

Acetylsalicylic Acid for the Prevention of Preeclampsia and Intra-uterine Growth Restriction in Women with Abnormal Uterine Artery Doppler: A Systematic Review and Meta-analysis

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Abstract

Background: Preeclampsia is a major global cause of maternal, neonatal and perinatal mortality. From studies of placental pathophysiology in women with preeclampsia, a potentially important role of low-dose acetylsalicylic acid (ASA) in the prevention of preeclampsia was expected, but the results from clinical trials have been disappointing. While recent evidence has shown that uterine Doppler can predict preeclampsia as early as in the first trimester of pregnancy, most clinical trials have evaluated ASA in the second and third trimesters.

Objectives: We performed a meta-analysis to assess the influence of gestational age at the time of introduction of ASA on the incidence of preeclampsia in women at increased risk, on the basis of abnormal uterine artery Doppler.

Methods: Computerized searches of randomized controlled trials were conducted to retrieve studies in which pregnant women at increased risk of preeclampsia had been identified on the basis of abnormal uterine Doppler measurements. The trials compared women who received ASA with a control group. The primary outcome was preeclampsia. Secondary outcomes included severe preeclampsia, gestational hypertension, preterm birth, intrauterine growth restriction, placental abruption, birth weight and gestational age at delivery. Statistical analyses used fixed effects of risk ratio

(RR) with the Mantel-Haenszel method and 95% confidence intervals.

Results: Nine randomized controlled trials with a total of 1317 women met the inclusion criteria. ASA treatment beginning in early gestation was associated with a greater reduction in the incidence of preeclampsia than treatment beginning in late gestation: ASA treatment started at ≤ 16 weeks' gestation resulted in RR 0.48 (95% CI 0.33 to 0.68), at 17–19 weeks RR 0.55 (95% CI 0.17 to 1.76), and at ≥ 20 weeks RR 0.82 (95% CI 0.62 to 1.09). ASA treatment started before 16 weeks was also linked with a significant reduction in the incidence of severe preeclampsia (RR 0.10; 95% CI 0.01 to 0.74), gestational hypertension (RR 0.31; 95% CI 0.13 to 0.78) and IUGR (RR 0.51; 95% CI 0.28 to 0.92).

Conclusion: ASA treatment initiated early in pregnancy is an efficient method of reducing the incidence of preeclampsia and its consequences in women with ultrasonographic evidence of abnormal placentation diagnosed by uterine artery Doppler studies.

Résumé

Contexte : La prééclampsie est une cause globale majeure de mortalité maternelle, néonatale et périnatale. On s'attendait à ce que les études sur la pathophysiologie placentaire chez les femmes présentant une prééclampsie indiquent que l'acide acétylsalicylique (AAS) à faible dose joue un rôle potentiellement important dans la prévention de la prééclampsie, mais les résultats issus des essais cliniques se sont avérés décevants. Bien que de récentes données aient indiqué que la tenue d'un Doppler utérin pouvait prédire la survenue d'une prééclampsie dès le premier trimestre de la grossesse, la plupart des essais cliniques ont évalué l'AAS au cours des deuxième et troisième trimestres.

Key Words: Preeclampsia, Doppler, intra-uterine growth restriction, acetylsalicylic acid, systematic review, meta-analysis, pregnancy, placenta

Competing Interests: None declared.

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Objectifs : Nous avons mené une méta-analyse afin d'évaluer l'influence de l'âge gestationnel au moment de la mise en œuvre du traitement à l'AAS sur l'incidence de la prééclampsie chez les femmes exposées à des risques accrus, en fonction de l'obtention de résultats anormaux à la suite d'un Doppler de l'artère utérine.

Méthodes : Des recherches informatisées visant les essais comparatifs randomisés ont été menées en vue d'extraire les études dans le cadre desquelles les femmes enceintes courant un risque accru de prééclampsie avaient été identifiées en fonction de l'obtention de mesures anormales à la suite d'un Doppler utérin. Les essais comparaient les femmes recevant de l'AAS à un groupe témoin. La prééclampsie constituait le critère d'évaluation principal. Parmi les critères d'évaluation secondaires, on trouvait la prééclampsie grave, l'hypertension gestationnelle, l'accouchement préterme, le retard de croissance intra-utérin, le décollement placentaire, le poids de naissance et l'âge gestationnel au moment de l'accouchement. Les analyses statistiques faisaient appel à un modèle à effets fixes et à un risque relatif (RR), conjointement avec la méthode Mantel-Haenszel et des intervalles de confiance à 95 %.

