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Randomized controlled trial using low-dose aspirin in the prevention of pre-eclampsia in women with abnormal uterine artery Doppler at 23 weeks' gestation

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KEYWORDS: aspirin; Doppler; fetal growth restriction; pre-eclampsia; screening; uterine artery

ABSTRACT

Objective *Pre-eclampsia, which is a major cause of perinatal and maternal morbidity and mortality, is thought to be due to impaired perfusion of the placenta. There is contradictory evidence that the administration of low-dose aspirin may provide effective prophylaxis against the subsequent development of pre-eclampsia. In this study we tested the hypothesis that in women identified as being at high-risk for pre-eclampsia, because of impaired flow in the uterine arteries, the prophylactic use of low-dose aspirin from 23 weeks of gestation can reduce the incidence of pre-eclampsia.*

Methods *We used color and pulsed Doppler to measure the flow in the uterine arteries in 19 950 singleton pregnancies at 22–24 weeks of gestation. Those women exhibiting increased impedance were recruited into a randomized study of aspirin 150 mg per day or placebo. We compared the two groups for the incidence of pre-eclampsia and the other consequences of impaired placentation.*

Results *The screening study identified 844 women (4.2%) as being at high risk of uteroplacental insufficiency. After exclusion and refusal, 560 women were randomly allocated to aspirin 150 mg or placebo per day until 36 weeks' gestation. There were no significant differences between the aspirin and placebo groups in either the incidence of pre-eclampsia (18% vs. 19%, P = 0.6) or pre-eclampsia requiring delivery below 34 weeks (6% vs. 8%, P = 0.36). Furthermore, the administration of aspirin did not significantly alter the incidence of preterm delivery (24% vs. 27%, P = 0.46), birth weight below the 5th centile (22% vs. 24%, P = 0.4), perinatal death (3% vs. 1%, P = 0.33) or placental abruption (4% vs. 2%, P = 0.12).*

Conclusion *In pregnancies with impaired placentation, as demonstrated by increased impedance to flow in the uterine arteries, the daily administration of 150 mg aspirin after 23 weeks of gestation does not prevent the subsequent development of pre-eclampsia. Copyright © 2003 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Pre-eclampsia is a disease that complicates about 5% of pregnancies and is a major cause of perinatal and maternal morbidity and mortality[1]. Essential prerequisites for the prevention of the disease are (1) the availability of a reliable screening test and (2) an intervention to correct the underlying pathology[2].

Pre-eclampsia is thought to be the consequence of circulatory maladaptation, characterized by defective trophoblastic invasion and an inadequate maternal vascular response to placentation[3]. The uteroplacental circulation remains in a state of high resistance, which causes generalized endothelial cell injury[4–6]. The disease is characterized by reduced endothelial production of prostacyclin and increased production of thromboxane A2 by platelets. Prostacyclin is a vasodilator, an inhibitor of platelet aggregation and an inhibitor of uterine contractility. Thromboxane is a

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vasoconstrictor and promotes platelet aggregation. The enzyme cyclo-oxygenase, which plays a central role in the production of both prostacyclin and thromboxane A2, can be inhibited by aspirin. However, the oral administration of low-dose aspirin may prevent or delay the onset of pre-eclampsia by altering the prostacyclin : thromboxane A2 ratio in placental tissues by selectively inhibiting cyclo-oxygenase activity in platelets but not in the vascular endothelium[7,8].

Several randomized studies have examined the potential value of low-dose aspirin, in women considered to be at high-risk of developing pre-eclampsia, in preventing this pregnancy complication. A recent meta-analysis on the use of aspirin in 39 studies, on a total of 30 000 pregnancies, has reported that the prophylactic use of aspirin is associated with a moderate reduction in the incidence of pre-eclampsia[9]. However, the studies varied substantially in entry criteria, in terms of clinical risks, the dose of aspirin and gestational age at entry.

