had no impact on the risk of fetal growth restriction.
- Except for preterm delivery and any hypertensive disorder of pregnancy, sensitivity analysis demonstrated similar observations; confirming the robustness of our analysis.

What does this add to what is known?

- Administration of low-dose aspirin at <11 weeks' gestation to high risk women does not reduce the risk of preeclampsia, gestational hypertension, any hypertensive disorder of pregnancy and fetal growth restriction but might reduce the risk of preterm delivery at <37 weeks of gestation.

ABSTRACT

OBJECTIVE DATA: Pre-conception or early administration of low-dose aspirin might improve endometrial growth, placental vascularization and organogenesis. Most studies have evaluated the potential benefit of pre-conception or early administration of low-dose aspirin in women with a history of recurrent pregnancy loss, women who have undergone *in vitro* fertilization or women with thrombophilia or antiphospholipid syndrome. These women are at an increased risk of placenta-associated complications of pregnancy, including preeclampsia, preterm delivery and fetal growth restriction.

STUDY: We performed a systematic review and meta-analysis to evaluate the effect of low-dose aspirin initiated at <11 weeks' gestation on the risk of preeclampsia, gestational hypertension, or any hypertensive disorder of pregnancy. Secondary outcomes included preterm delivery at <37 weeks' gestation and fetal growth restriction.

STUDY APPRAISAL AND SYNTHESIS METHODS: We searched in MEDLINE via PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.Gov and the World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) from 1985 to November 2018. Entry criteria were randomized controlled trials evaluating the effect of aspirin administered at <11 weeks' gestation in preventing preeclampsia and/or hypertensive disorders in pregnancy or improving pregnancy outcomes in women with recurrent miscarriage as compared to placebo or no-treatment and outcome data available or provided by authors for >85% of the study population. Relative risks (RR) with 95% confidence intervals (CI) were calculated for each study and pooled for global analysis as the effect measure. We assessed statistical heterogeneity in each meta-analysis using the Chi^2 statistics, I^2

and Tau². Heterogeneity was considered substantial if an I^2 was greater than 50% and either the Tau² was greater than zero, or there was a low P-value (<0.10) in the Chi^2 test for heterogeneity. Random-effects meta-analysis, weighted by the size of the studies, was performed to produce an overall summary on aspirin effect for each outcome. Sensitivity analysis by sequential omission of each individual study and by fixed-effects model was performed. Publication bias was not assessed due to the small number of included studies. Statistical analysis was performed using Stata release 14.0 (StataCorp, College Station, TX).

RESULTS: The entry criteria were fulfilled by eight randomized controlled trials on a combined total of 1,426 participants. Low-dose aspirin initiated at <11 weeks' gestation was associated with a non-significant reduction in the risk of preeclampsia (RR 0.52; 95% CI: 0.23-1.17, P=0.115), gestational hypertension (RR 0.49; 95% CI: 0.20-1.21; P=0.121) and any hypertensive disorder of pregnancy (RR 0.59; 95% CI 0.33-1.04, P=0.067). Early low-dose aspirin reduced the risk of preterm delivery (RR 0.52; 95% CI: 0.27-0.97, p=0.040) but had no impact on the risk of fetal growth restriction (RR 1.10; 95% CI 0.58-2.07, P=0.775). Except for preterm delivery and any hypertensive disorder of pregnancy, sensitivity analysis demonstrated similar observations; therefore confirming the robustness of the analysis.

CONCLUSION: The administration of low-dose aspirin at <11 weeks' gestation in high risk women does not decrease the risk of preeclampsia, gestational hypertension, any hypertensive disorder of pregnancy and fetal growth restriction. However, it might reduce the risk of preterm delivery. Larger randomized controlled trials will be required to substantiate the findings.