Résultats : Neuf essais comparatifs randomisés (comptant, en tout, 1 317 participantes) ont répondu aux critères d'inclusion. Le traitement à l'AAS entamé aux débuts de la gestation a été associé à une plus grande baisse de l'incidence de la prééclampsie que le traitement entamé aux derniers moments de la gestation : le traitement à l'AAS entamé à ≤ 16 semaines de gestation a donné lieu à un RR de 0,48 (IC à 95 %, 0,33 à 0,68); à 17–19 semaines, à un RR de 0,55 (IC à 95 %, 0,17 à 1,76); et à ≥ 20 semaines, à un RR de 0,82 (IC à 95 %, 0,62 à 1,09). Le traitement à l'AAS entamé avant la 16^e semaine de gestation a également été lié à une baisse significative de l'incidence de la prééclampsie grave (RR, 0,10; IC à 95 %, 0,01 à 0,74), de l'hypertension gestationnelle (RR, 0,31; IC à 95 %, 0,13 à 0,78) et du RCIU (RR, 0,51; IC à 95 %, 0,28 à 0,92).

Conclusion : Le traitement à l'AAS entamé aux débuts de la grossesse constitue une méthode efficace de réduire l'incidence de la prééclampsie et d'atténuer les conséquences de cette dernière chez les femmes ayant obtenu des résultats échographiques indiquant une placentation anormale diagnostiquée au moyen d'études Doppler de l'artère utérine.

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INTRODUCTION

Preeclampsia is a leading cause of maternal mortality. The World Health Organization estimates that, worldwide, over 100 000 women die from preeclampsia each year, and the condition continues to be responsible for maternal deaths in developed countries.¹ The prevalence of the condition varies between 5% and 10%, but could be as high as 18% in developing countries.^{2,3} Moreover, preeclampsia is associated with high perinatal mortality and morbidity, including intrauterine growth restriction (IUGR) and prematurity.⁴ Preeclampsia and IUGR are characterized by abnormal placental implantation and inadequate uteroplacental blood flow. Normal placentation comprises trophoblast cell invasion of the decidual and myometrial segments of spiral arteries, which results in reversible changes in the normal arterial wall architecture.⁵ Trophoblastic invasion develops from eight weeks' gestation, with most of the physiological transformation of spiral arteries being completed between 16 and 20 weeks.^{6–8}

Failure of physiological spiral artery transformation in the myometrium is now recognized as a hallmark of defective placentation and can be found in the great majority of women with early onset preeclampsia.⁹ This failure of physiological transformation is associated with resistance in utero-placental blood flow that is characterized by abnormal uterine artery velocity when evaluated by Doppler ultrasonography. Indeed, recent studies have shown that abnormal uterine artery Doppler as early as the first trimester can identify women at high risk of preeclampsia and IUGR.^{10,11} However, without the demonstration of clinical benefit, it is not standard care to perform a uterine artery Doppler study during pregnancy.

Acetylsalicylic acid (ASA) therapy has been implicated in the physiological transformation of spiral uterine arteries: it inhibits thromboxane-mediated vasoconstriction more than prostacyclin-mediated vasodilatation, and may thereby offer protection against vasoconstriction and pathological blood coagulation in the placenta. Its use was expected to prevent failure of physiological spiral artery transformation as well as the development of preeclampsia. However, several large, prospective, multicentre studies conducted to establish whether or not ASA use should be a standard of care have failed to demonstrate the clinical efficacy of ASA in preventing preeclampsia.^{8,9} On the other hand, the late initiation of treatment (after 18 to 20 weeks) reported in most trials, and the inclusion of low-risk patients in some, were potential reasons for the negative or weakly positive results obtained. A meta-analysis published in 2001 suggested that ASA therapy in women with abnormal uterine artery Doppler studies was accompanied by a significant but modest reduction in rates of preeclampsia but not a decrease in IUGR.¹² In this meta-analysis there was no stratification of subjects by gestational age at the beginning of ASA prophylactic treatment.¹² Therefore, we aimed to assess the influence of gestational age at the introduction of ASA therapy on rates of preeclampsia and IUGR in women identified (by abnormal uterine artery Doppler studies during pregnancy) as being at high risk of preeclampsia.

