Ultrasound Obstet Gynecol 2013; **41**: 491–499
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.12421

Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis

S. ROBERGE*, K. H. NICOLAIDES†, S. DEMERS‡, P. VILLA§ and E. BUJOLD*‡

**Department of Social and Preventive Medicine, Faculty of Medicine, Université Laval, Quebec City, QC, Canada; †Harris Birthright Research Centre of Fetal Medicine, King's College Hospital, London, UK; ‡Department of Obstetrics and Gynecology, Faculty of Medicine, Université Laval, Quebec City, QC, Canada; §Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland*

KEYWORDS: aspirin; meta-analysis; perinatal death; pre-eclampsia

ABSTRACT

Objective *To compare early* vs *late administration of low-dose aspirin on the risk of perinatal death and adverse perinatal outcome.*

Methods *Databases were searched for keywords related to aspirin and pregnancy. Only randomized controlled trials that evaluated the prophylactic use of low-dose aspirin (50–150 mg/day) during pregnancy were included. The primary outcome combined fetal and neonatal death. Pooled relative risks (RR) with their 95% CIs were compared according to gestational age at initiation of low-dose aspirin (≤ 16* vs *> 16 weeks of gestation).*

Results *Out of 8377 citations, 42 studies (27 222 women) were included. Inclusion criteria were risk factors for pre-eclampsia, including: nulliparity, multiple pregnancy, chronic hypertension, cardiovascular or endocrine disease, prior gestational hypertension or fetal growth restriction, and/or abnormal uterine artery Doppler. When compared with controls, low-dose aspirin started at ≤ 16 weeks' gestation compared with low-dose aspirin started at >16 weeks' gestation was associated with a greater reduction of perinatal death (RR = 0.41 (95% CI, 0.19–0.92)* vs *0.93 (95% CI, 0.73–1.19),* P = *0.02), pre-eclampsia (RR = 0.47 (95% CI, 0.36–0.62)* vs *0.78 (95% CI, 0.61–0.99),* P < *0.01), severe pre-eclampsia (RR = 0.18 (95% CI, 0.08–0.41)* vs *0.65 (95% CI, 0.40–1.07),* P < *0.01), fetal growth restriction (RR = 0.46 (95% CI, 0.33–0.64)* vs *0.98 (95% CI, 0.88–1.08),* P < *0.001) and preterm birth (RR = 0.35 (95% CI, 0.22–0.57)* vs *0.90 (95% CI, 0.83–0.97),* P < *0.001).*

Conclusion *Low-dose aspirin initiated at ≤ 16 weeks of gestation is associated with a greater reduction of perinatal death and other adverse perinatal outcomes than when initiated at >16 weeks.* *Copyright © 2013 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

The leading causes of perinatal death are preterm birth, fetal abnormalities and impaired placentation leading to pre-eclampsia and fetal growth restriction (FGR)[1–4]. Meta-analyses of randomized studies suggest that prophylactic use of low-dose aspirin initiated at or before the 16th week of pregnancy is associated with significant reduction in the prevalence of severe pre-eclampsia, FGR and preterm birth, all placenta-related complications of pregnancy[5–7]. The mechanism of action of aspirin remains unclear but it could include an improvement of the transformation of uterine spiral arteries, which is typically incomplete in pre-eclampsia[8,9]. Haapsamo *et al.* observed that low-dose aspirin could lead to an improvement of uterine artery blood flow that is related to the transformation of uterine spiral arteries[10,11]. Trophoblastic invasion of uterine spiral arteries normally starts at around 8–10 weeks; is mostly completed by 16–18 weeks; but can continue until 22 weeks[12]. We believe that intervention aiming at the improvement of this process should probably be initiated as early as 8–10 weeks and no later than 16–18 weeks, when possible. We suggest that improvement of deep placentation could lead to a reduction of several adverse pregnancy outcomes and to a reduction of perinatal death.

The objective of the current work was to perform a systematic review and meta-analysis including recent randomized trials and to compare the effect of early and late administration of aspirin on the risk of perinatal death and other adverse perinatal outcomes.