KEY WORDS: Abortion, antiphospholipid syndrome, anti-platelet, aspirin, early aspirin, fetal growth restriction, fixed effect, gestational hypertension, habitual abortion, hypertension, hypertensive disorder, ICSI, intracytoplasmic sperm injection, IVF, *in vitro* fertilization, meta-analysis, miscarriage, PE, platelet, preeclampsia, pre-pregnancy, pregnancy, preterm, preterm delivery, prevention, recurrent abortion, recurrent miscarriage, recurrent pregnancy loss, salicylic acid, sensitivity analysis, systematic review, random effect, thrombophilia.

INTRODUCTION

Aspirin, also known as acetylsalicylic acid, is the most widely used medication with 50 to 120 billion pills consumed each year.[1] Aspirin was first discovered over 3,500 years ago - its analgesic effect was described when willow leaves were used to treat inflammatory rheumatic diseases.[2] In 1828, Joseph Bucher extracted the active ingredient from the willow bark and it was named as “salicin”.[3] The purest and most stable form of acetylsalicylic acid was obtained on 10 August 1897 and, since then this medication has gained therapeutic success worldwide. Thus far, aspirin is recommended for the primary and secondary prevention of cardiovascular disease,[4-6] as well as several cancers such as colorectal, gastro-esophageal, breast and prostate.[7, 8]

In obstetrics, low-dose aspirin has been shown to be effective in preventing preterm preeclampsia, with delivery at <37 weeks’ gestation, in women at risk.[9-26] The ASPRE (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) trial demonstrated that in high risk women, identified by the first-trimester combined test, who were randomized to receive aspirin (150 mg per night) vs. placebo from 11-14 until 36 weeks’ gestation, the rate of preterm preeclampsia was substantially reduced (aspirin: 1.6% [13/798] vs. placebo: 4.3% [35/822]; odds ratio [OR] 0.38, 95% confidence intervals [CI], 0.20-0.74).[27] The latest systematic review and meta-analysis demonstrated that the reduction in the rate of preterm preeclampsia was confined to the subgroup in which aspirin was initiated at ≤16 weeks’ gestation and at a daily dose of ≥100 mg (relative risk [RR], 0.33; 95% CI, 0.19-0.57).[20]

Evidence suggests that pre-conception or early administration of low-dose aspirin might improve endometrial growth, placental vascularization and organogenesis.[17, 28-36] Following the success of the ASPRE trial, the question that remains is whether high risk women should start low-dose aspirin before pregnancy or during the very early stage of pregnancy. To date, most studies have evaluated the potential benefit of pre-conception or early administration of low-dose aspirin in women with a history of recurrent pregnancy loss,[37-40] women who have undergone in *vitro* fertilization (IVF)[28, 41-54] or women with thrombophilia or antiphospholipid syndrome.[55-65] It is recognized that these women are at an increased risk of placenta-associated complications of pregnancy, including hypertensive disorder of pregnancy,[66-69] preterm delivery,[70, 71] and fetal growth restriction.[70, 72]

The objective of this study was to perform a systematic review and meta-analysis to estimate the effect of low-dose aspirin initiated at <11 weeks' gestation on the risk of preeclampsia, gestational hypertension, or any hypertensive disorder of pregnancy.

MATERIALS AND METHODS

Type of studies

This is a systematic review and meta-analysis of randomized controlled trials including studies that recruited women for the prevention of preeclampsia with the use of aspirin commenced at <11 weeks' gestation. Treatment includes aspirin compared with placebo or no-treatment. We did not include cross-over trials or studies of observational designs such as case-control studies or cohort studies in this meta-

analysis but we considered such evidence in the discussion, where relevant. Studies were excluded if pregnant women started treatment at or after 11 weeks' gestation or there was no placebo or no-treatment group.

Research strategy

In clinical practice, pre-conception or very early aspirin administration is advised for women with recurrent miscarriage.[73] Therefore, we have included the terms recurrent abortion and habitual abortion in the keywords. Keywords and MeSH terms (aspirin, preeclampsia, recurrent abortion, habitual abortion) related to aspirin commenced at <11 weeks' gestation for preeclampsia prevention were searched in MEDLINE via PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.Gov and World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) from 1985 to November 2018. No language restrictions were applied.