METHODS

We performed a systematic review and meta-analysis of randomized trials of ASA therapy in preventing preeclampsia. To identify all the trials published between 1965 and 2008, we searched Medline, PubMed, Embase, and the Cochrane Library with the following key words: "aspirin," "antiplatelet," "salisyl," "acetylsalicylic," "platelet aggregation inhibitors," "ultrasonography," "ultrasound," and "Doppler." Trials published in any language were considered for inclusion. The complete search strategy is available on request.

Table 1. Quality of studies included in the review

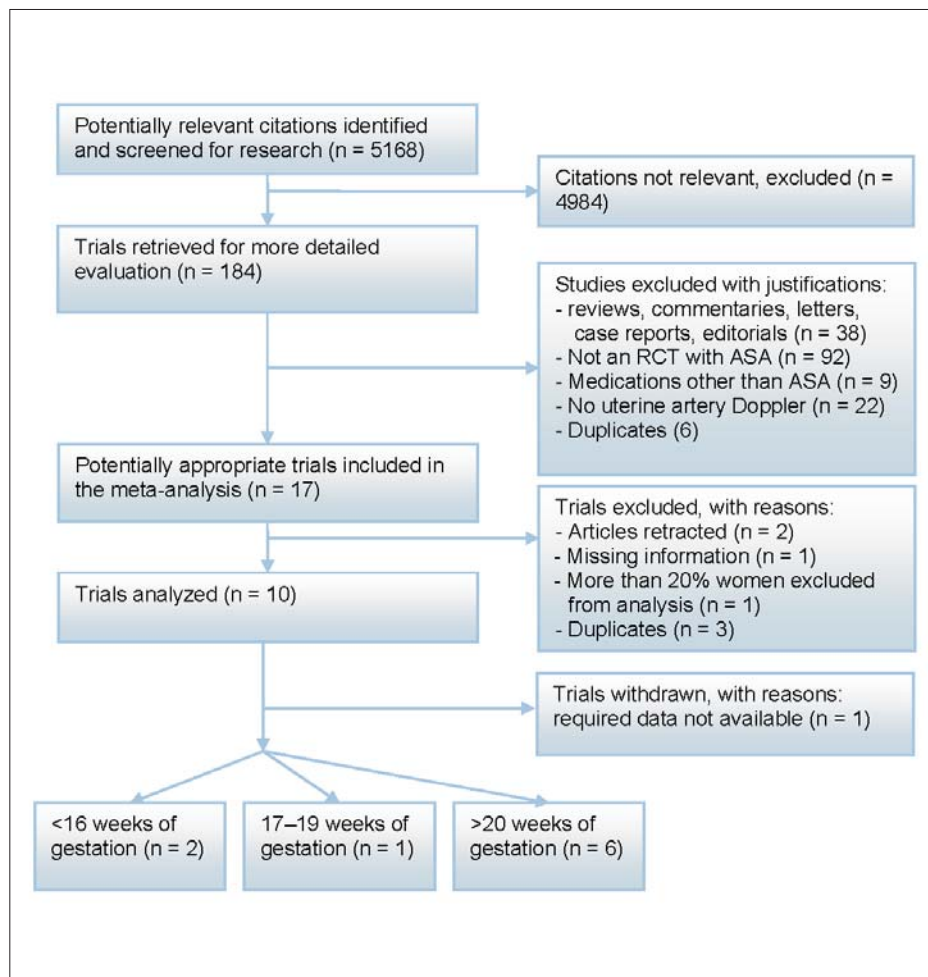
Study	Method of randomization	Blinding	Intention to treat	Lost to follow-up (%)
Ebrashy A, 2005 ¹⁹	Computer-generated list of random numbers	None	Yes	2.2
Zimmermann P, 1997 ²⁶	Randomized, no other information	None	Yes	Unclear
Vainio M, 2002 ²⁰	Randomization in pharmacy	Double	Unclear	4.4
McParland P, 1990 ²⁴	Computer-generated randomization list	Double	Yes	5.7
Yu CKH, 2003 ²⁵	Computer-generated random number lists	None	Yes	1.1
Ferrier C, 1996 ¹⁸	Randomized, no more details	Double	Unclear	Unclear
Harrington K, 2000 ²³	Randomization: pre-prepared, sealed envelopes, no further details	None	No	2.8
Morris JM, 1996 ²¹	Randomization by taking the next in a series of numbered, identical blister packs	Double	Yes	1.9
Bower SJ, 1996 ²²	By telephoning a central computerized randomization service	Double	Yes	4.8