Extensive studies in the last 15 years have demonstrated that Doppler ultrasound study of the uterine arteries provides effective screening in identifying women at high risk of developing pre-eclampsia[10]. In a recent study involving transvaginal Doppler assessment of the uterine arteries at 23 weeks of gestation in 8000 pregnancies we found that in women with an increased mean pulsatility index (PI) there is a six-fold increase in the likelihood of subsequent development of pre-eclampsia[11].

The aim of the present study was to establish whether a prophylactic intervention with low-dose aspirin reduces the risk of pre-eclampsia in women defined as high-risk by abnormal uterine artery Doppler.

METHODS

All women with singleton pregnancies attending routine ultrasound examination at 22–24 weeks' gestation were offered transvaginal color Doppler examination of the uterine arteries for measurement of the mean PI and identification of an early diastolic notch in the waveform, as previously described[11]. The study period was from January 2001 to July 2002. The participating hospitals were Basildon Hospital, Basildon; Greenwich Hospital, London; Harold Wood Hospital, Romford; King George Hospital, Ilford; King's College Hospital, London; Queen Mary's Hospital, Sidcup; University Hospital of Lewisham, London, UK; Hospital de Clinicas de Porto Alegre, Federal University of Rio Grande do Sul, Porto Alegre, Brazil; Hospital Clinico Universidad de Chile, Santiago, Chile; and Johannesburg General Hospital, Pretorio, South Africa. The study was approved by the Multi-Center Research Ethics Committee, Medicine Control Agency, as well as the local ethics committees of the individual hospitals.

Quality control of screening, handling of data and verifications of adherence to protocols at the different centers was performed on a regular basis by the trial coordinators. Sonographers who performed the Doppler studies had received the Certificate of Competence in Doppler of The Fetal Medicine Foundation.

Participants

Women with a mean PI above 1.6, which was the 95th centile in our previous screening study[11], were offered the option of participating in the trial and those agreeing gave written consent. Exclusion criteria were: pre-existing hypertensive, renal or cardiovascular disease, diabetes mellitus, bleeding disorders, systemic lupus erythematosus, peptic ulceration, hypersensitivity to aspirin, and the finding at the 23-week scan of a fetal abnormality or fetal growth restriction.

Interventions

Study participants were randomly allocated to either 150 mg aspirin daily or identical placebo tablets containing lactose (Penn Pharmaceuticals Ltd, Tredegar, UK). Computer-generated random number lists, in blocks of ten, were created by Penn Pharmaceuticals Ltd and the appropriately numbered drug was dispensed by each hospital pharmacy. Each bottle contained 12 weeks' supply (84 tablets) and was labelled 'Aspirin Study'. Strict instructions were given to the women, both verbally and in writing, to swallow the tablets whole and to avoid aspirin-containing compounds and other non-steroidal anti-inflammatory drugs. The general practitioners of the patients were informed in writing about their participation in the study and their hospital notes were marked with a sticker labeled 'Aspirin Trial'. Follow-up visits, for measurement of blood pressure, urinalysis for proteinuria and ultrasound assessment of fetal growth, were carried out at 28, 32 and 36 weeks. Compliance was checked by random tablet counting at these follow-up appointments and by telephone calls on a regular basis by the trial coordinators. All investigators, participants and clinicians were unaware of the treatment groups.

Outcome measures

The primary outcome measure was pre-eclampsia, as defined by the International Society for the Study of Hypertension in Pregnancy[12]. This requires two recordings of diastolic blood pressure of 90 mmHg or higher at least 4 h apart or one recording of diastolic blood pressure of at least 120 mm Hg, in a previously normotensive woman, and urine protein excretion of at least 300 mg in 24 h or two readings of 2+ or higher on dipstick analysis of midstream or catheter urine specimens if no 24-h collection is available.