Selection of the articles

Titles were selected from first screening and abstracts of citations were reviewed by two independent reviewers (P.C. and D.C.G.) to identify all potentially relevant articles, which were subsequently fully evaluated by the same reviewers. Reference lists of relevant original and review articles were searched for additional reports. Disagreements were resolved by the opinion of a third party (L.C.P.). Entry criteria were randomized controlled trials evaluating the effect of aspirin administered at <11 weeks' of gestation in preventing preeclampsia and/or other hypertensive disorders in pregnancy as compared to placebo or no-treatment and outcome data available or provided by authors for >85% of the study population.

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195 Data extraction, construction of contingency tables and outcome measures

196 The following information was extracted from the articles: author names, publication
197 year, study design, method of randomization, blinding, type of comparison group,
198 sample size in each group, gestational age at randomization, duration, dose and
199 compliance of aspirin treatment. The primary end-point of this study was the rate of
200 preeclampsia. Secondary end-points were the rates of gestational hypertension, any
201 hypertensive disorder of pregnancy, preterm delivery at <37 weeks' gestation and fetal
202 growth restriction. Not all studies reported on the individual rates of preeclampsia and
203 gestational hypertension, therefore, we divided outcomes as: 1) preeclampsia; 2)
204 gestational hypertension (hypertension without proteinuria); and 3) any hypertensive
205 disorder of pregnancy, which included either preeclampsia, HELLP (hemolysis,
206 elevated liver enzymes, and a low platelet count) syndrome or gestational
207 hypertension. Data on primary and secondary end-points were documented in
208 contingency tables. For all outcomes, analyses were carried out, as far as possible,
209 on an intention-to-treat basis, i.e. we attempted to include all participants randomized
210 to each group in the analyses. The denominator for each outcome in each trial was
211 the number randomized minus any participants whose outcomes were missing or
212 whose pregnancy did not reach 20 weeks. We contacted the authors directly when
213 further clarification on their data, such as the precise gestational age for trial drug
214 administration[74, 75] and the results according to singleton or multiple pregnancies,[40,
215 50, 56, 76] were required. Only one author responded[40] and reported that for singleton
216 pregnancies there were three and six cases of preeclampsia in the aspirin and placebo
217 groups, respectively; and there were two cases of gestational hypertension in each

218 treatment group. Statistical heterogeneity between the studies was evaluated with
219 interaction terms between aspirin and trial.
220
221 Quality evaluation
222 The quality of this review was validated with the Preferred Reporting Items for
223 Systematic Reviews and Meta-Analyses (PRISMA) tool,[77] and the quality of each
224 included trial was assessed by the Cochrane Handbook.[78] The methodological quality
225 of the selected studies in terms of risk of bias and applicability was evaluated by three
226 assessors (P.C., D.C.G., M.M.G.) using the Cochrane Risk of bias tool 2 (Rob 2).[79]
227
228 Analyses
229 Relative risks with 95% CI were calculated for each trial and pooled for global analysis
230 as the effect measure. We assessed statistical heterogeneity in each meta-analysis
231 using the Chi^2 statistics, I^2 and Tau^2. Heterogeneity was considered substantial if an I^2
232 was greater than 50% and either the Tau^2 was greater than zero, or there was a low
233 P-value (<0.10) in the Chi^2 test for heterogeneity.[80, 81] In order to take into account
234 clinical variability and/or heterogeneity between studies, random-effects meta-
235 analysis, weighted by the size of the trials, was performed to produce an overall
236 summary on aspirin effect for each outcome.[82, 83] We have performed sensitivity
237 analyses to examine statistical heterogeneity in two different ways, first, by omitting
238 each study sequentially and assessing the effect estimate from remaining studies and
239 second by calculating global estimates derived from fixed-effects model. Publication
240 bias was not assessed due to the small number of included studies. We intended to
241 perform meta-regression analyses to assess the effect of aspirin dosage for each
242 outcome if the number of studies included for such purpose was at least ten.[78]

Statistical analysis was performed using Stata release 14.0 (StataCorp, College Station, TX).