METHODS

We generated a list of keywords and MeSH terms 'aspirin', 'antiplatelet', 'acetylsalicylic acid', 'ASA', 'pregnancy-complication' and 'pregnancy', for extensive databases search. EMBASE, PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science

Correspondence to: Dr E. Bujold, Department of Obstetrics and Gynecology, Faculty of Medicine, Université Laval, 2705 boulevard Laurier, Québec, QC, Canada, G1V 4G2 (email: emmanuel.bujold@crchul.ulaval.ca)

Accepted: 19 January 2013

were used and relevant citations were extracted from 1965 to October 2011. No language restriction was imposed. A first reviewer (S.R.) screened all titles and selected citations for more detailed evaluation. The second sort retrieved citations and abstracts and was revised by two reviewers (S.R. and S.D.). The same two reviewers read and selected all relevant trials. Other systematic reviews were used for additional search[5–7,13–16]. Corresponding or primary authors were contacted for additional information when necessary. The quality and integrity of this review were validated with PRISMA: preferred reporting items for systematic reviews and meta-analyses[17].

Only prospective, randomized, controlled trials involving pregnant women treated with low-dose aspirin (150 mg or less), with or without dipyridamole (300 mg or less), were included. The control group had to be allocated to placebo or no treatment. Trials that involved other treatment, such as subcutaneous heparin or calcium, were excluded. All studies that involved women who initiated treatment at ≤ 16 weeks of gestation and at >16 weeks of gestation were included in the meta-analysis. The quality of studies was evaluated using Cochrane Handbook Criteria tool for judging risk of bias, and studies with high risk of bias were considered for sensitivity analysis[18,19].

The principal outcome of interest was perinatal mortality defined as fetal death after 16 weeks' gestation or neonatal death before 28 days of age or similar definition. We collected the reasons for perinatal death when available. Our secondary outcomes included pre-eclampsia, severe pre-eclampsia, FGR (reported as below the 10th, the 5th or the 3rd percentile), preterm birth, placental abruption, birth weight and gestational age at delivery.

Statistical analysis

Review Manager 5.0.25 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and the SAS 9.2 software (SAS Institute Inc., Cary, NC, USA) were used for analysis. Relative risks (RR) were calculated for each study and were pooled for global analysis with 95% CIs and stratified according to gestational age at entry (≤ 16 weeks *vs* >16 weeks; determined pre-hoc). Difference between subgroups of gestational age at entry was evaluated by mixed regression, weighted by the size of each study. Global RR was calculated according to DerSimonian and Laird random-effect models in case of significant heterogeneity and with fixed effect in case of homogeneity between studies[20,21]. Heterogeneity between studies was analyzed using the Higgins I^2 statistic[22,23]. The distribution of trials was examined using funnel plots to assess publication bias[24]. Sensitivity analysis was conducted to investigate robustness of the findings and heterogeneity between studies, with comparison for the dose of aspirin, use of dipyridamole, blinding, statistical model, trial size and risk of bias.

RESULTS

The literature search identified 8377 citations from which we identified 1104 potentially eligible studies that were completely reviewed (Figure 1). The inclusion criteria were met by 66 studies, but only 42 of those were included (27 222 women randomized)[25–68] in the final analysis because several studies recruited over a range of gestational age overlapping 16 weeks. Studies included nulliparous women or women identified at high risk for pre-eclampsia based on medical history and/or ultrasonographic findings (Table S1). In two