We selected randomized controlled trials that included women identified, by abnormal uterine artery Doppler examination, to be at high risk of preeclampsia. The definition of abnormal uterine artery Doppler was unrestricted. Treatment consisted of low-dose ASA (50 to 150 mg/day), with the control group receiving either a placebo or no treatment (i.e., usual care). Studies were excluded if more than 20% of women were lost during follow-up or excluded from the analyses. The primary outcome was the development of preeclampsia according to gestational age at the initiation of treatment. Preeclampsia was defined by the combination of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, with ≥ 300 g of urinary protein /24 h (or 1+ or more on dipstick). Secondary outcomes included IUGR and mean birth weight. We defined IUGR as a birth weight < 10 th percentile for gestational age. If this definition of IUGR was unavailable, the following definitions were also accepted: birth weight < 5 th percentile for gestational age or < 2500 g. Severe preeclampsia was defined by any one of the following criteria: severe hypertension (blood pressure of ≥ 160 mmHg systolic, or 110 mmHg diastolic), severe proteinuria ($\geq 2, 3$, or 5 g of protein in 24 h, or 3+ on dipstick), reduced urinary volume (< 400 to 500 mL in 24 h), neurological disturbances, such as headache and visual perturbations, upper abdominal pain, pulmonary edema, impaired liver function tests, high serum creatinine, low platelet count, IUGR or preeclampsia requiring delivery prior to 37 or 34 weeks if the prior criteria were not reported.¹³ Preeclampsia associated with one or more of these criteria was considered severe.

After extraction of all articles from the databases, the citations were reviewed by two investigators and categorized as

potentially relevant or irrelevant. All potentially relevant reports were independently examined in detail by two other investigators and categorized as relevant, possibly relevant, or irrelevant on the basis of our research criteria. Any disagreement was resolved by consensus. Quality and integrity of the studies were assessed and reported by evaluating quality criteria for each study (method of randomization, blinding, intention-to-treat, lost to follow-up) (Table 1). All possibly relevant references cited by two recent meta-analyses were reviewed for validation of the literature search to confirm that no trial had been overlooked.^{12,14}

The analyses were performed by Review Manager 5.0.12 (RevMan. 5.0. ed. Copenhagen). Risk ratios (RR) from individual studies were combined according to a fixed effect model, using the Mantel-Haenszel method. The data were stratified according to gestational age at entry (beginning of ASA therapy) in the trial ($\leq 16, 17-19, \geq 20$ weeks' gestation). These thresholds in gestational age were determined a priori on the basis of the physiological evolution of spiral uterine artery transformation during pregnancy that usually ends between 16 and 20 weeks' gestation.^{8,15} The analyses were also adapted according to type of variable (dichotomous vs. continuous). Each study was weighted with standard deviation for both dichotomous and continuous data. The heterogeneity of treatment was evaluated by χ^2 and I^2 , and was considered to be significant if P was less than 0.05 or if I^2 was larger than 50%, according to Higgins et al.¹⁶ Publication bias was investigated by the evaluation of asymmetry of a funnel plot. Agreement between reviewers was analyzed by percentage agreement and weighted kappa (κ) statistic, with κ of 0.7 as the minimum acceptable agreement.¹⁷ These data were analyzed by the SAS version 9.1 (SAS Institute Inc., Cary NC).

Figure 1. Summary of selection process for the systematic review of aspirin to prevent preeclampsia

RESULTS

Through our literature search, we identified 178 published reports, including nine randomized controlled trials that met our inclusion criteria (Figure 1). Agreement between reviewers in identifying the 17 studies was associated with a weighted κ of 0.76. All reviewers concurred on the adequacy of nine trials that were finally included in the review. A review of the references from two recent meta-analyses did not lead to additional relevant reports, except for the identification of an abstract that was cited differently in the Cochrane Library.¹⁸ The nine trials involved a total of 1317 participants (Table 2). Two of the trials had recruited women prior to 16 weeks (222 patients),^{19,20} one had recruited women between 17 and 19 weeks (102 patients),²¹ and six had recruited women at or after 20 weeks' gestation (993 patients).^{18,22-26} No study had recruited pregnant women in two overlapping gestational age periods. Every trial used ASA (50 to 150 mg) daily as treatment, and in six

studies (67%) a placebo was given to subjects in the control group. The average rate of preeclampsia in the control group was 22.6%, and confirmed the selection of a group of patients at high risk for preeclampsia. Finally, the funnel plot (Figure 2) indicated no evidence of publication bias, but was limited by the small number of studies included.²⁷ The stringency of the inclusion criteria also allowed us to confirm the quality of small studies.