RESULTS

The literature search identified 766 citations: after removing duplicate articles (n=21) and articles that were not relevant (n=632), 113 articles were reviewed and eight randomized controlled trials on a combined total of 1,426 participants met the inclusion criteria (Figure 1). Table 1 demonstrated the characteristics of included studies. There were no studies with >15% drop out rate.

Six out of the eight trials reported the effect of aspirin commenced at <11 weeks' gestation on the rates of preeclampsia.[38, 40, 50, 56, 84, 85] Four out of the eight trials reported the effect of aspirin started at <11 weeks' gestation on the rates of gestational hypertension.[40, 50, 84, 85] For any hypertensive disorder of pregnancy, there were eight trials reporting the effect of aspirin initiated at <11 weeks' gestation.[38, 40, 50, 56, 76, 84-86] Lastly, six and five of the eight trials reported the effect of aspirin commenced at <11 weeks' gestation on the preterm delivery [40, 56, 76, 84-86] and fetal growth restriction,[38, 40, 50, 56, 86] respectively. Seven of the included trials were considered to be good or unclear quality; one trial was considered at high risk of bias because some cases were excluded from final analysis due to loss to follow up. (Figure 2) The heterogeneity between the trials for each of the assessed outcomes is reported in Table 2.

Low-dose aspirin initiated at <11 weeks' gestation was associated with a non-significant reduction in the risk of preeclampsia (RR 0.52; 95% CI: 0.23-1.17, P=0.115), gestational hypertension (RR 0.49; 95% CI: 0.20-1.21; P=0.121) and any hypertensive disorders in pregnancy (RR 0.59; 95% CI 0.33-1.04, P=0.067). Early low-dose aspirin was associated with a significant reduction in the risk of preterm delivery (RR 0.52; 95% CI: 0.27-0.97, p=0.040) but had no impact on the risk of fetal growth restriction (RR 1.10; 95% CI 0.58-2.07, P=0.775) (Figures 3-7, Table 2).

Sensitivity analysis demonstrated that the overall results were similar in both direction and magnitude to the aforementioned results (Tables 2 and 3). Results derived from fixed-effects model analysis (Table 2) must only be interpreted for sensitivity analysis but not for treatment effect assessment because this type of analysis, which does not allow population parameters to vary across studies, leads to narrower confidence intervals and higher Type I error rates when there is any statistical or clinical variation between studies. By sequentially omitting studies, the pooled RR for preeclampsia ranged from 0.39 (95% CI: 0.16-1.00) to 0.68 (95% CI: 0.31-1.50). For gestational hypertension, the pooled RR ranged from 0.35 (95% CI: 0.09-1.37) to 0.69 (95% CI: 0.27-1.76). The pooled RR for any hypertensive disorder during pregnancy ranged from 0.50 (95% CI: 0.24-1.04) to 0.77 (95% CI: 0.51-1.16), however, when the study by Kaandorp et al was omitted,[56] the estimated effect became significant (0.54; 95% CI: 0.30-0.98). For fetal growth restriction, the pooled RR ranged from 0.91 (95% CI: 0.42-1.97) to 1.27 (95% CI: 0.65-2.47). For preterm birth, the results were more heterogeneous; only when Pattison et al 's study or Lambers et al's study was omitted, the result remained significant. The pooled RR for preterm delivery ranged from 0.47 (95% CI: 0.27-0.82) to 0.63 (95% CI: 0.37-1.06) (Table 3).

All eight included studies provided information on the dosage of aspirin, ranging from 50-100 mg daily. All except one study[38] used a dosage >75 mg/day. We did not perform meta-regression analysis since it required a large volume of individual studies to make meaningful interpretations from the data and should generally not be considered when there are fewer than ten studies in a meta-analysis.[78]

COMMENT

Principal findings of this study: The administration of low-dose aspirin at <11 weeks' gestation in women with a history of recurrent pregnancy loss, women who have undergone IVF or women with thrombophilia or antiphospholipid syndrome is associated with a non-significant decrease in the risk of preeclampsia, gestational hypertension, and any hypertensive disorder of pregnancy. Early low-dose aspirin might reduce the risk of preterm delivery; but there is no significant impact on the rate of fetal growth restriction.