Secondary outcome measures included fetal growth restriction (birth weight below the 5th centile for gestational age)[13], preterm delivery (before 37 weeks of gestation) and early preterm delivery (before 34 weeks), stillbirth or neonatal death, neonatal intensive care unit admission, placental abruption (clinical diagnosis of antepartum hemorrhage and abdominal pain associated

with the finding of retroplacental clot at delivery), postpartum hemorrhage (> 500 mL) and hemorrhage requiring blood transfusion.

All outcomes were determined before the randomization code of the trial was broken.

Sample size calculations and statistical analysis

The sample size calculation was based on a reduction in the incidence of pre-eclampsia from 20% in the placebo group to 10% in the aspirin group, with a power of 90%. To detect this difference at a significance level of 5%, we needed to recruit 560 patients. Assuming that 75% of eligible patients would accept randomization, we would need to identify 750 women at risk. We estimated that 15 000 women would need to be screened, with an expected 5% incidence of uterine artery mean PI above 1.6.

Interim analysis was prospectively planned and performed by the data monitoring committee after randomization of 280 patients. This was done to judge the progress of the trial and to ensure that the stopping rules had not been met. These included significant maternal or perinatal morbidity and mortality.

Baseline data for the aspirin and placebo groups were summarized by the median and interquartile range (IQR) and comparisons between groups were made using the Mann–Whitney *U*-test. Univariate comparisons of dichotomous data were made using the Chi-square or Fisher's exact test as appropriate. The *P*-values for all hypothesis tests were two-sided and statistical significance was set at $P < 0.05$. The risk of adverse outcome comparing aspirin with placebo was quantified by the odds ratio and 95% CI. Multivariate analysis was performed using logistic regression analysis. The goodness of fit of logistic regression models was assessed using the Hosmer and Lemeshow test[14]. Subgroup analysis was performed using interaction terms between aspirin and the other maternal covariates in the multivariate logistic regression model. The statistical significance of interaction terms was assessed using the likelihood ratio test and significance of interactions was assumed at $P < 0.01$ due to the large number of comparisons made. In addition, the risk of pre-eclampsia was assessed using time-to-event analysis in order to detect interactions between aspirin