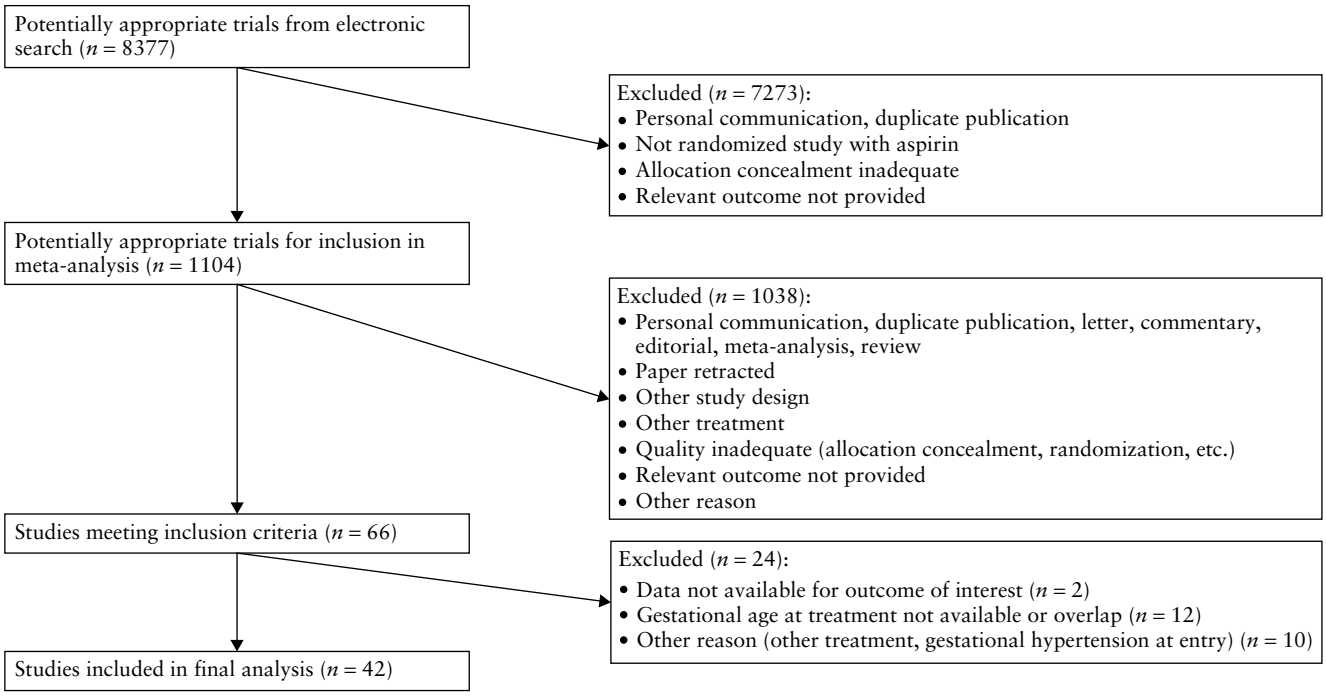

Figure 1 Flow diagram showing selection process of articles.