It has recently been demonstrated that aspirin given at 11-14 weeks' gestation to women at risk reduces the frequency of preterm preeclampsia.[27] This approach for the prevention of preterm preeclampsia has now been endorsed by the International Federation of Gynecology and Obstetrics (FIGO).[23] However, the effect of aspirin on the enhancement of physiologic transformation in the spiral arteries of the placental bed is still questionable and unproven. Previous studies have demonstrated that uterine artery Doppler resistance index at 24-28 weeks' gestation is not significantly different between women who receive and do not receive low-dose aspirin starting in

317 the first trimester of pregnancy,[10, 87-89] suggesting that the aspirin effect in preventing
318 preeclampsia might be related to its action on platelets, rather than placental
319 development. However, a recent *in vitro* study using trophoblast-derived cell line has
320 demonstrated that the administration of low-dose aspirin can increase trophoblast
321 placental growth factor secretion and restore perturbed cytokine levels (activated
322 leukocyte cell adhesion molecule, chemokine (C-X-C motif) ligand (CXCL)-16, and
323 Erb-B2 Receptor Tyrosine Kinase 3) induced by preeclampsia serum.[90] These
324 findings indicate that aspirin might also modulate trophoblastic cell function.
325
326 In relation to the treatment effect of preconception or early administration of aspirin in
327 preventing placental associated complications, several hypotheses have been
328 proposed. Low-dose aspirin, hypothetically, can improve endometrial growth and
329 embryo implantation by: 1) reducing sub-endometrial contractility; 2) reducing
330 endometrial inflammation by inhibiting cyclooxygenase and prostaglandin
331 biosynthesis; and 3) increasing endometrial blood flow.[91, 92] Aspirin-mediated
332 resolution of inflammation has been recently described as an alternative hypothesis.
333 Aspirin is able to acetylate cyclooxygenase-2 to preserve and redirect its catalytic
334 activity, leading to the production of 15(R)-hydroxyeicosatetraenoic acid, which is then
335 converted by 5-lipoxygenase into aspirin-triggered lipoxins (ATLs).[93] ATLs act to
336 resolve inflammation through their immune and angiogenic modulatory properties. In
337 endothelial cells, ATLs can reduce the production of reactive oxygen species and
338 differentially regulate neutrophil and monocyte chemotaxis. In immune cells, ATLs can
339 inhibit NF-kappa B activity and pro-inflammatory cytokine production.[93] In addition,
340 aspirin has been shown to improve trophoblast-endothelial cell integration in *in vitro*
341 studies by inhibiting the effect of tumor necrosis factor-alpha via prostacyclin

production without any effects on anti-angiogenic, invasive (matrix metalloproteinase) or endothelial activation markers.[94, 95] However, in an *in vivo* study, aspirin has been shown to inhibit the expression of soluble fms-like tyrosine kinase (sFlt-1) in cytotrophoblast cultured cells, under a hypoxic state, from placentas of women with confirmed preeclampsia.[96] The result of the current meta-analysis indicates that the administration of low-dose aspirin at <11 weeks' gestation is associated with a non-significant decrease in the risk of preeclampsia, gestational hypertension, and any hypertensive disorder of pregnancy. However, when Kaandorp et al 's study[56] is excluded, the effect of aspirin on the rate of any hypertensive disorder of pregnancy becomes significant (Table 3). It is probable that patient selection in this study has attributed to this finding. This study included women with ≥2 miscarriages without antiphospholipid syndrome, with or without inherited thrombophilia (rate of inherited thrombophilia ~16%). Thus far, the benefit of aspirin in the prevention of preeclampsia in women with thrombophilia is not established.[60] Of note, frequency of preeclampsia in this study was relatively low (aspirin group 3.3% (2/61) vs. placebo group 1.4% (1/70)).[56]