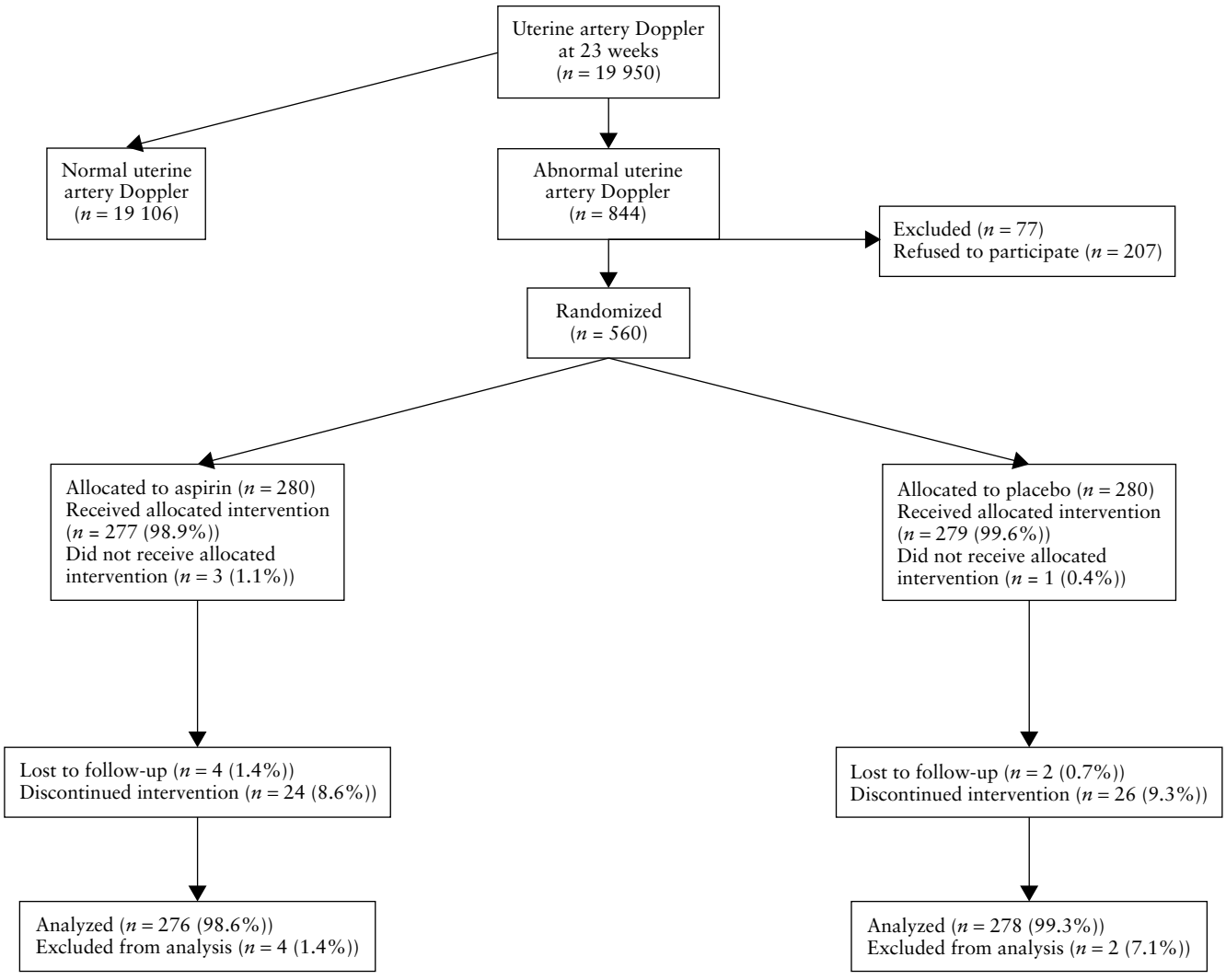

Figure 1 Trial profile.

use and gestational age. Gestational age in days was used as the timescale, a diagnosis of pre-eclampsia was defined as the event, and delivery without a diagnosis of pre-eclampsia was treated as censored. Data were plotted as one minus the survivor function as recommended[15] and univariate statistical comparisons were made using the log rank test. An interaction between any effect of aspirin and gestational age was tested using the global test of Grambsch and Therneau[16]. All statistical analyses were performed using the Stata software package (Stata Corporation, College Station, TX, USA), version 7.0.

RESULTS

Doppler screening was performed in 19 950 women, the uterine artery mean PI was above 1.6 in 844 (4.2%), but 77 of these women were not eligible for entry to the trial (29 were already on low-dose aspirin, 25 were on antihypertensive drugs, 10 had fetuses with early-onset growth restriction and five had fetuses with a structural abnormality, five were allergic to aspirin and three had a possible bleeding disorder) and 207 did not agree to take part in the randomized study (Figure 1). The remaining 560 women agreed to randomization. Six women were lost to follow-up as they had moved away to another country, two in the placebo group and four in the aspirin group ($P = 0.69$). These cases were excluded from the analysis and all further analyses were performed on the basis of intention to treat.

There were no systematic differences in the baseline characteristics between the two groups (Table 1). The percentage tablets taken (median, (IQR)) were 95 (80–100) for the placebo group and 95 (80–100) for the aspirin group ($P = 0.90$). Of the participants, four were subsequently prescribed aspirin by their obstetrician, fifty changed their minds about participation in the trial and withdrew, two stopped their medication after 3 days due to epigastric pain (one in the aspirin group, one in the placebo group) and one took aspirin-like medication for 6 days during the trial period.

The cumulative probability of pre-eclampsia is plotted against gestational age in Figure 2. There was no difference in the incidence of pre-eclampsia between the aspirin- and placebo-treated groups across the range of gestation. All further statistical analysis of outcomes was performed using logistic regression.