Maternal Outcomes

In women with early abnormal uterine artery Doppler studies, there was a 52% reduction in the risk of preeclampsia, compared with the control group, when ASA treatment was started before 16 weeks of gestation (RR 0.48; 95% CI 0.33 to 0.68) (Figure 3). The number needed to treat to prevent one additional case of preeclampsia, in these women with early abnormal Doppler, was five. On the other hand, ASA therapy started at 17-19 weeks (RR 0.55; 95% CI 0.17 to 1.76) or at ≥ 20 weeks (RR 0.82; 95% CI 0.62 to 1.09) was

Table 2. Characteristics of the studies included in the review

Study	Participants	% of event in control group	Inclusion criteria	Intervention	Outcome
Ebrashy A, 2005 ¹⁹	139 women at 14–16 weeks	22.5	abnormal uterine artery Doppler and other risk factors for PE and IUGR	ASA 75 mg vs. no treatment	PE; PE onset < 37 weeks; severe PE maternal bleeding SGA (< 10th percentile); preterm birth; birthweight; neonatal bleeding
Zimmermann P, 1997 ²⁶	26 women at 22–24 weeks	15.40	uterine artery bilateral notches on Doppler	ASA 50 mg vs. no treatment	GH; PE; placental abruption; delivery < 37 weeks; IUGR (< 10th centile); gestation at delivery; birthweight
Vainio M, 2002 ²⁰	90 women at 12–14 weeks	23.0	anamnestic risk factor and abnormal uterine Doppler	ASA 0.5 mg/kg/day vs. placebo	GH; PE; Caesarean section; gestation at delivery (mean); IUGR (< 10th percentile); birthweight < 2500 g
McParland P, 1990 ²⁴	106 women at 24 weeks	28.80	persistently abnormal Doppler waveform	ASA 75 mg vs. placebo	GH; proteinuria; hypertension < 37 weeks' gestation; Caesarean section; mean gestation age at delivery
Yu CKH, 2003 ²⁵	560 women at 22–24 weeks	18.70	Doppler pulsatility index > 1.6 (95th percentile)	ASA 150 mg vs. placebo	PE; early PE < 34 weeks; placental abruption; preterm birth < 37 weeks; very preterm birth < 34 weeks; SGA (< 5th percentile)
Ferrier C, 1996 ¹⁸	43 women at 22–24 weeks	5.0	placental side uterine artery resistance index > 90th percentile, or a notch in early diastole	ASA 60 mg vs. placebo	GH, PE
Harrington F, 2000 ²³	216 women at 20 weeks	8.20	abnormal uterine artery Doppler	ASA 100 mg vs. no treatment (the intervention was stopped at 24 weeks if the Doppler was normalized)	PE; PE < 34weeks, SGA (< 10th percentile; 3rd percentile); placental abruption; Caesarean section; gestational age at delivery; birthweight
Morris JM, 1996 ²¹	104 women at 18 weeks	14.0	abnormal uterine Doppler flow (systolic/diastolic ratio > 3.3 or S/D > 3 and early diastolic notch)	ASA 100 mg vs. placebo	GH; PE; eclampsia; preterm birth; SGA (< 10th percentile)
Bower SJ, 1996 ²²	63 women at 24 weeks	41.40	abnormal uterine artery Doppler flow velocity waveform	ASA 60 mg vs. placebo	PE; severe PE; birthweight (mean) and centile (< 3rd); gestation at delivery; preterm birth (< 34, < 37weeks)

ASA: acetyl salicylic acid; PE: preeclampsia; GH: gestational hypertension; IUGR: intrauterine growth restriction; SGA: small for gestational age.