Regarding preterm delivery, previous studies have demonstrated that a subset of pregnant women with spontaneous preterm birth has placental lesions associated with uteroplacental ischemia[97-102] and abnormal uterine artery Doppler.[103, 104] Such findings are frequently observed in women with preeclampsia.[101, 105-116] Therefore, the underlying mechanisms responsible for the reduction in the rate of preterm delivery by preconception or early administration of aspirin might be similar to those proposed for preeclampsia. The results of the current meta-analysis have demonstrated that the administration of aspirin at <11 weeks' gestation is associated with a significant

reduction in the risk of preterm birth. However, this observation becomes insignificant if some studies are excluded (Table 3), suggesting that, although there is an effect from aspirin, it is not robust enough. In Lambers et al's study, 50% (2/4) and 100% (2/2) of women with preterm delivery in the aspirin and placebo groups, respectively, had twin pregnancies,[84] thus, this might account for the heterogeneity of the result. In the current meta-analysis, cases of preterm delivery include those resulting from spontaneous onset of labor as well as medical indications, such as preeclampsia, and therefore, in this instance, the reduction in the rate of preterm delivery is also likely to be mediated via a reduction in the rate of preeclampsia, which is one of the leading causes of medically indicated preterm delivery.

Concerning the potential risks of aspirin usage during the very early stage of pregnancy, evidence from clinical trials and meta-analyses on low-dose aspirin in women with previous pregnancy loss has demonstrated that aspirin does not increase the risk of major bleeding, such as gastrointestinal bleeding, or major adverse events, such as congenital or neonatal abnormalities.[40, 50, 56, 60, 85, 86, 117] One study demonstrated that vaginal bleeding was more common in women receiving the treatment, (3.9% vs. 1.3%, p=0.004) but vaginal bleeding was not associated with an increased risk of miscarriage (13% vs. 12%, p=0.781).[117] The largest study included in this meta-analysis has also evaluated complications and safety of pre-conception low-dose aspirin in 1,228 American women.[76] The authors have demonstrated that the frequency of women with at least one possible aspirin-related symptom or at least one emergency care visit or maternal complication (except vaginal bleeding) during the trial is similar between treatment and placebo groups.[118] Although, vaginal bleeding is more commonly found in the low-dose aspirin group (22% compared with

17%, p=0.02), it is not associated with an increased risk of fetal and neonatal complications (stillbirth and neonatal death). The remaining seven studies have also reported that the administration of aspirin has not increased the risk of bleeding, postpartum hemorrhage or congenital anomalies.[38, 40, 50, 56, 84-86] In addition, a meta-analysis of 22 studies has shown that maternal therapeutic use of aspirin in the first trimester is not associated with an overall increase in the risk of major congenital malformations, except for gastroschisis (OR 2.37, 95% CI: 1.44-3.88).[119] The latter finding has only been demonstrated in a case-control study [119] and it has not been confirmed in several large prospective cohort studies.[120-122] On the whole, the initiation of low-dose aspirin from the early stage of pregnancy is not associated with an increased risk of miscarriage or major congenital malformation.

Comparison with previous studies on pre-conception or early administration of aspirin

In addition to the randomized controlled trials included in the current meta-analysis, a number of observational studies, including three retrospective[123-125] and one prospective cohort studies,[126] have reported on the relationship between early administration of low-dose aspirin and the risk of preeclampsia. All studies included women with history of previous preeclampsia and/or other pregnancy complications such as preterm delivery or fetal death. The results are conflicting, in which three studies have reported that aspirin has no effect on the rate of preeclampsia,[123-125] while one study has demonstrated a reduction in the risk of the disorder (no treatment group 23.1% [3/13] vs. aspirin group 8.3% [1/12]).[126]