There were no significant differences between the aspirin and placebo groups in either the incidence of pre-eclampsia or any of the secondary outcomes (Table 2). Comparison between aspirin and placebo was essentially unaltered by adjusting for all the maternal covariates, although there was a trend towards a lower risk of neonatal intensive care admission in the aspirin group. However, this observation should be interpreted with caution since it was not a primary outcome and, given a P-value of 0.04, is likely to reflect the large number of statistical comparisons performed. There were 11 perinatal deaths in total, and these are described in Table 3. One woman had a hysterectomy in the aspirin group due to postpartum hemorrhage. The goodness of fit of all multivariate logistic models was satisfactory (all $P > 0.05$). There were no statistically significant

Table 1 Characteristics of those women randomized to aspirin or placebo

Maternal characteristics		*Placebo* (n = *278*)	*Aspirin* (n = *276*)	P
Age (years)	Median (IQR)	29 (24–33)	29 (23–33)	0.19
Parity (*n* (%))	Nulliparous	65 (23.4)	74 (26.8)	
	Multiparous	213 (76.7)	202 (73.2)	0.35
Age leaving full-time education (years)	Median (IQR)	16 (16–18)	16 (16–18)	0.94
Ethnic group (*n* (%))	White	162 (58.3)	183 (66.3)	
	Black	86 (30.9)	67 (24.3)	
	Other	30 (10.8)	26 (9.4)	0.14
Smoking status (*n* (%))	Non-smoker	251 (90.3)	250 (90.6)	
	Smoker	27 (9.7)	26 (9.4)	0.91
Previous pregnancies (*n* (%))	Same partner	126 (45.3)	111 (40.2)	
	Different partner	76 (27.3)	84 (30.4)	
	Not stated	76 (27.3)	81 (29.4)	0.47
Previous PET (*n* (%))	No	254 (91.4)	245 (88.8)	
	Yes	24 (8.6)	31 (11.2)	0.31
Family history of PET (*n* (%))	No	242 (87.0)	245 (88.8)	
	Yes	36 (13.0)	31 (11.2)	0.54
Body mass index	Median (IQR)	25.6 (22.2–29.9)	25.0 (22.5–28.6)	0.27
Systolic blood pressure (mmHg)	Median (IQR)	110 (110–120)	110 (102–120)	0.24
Diastolic blood pressure (mmHg)	Median (IQR)	70 (60–75)	70 (60–70)	0.26
Mean PI	Median (IQR)	1.82 (1.71–1.98)	1.79 (1.70–1.98)	0.49
Early diastolic notch (*n* (%))	No notch	42 (15.1)	36 (13.0)	
	Unilateral notch	48 (17.3)	40 (14.5)	
	Bilateral notch	188 (67.6)	200 (72.5)	0.46
Gestation at randomization (days)	Median (IQR)	164 (161–168)	164 (161–167)	0.28

IQR, interquartile range; PET, pre-eclampsia; PI, pulsatility index.

Table 2 Outcome data according to randomization to aspirin or placebo

Outcome	*Placebo* (n *(%))* (n = *278)*	*Aspirin* (n *(%))* (n = *276)*	*Crude OR (95% CI)*	P	*Adjusted OR (95% CI)*	P
Pre-eclampsia	52 (18.7)	49 (17.8)	0.94 (0.61–1.44)	0.77	0.88 (0.56–1.40)	0.60
Pre-eclampsia (< 34 weeks)	21 (7.6)	17 (6.2)	0.80 (0.42–1.54)	0.52	0.72 (0.35–1.46)	0.36
Birth weight < 5th percentile	68 (24.4)	61 (22.1)	0.88 (0.59–1.30)	0.55	0.83 (0.54–1.28)	0.40
Preterm birth (< 37 weeks)	75 (27.0)	67 (24.3)	0.87 (0.59–1.27)	0.47	0.86 (0.57–0.29)	0.46
Preterm birth (< 34 weeks)	32 (11.5)	30 (10.9)	0.94 (0.56–1.58)	0.81	0.91 (0.51–1.63)	0.76
Perinatal death (all)	4 (1.4)	7 (2.5)	1.63 (0.55–4.80)	0.42	1.89 (0.52–6.83)	0.33
Admission to NICU	52 (18.7)	35 (12.7)	0.63 (0.40–1.00)	0.06	0.59 (0.36–0.97)	0.04
Placental abruption	5 (1.8)	10 (3.6)	2.05 (0.72–5.81)	0.20	2.54 (0.78–8.21)	0.12
Postpartum hemorrhage	71 (25.5)	73 (26.4)	1.05 (0.72–1.53)	0.85	1.09 (0.73–1.62)	0.67
Blood transfusion	7 (2.5)	6 (2.2)	0.86 (0.30–2.48)	1.00	1.16 (0.35–3.93)	0.81