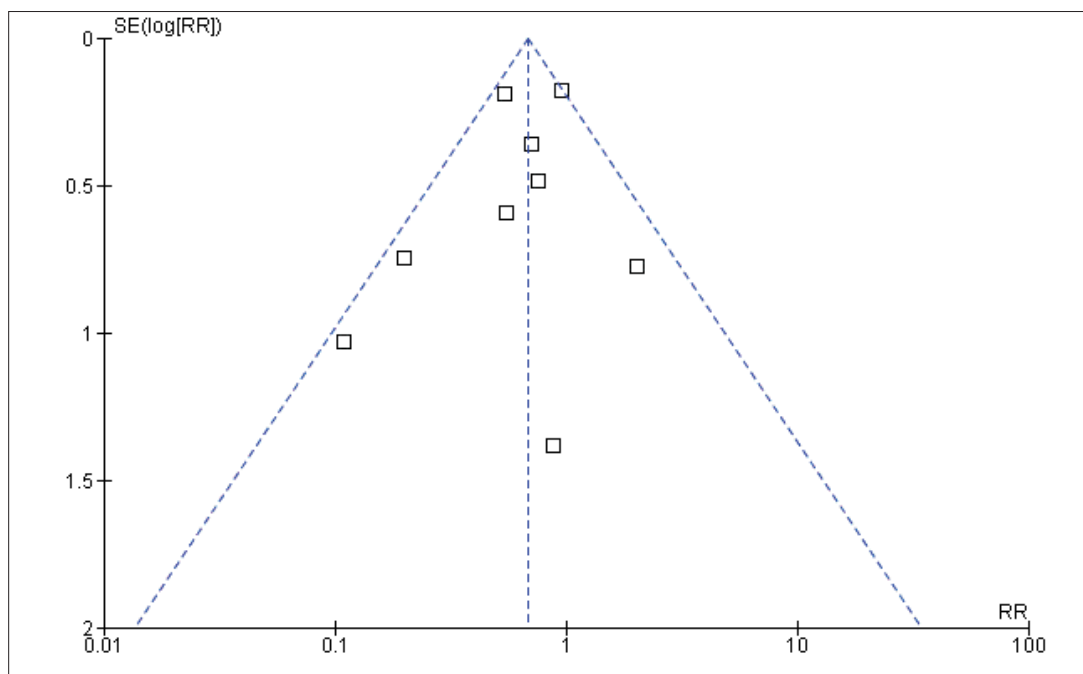
not associated with a significant decrease in the incidence of preeclampsia compared with the control group. In addition, when ASA was initiated before 16 weeks, a significant decline in the rate of severe preeclampsia (RR 0.38; 95% CI 0.15 to 0.98) and GH (RR 0.61; 95% CI 0.40 to 0.93) was seen, whereas no significant reduction was observed in comparison to the control group when ASA was started between 17 and 19 weeks or at ≥ 20 weeks of gestation (Table 3). Detailed outcomes according to gestational age at the beginning of treatment are reported in Tables 3 and 4. Use of ASA was not associated with significant changes in the rate of preterm births, regardless of gestational age at the initiation of treatment. The rate of placental abruption

was greater in the subjects treated with ASA than in the control group, but was reported only in three trials (all recruiting at ≥ 20 weeks), and the difference was not statistically significant (RR 2.34; 95% CI 0.91 to 6.01).

Neonatal Outcomes

Statistically significant decreases in adverse neonatal outcomes occurred only in the subgroup ≤ 16 weeks of gestation and in the overall effect (Table 3). The IUGR rate was reduced by 49% in the subgroup of women treated ≤ 16 weeks (2 trials involving 222 women; RR 0.51; 95% CI 0.28 to 0.92) compared with only 18% in the studies overall (8 trials involving 1274 women; RR 0.82; 95% CI 0.68 to 1.00).

Figure 2. Funnel plot of comparison for outcome: preeclampsia



DISCUSSION

We evaluated the effect of gestational age at the time of randomization in trials of ASA for the prevention of preeclampsia in women with abnormal uterine artery Doppler studies. While ASA treatment was associated with overall reductions of preeclampsia, severe preeclampsia, gestational hypertension, and IUGR, a significant effect was observed only in the subgroup of women randomized prior to 16 weeks' gestation. More importantly, ASA therapy reduced the risk of developing these outcomes by one half in this subgroup of women. The importance of these findings is magnified by the very low cost, the relative safety, and the wide availability of ASA throughout the world, as well as the very low number needed to treat to avoid one adverse outcome.

In a similar review, Coomarasamy et al. reported a comparable decrease in adverse outcomes in the overall population, but did not stratify the analysis according to gestational age at randomization.¹² Other reviews evaluating the effect of ASA in the prevention of preeclampsia also did not stratify the analysis for women recruited at ≤ 16 weeks,^{11,14,28,29} eliminating the possibility of making conclusions about potential benefits from early ASA prophylaxis.

The strengths of this study include the extensive literature review without language restrictions, respect of the QUOROM statement,³⁰ and the homogeneity of the

studies. However, our investigation was limited by the small number of studies and participants in each gestational age subcategory, especially in the subgroup of women recruited between 16 and 20 weeks' gestation. Therefore, few conclusions can be drawn for that particular subgroup. Moreover, the confidence intervals were very wide for rare outcomes, such as severe preeclampsia. While we found a significant reduction in the incidence of severe preeclampsia when ASA treatment began before 16 weeks' gestation, it was difficult to estimate if the expected decrease was two-fold or ten-fold. Our study emphasizes the need for a large investigation in this area.