Limitations of the study

A major limitation of this meta-analysis was that not all trials reported on the rate of preeclampsia and that some studies did not differentiate preeclampsia from gestational hypertension.[76, 86] The effect of compliance on the treatment effect size could not be evaluated as only four of the eight trials provided details of trial drug compliance. In addition, it was not possible to evaluate the effect of dose, exact timing, and indications of aspirin administration due to the small sample size of trials. With regard to duration of aspirin intake, all except one study administered aspirin until 36 weeks' gestation or delivery. [38, 40, 50, 56, 76, 85, 86] One study stopped aspirin at 12 weeks' gestation.[84] The sensitivity analysis has demonstrated that the omission of this study does not alter the results (Table 3). The most frequent indications for the initiation of preconception or early administration of aspirin were recurrent miscarriage (five studies; total subjects N=1,022),[38, 40, 56, 76, 86] followed by IVF treatment (two studies; total subjects N=122).[50, 84] Only one study evaluated the effect of early administration of aspirin on unselected nulliparous pregnant women.[85] Our results suggest that high risk women, in particular those with a history of recurrent miscarriage, might benefit from early administration of low-dose aspirin. All studies provided information about dosage of aspirin and all except one[38] used a dosage of more than 75 mg/day. Although it would be of interest to examine further the effect of aspirin dose in pregnancy outcome, the insufficient number of studies did not allow us to accurately perform meta-regression analysis. Lastly, two of the eight trials did not differentiate the results between singleton and multiple pregnancies but the number of multiple pregnancies included was very small (total n=6; 0.4%) and therefore we decided to include these trials in the meta-analysis.[56, 76] Although most studies (6/8) were considered as low risk of bias, [38, 40, 50, 56, 76, 86] one study was considered as having some concerns,[85] because of insufficient information to assess the quality of the

randomization and concealment process, and another study was considered as high risk of biased because some cases were excluded from final analysis due to loss to follow up.[84]

Clinical implications of the study

The key research question that has driven this meta-analysis is whether certain women, such as those with antiphospholipid syndrome or thrombophilia, would benefit from low-dose aspirin before pregnancy or during the very early stage of pregnancy as these women are considered to have the highest risk for the development of preterm preeclampsia and that waiting till 11-13 weeks' gestation for screening and treatment is perceived to delay potential beneficial prophylaxis.

Although, the primary objective for pre-conception or early administration of low-dose aspirin from the included randomized controlled trials was to improve the rate of live births in high risk pregnant women, the observations from our study suggest that such administration of aspirin was not associated with a reduction in the rates of preeclampsia, gestational hypertension any hypertensive disorder of pregnancy and fetal growth restriction.. However, it might be associated with a reduction in the rate of preterm delivery. The potential benefit might only be applicable to high risk women with a history of recurrent pregnancy loss or those who have undergone IVF treatment or those with thrombophilia or antiphospholipid syndrome. At present, there is no high quality evidence to support recommendation of preconception or early administration of low-dose aspirin for high risk women to prevent placenta-associated complications of pregnancy. Large prospective randomized controlled trials are needed to

substantiate our observations. Further work is also required to determine the optimal dosage, timing and duration of aspirin treatment.

Conclusion

This study has demonstrated that the administration of low-dose aspirin at <11 weeks' gestation in high risk women does not reduce the risk of preeclampsia, gestational hypertension, any hypertensive disorder of pregnancy and fetal growth restriction. It might reduce the risk of preterm delivery.

Acknowledgments: We wish to thank Emma J. Guo and Kubi Appiah in assisting with obtaining full-text articles and Marisa Maquedano from iMaterna Foundation for assisting with the literature search. This study is part of the PhD thesis of Diana Cuenca Gómez for Universidad de Alcalá, Spain.

Sources of Funding: No funding

Disclosures: The authors have no conflict of interest.

Figure legend

Figure 1: The flow diagram depicts the flow of information through the different phases of a the current meta-analysis

Figure 2: Assessment of the risk of bias of included studies using the Cochrane Risk of bias tool 2.

Figures 3-7: Forest plots of random-effects model in assessing early administration of aspirin and risk of pregnancy complications such as preeclampsia **(Figure 3)**, gestational hypertension **(Figure 4)**, any hypertensive disorder of pregnancy **(Figure 5)**, preterm birth <37 weeks' gestation **(Figure 6)** and fetal growth restriction **(Figure 7)**

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