Odds ratios (OR) adjusted for maternal age, parity, ethnicity, education, smoking status, partner, previous pre-eclampsia, family history of pre-eclampsia, body mass index, blood pressure at randomization, mean pulsatility index, and the presence of unilateral or bilateral notch. NICU, neonatal intensive care unit.

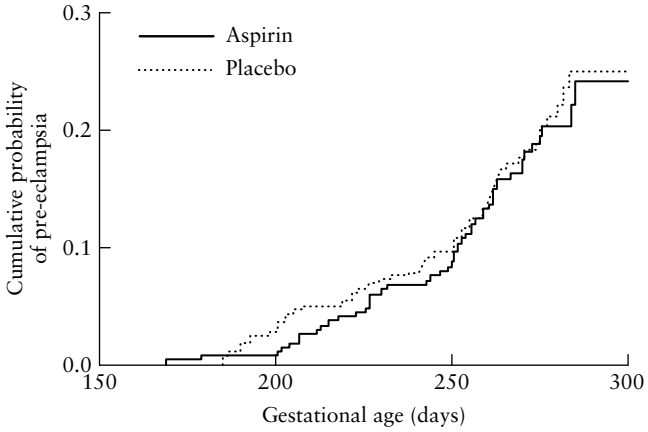

Figure 2 Cumulative incidence of pre-eclampsia. Y-axis = one minus the Kaplan–Meier survivor function. Comparison of curves by log rank test: $P = 0.73$. Test of proportional hazards assumption: $P = 0.48$. Hazard ratio for aspirin with reference to placebo = 0.93 (95% CI 0.63–1.38).

Table 3 Clinical details of perinatal deaths

Case	*Gestation (weeks)*	*Birth weight (g)*	*Cause of death*
Placebo			
1	26	480	Fetal growth restriction
2	26	800	Pre-eclampsia
3	35	2375	Abruption
4	26	700	Pre-eclampsia
Aspirin			
1*	24	420	Preterm delivery
2	26	400	Fetal growth restriction
3	29	1140	Unexplained
4	29	1300	Abruption
5	26	710	Fetal growth restriction
6	30	1500	Abruption
7	41	3040	Unexplained

*Neonatal death. All the others were intrauterine deaths.

interactions between aspirin and any of the maternal covariates (or compliance) and the risk of pre-eclampsia (all $P > 0.01$).

DISCUSSION

The findings of this multicenter randomized study demonstrate that in pregnancies with impaired placentation, as demonstrated by increased impedance to flow in the uterine arteries, the daily administration of 150 mg aspirin after 23 weeks' gestation does not prevent the subsequent development of pre-eclampsia. In addition, the administration of aspirin did not significantly alter the incidence of preterm delivery or other pregnancy complications thought to be associated with impaired placentation such as fetal growth restriction, perinatal death or placental abruption.