Study or Subgroup	ASA Events	ASA Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI
Studies with treatment ≤ 16 weeks						
August[25] (1994)	1	24	1	25	0.7%	1.04 (0.07–15.73)
Azar[26] (1990)	2	46	2	45	1.4%	0.98 (0.14–6.65)
Bakhti[29] (2011)	0	82	7	82	0.7%	0.07 (0.00–1.15)
Beaufils[27] (1985)	0	48	5	45	0.6%	0.09 (0.00–1.50)
Benigni[28] (1989)	0	16	1	17	0.5%	0.35 (0.02–8.08)
Chiaffarino[31] (2004)	1	16	2	19	1.0%	0.59 (0.06–5.96)
Dasari[32] (1998)	0	25	0	25		Not estimable
Ebrashy[33] (2005)	0	73	2	63	0.6%	0.17 (0.01–3.54)
Hermida[34] (1997)	0	50	0	50		Not estimable
Hermida[35] (1999)	2	176	5	174	2.0%	0.40 (0.08–2.01)
Vainio[40] (2002)	0	43	0	43		Not estimable
Villa[41] (2013)	1	61	1	60	0.7%	0.98 (0.06–15.37)
Subtotal (95% CI)		660		648	8.3%	0.41 (0.19–0.92)
Total events	7		26			
Heterogeneity: $Tau^2 = 0.00$; chi-square = 5.16, df = 8 ($P = 0.74$); $I^2 = 0\%$						
Test for overall effect: Z = 2.17 ($P = 0.03$)						
Studies with treatment > 16 weeks						
Byaruhanga[42] (1998)	5	114	13	122	5.3%	0.41 (0.15–1.12)
CLASP[44] (1994)	22	1321	35	1301	19.0%	0.62 (0.37–1.05)
Davies[45] (1995)	0	58	0	60		Not estimable
ECPPA[46] (1996)	23	286	21	329	16.3%	1.26 (0.71–2.23)
Gallery[48] (1997)	4	58	2	50	1.9%	1.72 (0.33–9.02)
Golding[50] (1998)	40	1253	35	1294	26.5%	1.18 (0.75–1.85)
Hauth[51] (1993)	1	302	1	302	0.7%	1.00 (0.06–15.91)
Kim[52] (1997)	1	32	3	38	1.1%	0.40 (0.04–3.62)
McCowan[53] (1999)	4	49	3	50	2.5%	1.36 (0.32–5.77)
McParland[54] (1990)	1	48	3	52	1.1%	0.36 (0.04–3.35)
Omrani[57] (1992)	0	21	1	19	0.5%	0.30 (0.01–7.02)
Rotchell[59] (1998)	16	747	15	752	10.9%	1.07 (0.53–2.16)
Schiff[60] (1989)	0	34	0	32		Not estimable
Schrocksnadel[61] (1992)	0	22	1	19	0.5%	0.29 (0.01–6.72)
Trudinger[62] (1988)	0	22	0	24		Not estimable
Wallenburg[63] (1986)	1	23	1	23	0.7%	1.00 (0.07–15.04)
Wallenburg[64] (1991)	0	18	0	18		Not estimable
Wang[65] (1996)	0	40	4	44	0.6%	0.12 (0.01–2.20)
Yu[67] (2003)	7	276	4	278	3.6%	1.76 (0.52–5.95)
Zimmermann[68] (1997)	0	13	1	13	0.5%	0.33 (0.01–7.50)
Subtotal (95% CI)		4737		4820	91.7%	0.93 (0.73–1.19)
Total events	125		143			
Heterogeneity: $Tau^2 = 0.00$; chi-square = 13.70, df = 15 ($P = 0.55$); $I^2 = 0\%$						
Test for overall effect: Z = 0.56 ($P = 0.57$)						
Total (95% CI)		5397		5468	100.0%	0.87 (0.69–1.10)
Total events	132		169			
Heterogeneity: $Tau^2 = 0.00$; chi-square = 22.49, df = 24 ($P = 0.55$); $I^2 = 0\%$						
Test for overall effect: Z = 1.16 ($P = 0.24$)						

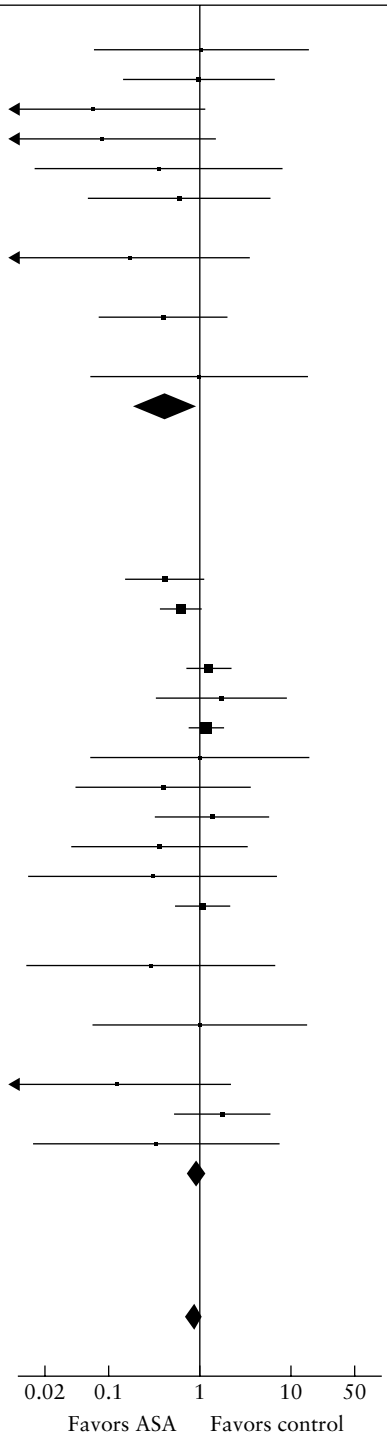

Figure 2 Forest plot of effect of low-dose aspirin on risk of perinatal death, subgrouped by gestational age at initiation of treatment. Only the first author of each study is given. df, degrees of freedom; M-H, Mantel-Haenszel.