Another limitation of our study was the definition of "abnormal uterine artery Doppler," which varied among authors. However, all definitions employed have been previously published as predictors of preeclampsia. In this regard, we were reassured by the fact that the preeclampsia rate was similar across the different studies. Therefore, we believe that the variable definition is unlikely to have led to biases in our results.

Our findings confirm original fundamental research that suggested major potential benefit from ASA treatment in the prevention of placental insufficiency, IUGR and preeclampsia. We remain hopeful that an inexpensive and readily available treatment such as ASA could eventually decrease the rate of preeclampsia, a leading cause of maternal mortality, in a high-risk population. Such findings will

Table 3. Relative risks of outcomes associated with low-dose ASA in women with abnormal uterine artery Doppler studies according to gestational age at the beginning of treatment

Outcomes and gestational age at randomization, weeks	Number of trials	Number of participants	Prevalence in control groups	RR	95% CI	<i>P</i>	NNT (95% CI)
Preeclampsia							
≤ 16	2	222	47.20	0.48	(0.33 to 0.68)	0.001	5 (3 to 8)
17–19	1	102	14.00	0.55	(0.17 to 1.76)	0.31	
≥ 20	6	993	17.37	0.82	(0.62 to 1.09)	0.18	
Overall	9	1317	21.97	0.68	(0.55 to 0.85)	0.001	16 (10 to 34)
Severe preeclampsia							
≤ 16	1	73	14.29	0.1	(0.01 to 0.74)	0.02	8 (5 to 25)
17–19	0	0	NA	NA	NA	NA	
≥ 20	3	824	8.53	0.53	(0.24 to 1.17)	0.12	
Overall	4	960	9.30	0.38	(0.15 to 0.98)	0.04	21(13 to 50)
Gestational hypertension							
≤ 16	1	86	37.21	0.31	(0.13 to 0.78)	0.01	4 (3 to 13)
17–19	1	102	28.00	0.82	(0.42 to 1.60)	0.57	
≥ 20	3	169	20.00	0.72	(0.36 to 1.42)	0.34	
Overall	5	357	26.40	0.61	(0.40 to 0.93)	0.02	10 (6 to 50)
Preterm birth							
≤ 16	1	136	19.05	0.93	(0.46 to 1.90)	0.85	
17–19	1	102	10.00	0.58	(0.15 to 2.29)	0.43	
≥ 20	3	640	25.94	0.83	(0.63 to 1.10)	0.20	
Overall	5	878	23.10	0.83	(0.65 to 1.08)	0.16	
Intrauterine growth restriction							
≤ 16	2	222	22.64	0.51	(0.28 to 0.92)	0.02	10 (5 to 50)
17–19	1	102	22.00	1.22	(0.62 to 2.43)	0.56	
≥ 20	5	950	27.18	0.85	(0.68 to 1.06)	0.14	
Overall	8	1274	25.99	0.82	(0.68 to 1.00)	0.05	
Placental abruption							
≤ 16	0	0	NA	NA	NA	NA	
17–19	0	0	NA	NA	NA	NA	
≥ 20	3	790	1.20	2.34	(0.91 to 6.01)	0.08	
Overall	3	790	1.20	2.34	(0.91 to 6.01)	0.08	

NNT: number needed to treat; NA: not available or not applicable

encourage research into early predictive biomarkers of preeclampsia, including Doppler and serum markers, in order to better identify high-risk women who could benefit greatly from ASA prophylaxis. First trimester ultrasound examination is becoming standard practice in many regions and countries throughout the world, to obtain accurate gestational age and to assess fetal nuchal translucency, and the addition of Doppler evaluation of the uterine arteries to routine screening processes is potentially useful in predicting pregnancy complications. However, it is clear that expertise would have to be developed and reproducibility

studies would have to be performed, even if Doppler screening is not likely to be offered widely. There is an increasing body of evidence suggesting that the diagnosis of abnormal placentation by Doppler screening and the prediction of placental insufficiency leading to preeclampsia and IUGR is more accurate when combined with serum markers.^{31,32} It remains unclear whether or not ASA treatment should be recommended in this high-risk population, or if uterine artery Doppler should be adopted as a screening or diagnostic tool for the diagnosis of abnormal placentation. Urgent confirmation of our findings in larger