The method of selecting our high-risk group was color Doppler assessment of the uterine arteries and demonstration of increased mean PI. The very high incidence of pregnancy complications in the screen-positive group, including pre-eclampsia in 18% of cases and fetal growth restriction in 23%, confirms the reliability of uterine artery Doppler in diagnosing impaired placentation, and the findings are compatible with those of our previous screening study[11]. This high positive predictive value compares favorably with that of a history of a previous affected pregnancy, which was the method of selecting the high-risk group in most previous randomized studies of aspirin. Thus, the mean incidence of pre-eclampsia and fetal growth restriction in the meta-analysis of 32 studies on the use of aspirin was 7% and 8%, respectively[9].

There are five previous randomized studies on the use of low-dose aspirin in high-risk women identified by abnormal second-trimester uterine artery Doppler[17] (Table 4). In two of the studies randomization was undertaken after the first screening test but three of the studies were carried out in two stages. McParland

Table 4 Meta-analysis of randomized aspirin trials to prevent pre-eclampsia in women with abnormal uterine artery Doppler in the second trimester

				Pre-eclampsia		
Reference	*Method*	*Gestation (weeks)*	*Aspirin (mg/day)*	*Aspirin* (n *(%))*	*Placebo* (n *(%))*	*Peto odds ratio (95% CI)*
McParland *et al.* (1990)[18]	Two-stage	24	75	1/48 (2)	10/52 (19)	0.18 (0.05–0.61)
Morris *et al.* (1996)[19]	One-stage	18	100	4/52 (8)	7/50 (14)	0.52 (0.15–1.82)
Bower *et al.* (1996)[20]	Two-stage	24	60	9/31 (29)	12/29 (41)	0.59 (0.20–1.68)
Zimmermann *et al.* (1997)[21]	One-stage	22–24	50	4/13 (31)	2/13 (15)	2.30 (0.38–13.77)
Harrington *et al.* (2000)[22]	Two-stage	20	100	7/107 (7)	9/103 (9)	0.73 (0.27–2.03)
Current study	One-stage	23	150	49/276 (18)	52/278 (19)	0.94 (0.61–1.44)
Totals				74/527 (14)	92/525 (18)	0.76 (0.55–1.07)

et al. used Doppler to examine the uterine arteries in 1226 nulliparous women at 16–20 weeks and the use of aspirin in those with persistent high impedance to flow at 24 weeks was associated with a 10-fold reduction in the incidence of pre-eclampsia[18]. In contrast, all other studies found no significant difference between the aspirin and placebo groups.

In the present study we chose to use 150 mg aspirin because previous studies suggested that this may be the lowest dose necessary to reduce the incidence of pre-eclampsia. Thus, studies using 60–75 mg aspirin daily have consistently failed to show any benefit, whereas those using 150 mg have demonstrated some benefit[23]. In terms of safety, a previous meta-analysis of studies using 150 mg aspirin on a total 322 patients has shown no significant increase in the incidence of hemorrhagic complications, such as abruption[24].

In pregnancy the uteroplacental vascular adaptation is dependent on the invasion of spiral arteries by trophoblasts. The first wave of trophoblastic invasion involves the decidual portion of the spiral arteries and starts at 8 weeks of gestation, whereas the second wave involves the myometrial segments and occurs at 14–24 weeks[25]. Failure of trophoblastic invasion and consequent underperfusion of the placenta leads to the release of hormonal factors into the maternal circulation. These placental factors cause endothelial dysfunction, which may be the underlying mechanism for the subsequent development of the clinical syndrome of hypertension and proteinuria[26]. Our finding that low-dose aspirin cannot disrupt this process may be a mere consequence of the relatively late gestation at which we attempted treatment. We have previously shown that screening for pre-eclampsia by uterine artery Doppler is possible from at least 11 weeks of gestation[27], and there is some evidence that the administration of low-dose aspirin to women with abnormal flow at this early gestation may provide effective prophylaxis against pre-eclampsia[28]. Consequently, the contradictory findings of studies examining the effectiveness of low-dose aspirin in the prevention of pre-eclampsia may be due to differences in the gestation at which this treatment is initiated[8].

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APPENDIX

Project coordinators:

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