studies the intervention was aspirin in combination with dipyridamole, and in the other studies aspirin was the only medication administered. In 32 studies, women allocated to the control group received a placebo and in 10 studies they received no treatment. The follow-up rate was greater than 80% in 14 out of 15 studies that initiated the treatment at ≤ 16 weeks and in 26 out of 27 studies that initiated the treatment after 16 weeks. The trial characteristics, including number of patients, inclusion criteria, treatment for cases and controls, and outcome measure in the studies where aspirin treatment was initiated at ≤ 16 weeks' gestation and > 16 weeks are summarized in Table S1.

Administration of low-dose aspirin starting at ≤ 16 weeks was associated with a significant reduction in the risk of perinatal death, but the effect of treatment was

Table 1 Perinatal outcomes associated with low-dose aspirin according to gestational age (GA) at initiation of intervention

Outcome/ GA at initiation of intervention	*Trials* (n)	*Participants* (n)	*Prevalence*		*Relative risk (95% CI) (random effect)*	P	I^2 *(Higgins test)*	P *(between subgroups)*
			Treated (%)	*Controls (%)*				
Perinatal death	32	10 865	2.4	3.1	0.87 (0.69 to 1.10)	NS	0%	
≤ 16 weeks	12	1308	1.1	4.0	0.41 (0.19 to 0.92)	0.03	0%	0.02
> 16 weeks	20	9557	2.6	3.0	0.93 (0.73 to 1.19)	NS	0%	
Pre-eclampsia	33	12 152	7.5	9.6	0.62 (0.49 to 0.78)	<0.001	53%	
≤ 16 weeks	13	1479	7.6	17.9	0.47 (0.36 to 0.62)	<0.001	0%	<0.01
> 16 weeks	20	10 673	7.5	8.4	0.78 (0.61 to 0.99)	0.04	49%	
Severe pre-eclampsia	11	2143	2.8	7.5	0.36 (0.20 to 0.63)	<0.001	24%	
≤ 16 weeks	6	649	1.5	12.3	0.18 (0.08 to 0.41)	<0.001	0%	<0.01
> 16 weeks	5	1494	3.3	5.5	0.65 (0.40 to 1.07)	NS	0%	
Fetal growth restriction	27	8260	10.7	12.3	0.86 (0.75 to 0.99)	0.04	28%	
≤ 16 weeks	10	1064	8.0	17.6	0.46 (0.33 to 0.64)	<0.001	0%	<0.001
> 16 weeks	17	7196	11.1	11.5	0.98 (0.88 to 1.08)	NS	0%	
Preterm birth	22	11 302	17.4	20.3	0.81 (0.71 to 0.92)	<0.01	39%	
≤ 16 weeks	6	904	4.8	13.4	0.35 (0.22 to 0.57)	<0.001	0%	<0.001
> 16 weeks	16	10 398	18.6	20.8	0.90 (0.83 to 0.97)	<0.01	0%	
Placental abruption	10	4175	2.3	1.9	1.24 (0.79 to 1.95)	NS	3%	
≤ 16 weeks	4	592	2.3	5.1	0.55 (0.21 to 1.47)	NS	5%	NS
> 16 weeks	6	3583	2.3	1.4	1.56 (0.96 to 2.55)	NS	0%	
			Mean difference (95% CI)			P		
Birth weight (g)	23	2787	124 (68 to 180)			<0.001	45%	
≤ 16 weeks	10	1061	209 (100 to 319)			<0.001	69%	NS
> 16 weeks	13	1726	71 (18 to 124)			<0.01	0%	
GA at delivery (weeks)	18	1860	0.57 (0.13 to 1.01)			0.01	88%	
≤ 16 weeks	9	959	1.06 (0.40 to 1.72)			0.002	93%	0.048
> 16 weeks	9	901	−0.01 (−0.55 to 0.52)			NS	55%	

NS, not significant.