Figure 3. Meta-analysis of randomized controlled trials evaluating the effect of ASA on the rate of preeclampsia according to gestational age at the initiation of treatment

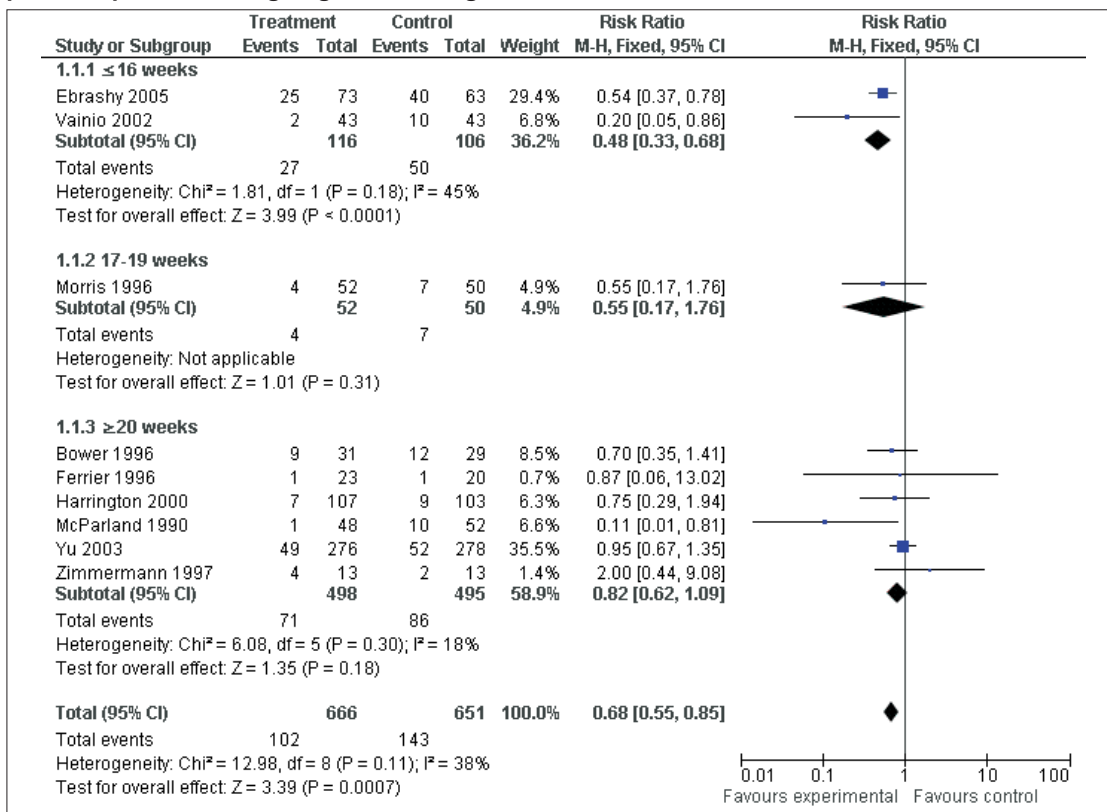


Table 4. Mean difference of outcomes associated with low-dose ASA in women with abnormal uterine artery Doppler studies according to gestational age at the beginning of treatment

Outcomes and gestational age at randomization	Number of trials	Number of participants	Mean in control group	Mean difference	95% CI	P
Birth weight, g						
≤ 16 weeks	2	222	3193	20	(-178 to 219)	0.42
17–19 weeks	1	102	3049	96	(-139 to 331)	0.27
≥ 20 weeks	4	396	2929	81	(-62 to 223)	0.86
Overall	7	720	3025	67	(-37 to 171)	0.86
Gestational age at delivery (weeks)						
≤ 16 weeks	1	86	39.2	0.3	(-0.5 to 1.1)	0.45
17–19 weeks	0	NA	NA	NA	NA	NA
≥ 20 weeks	4	396	38.3	0.4	(-0.3 to 1.0)	0.27
Overall	5	482	38.5	0.3	(-0.2 to 0.9)	0.89

NA: not available or not applicable

studies is necessary, including the assessment of the potential use of serum, biophysical, or genetic markers, for the identification of high-risk populations who could be targeted for ASA prevention.^{31,33–36} Our findings justify further investigation of the role of gestational age at the time of introduction of other treatments, such as anti-oxidants, folic acid, and other therapies that have been suggested for the prevention of preeclampsia.³⁹

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