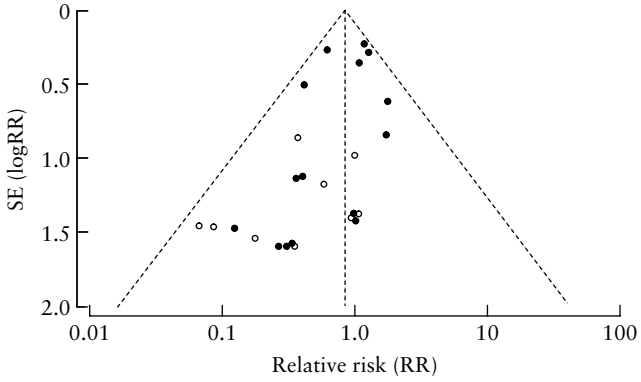

Figure 3 Funnel plot of distribution of relative risk for perinatal death associated with aspirin treatment for studies included in our analysis. Black circles represent studies in which aspirin treatment was initiated at or before 16 weeks' gestation and white circles represent studies in which treatment was initiated after 16 weeks. SE, standard error.

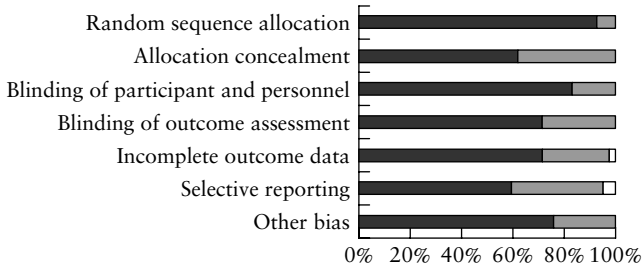

Figure 4 Assessment of risk of bias in studies included in our analysis (low (■), unclear (▩), high (□)) following the Cochrane Handbook[18].

not significant when aspirin was initiated after 16 weeks (Figure 2 and Table 1). The difference in RR according to gestational age at entry (≤ 16 weeks *vs* >16 weeks) was statistically significant ($P = 0.02$). The difference in RR according to gestational age at entry remained statistically significant ($P = 0.03$) when comparing women recruited at ≤ 16 weeks with those recruited between 17 and 24 weeks (RR = 1.01 (95% CI, 0.49–2.08), $P = 0.99$). Only seven (22%) studies reported the reasons for perinatal death and therefore few conclusions can be drawn[25,48,50,57,60,63,64]. However, 17 (65%) out of 26 perinatal deaths reported in those studies were related to placental-mediated complications of pregnancy (pre-eclampsia, FGR and/or placental abruption). Significant risk reductions were also observed for pre-eclampsia, severe pre-eclampsia, FGR, preterm birth, birth weight and gestational age at delivery when aspirin was administered at or before 16 weeks (Table 1). Low-dose aspirin administered after 16 weeks was associated with a modest, but significant, reduction of pre-eclampsia and preterm birth and with no significant reduction of FGR. There is insufficient evidence to conclude on the effect of low-dose aspirin given after 16 weeks on the risk of severe pre-eclampsia (RR = 0.65; 95% CI, 0.40–1.07).

The Higgins I^2 statistic did not show significant heterogeneity between studies in the global and the subgroup analyses ($I^2 = 0\%$) for perinatal death. However, for several outcomes there was significant

heterogeneity between studies that recruited after 16 weeks and consequently random effect was used. Analysis of the funnel plot for perinatal death suggests the possibility of publication bias because small studies with no beneficial effect were missing (Figure 3)[69]. According to the Cochrane Handbook Criteria tool for judging risk of bias, the majority of included studies were judged to have low or unclear risk of bias, except for one study with more than 20% of individuals lost to follow-up and two with a risk of selective reporting (Figure 4)[18,29,30,41,53]. Exclusion of these three studies did not affect the results. No statistical difference was observed between any of the subgroups identified in the sensitivity analysis (Figure 5).

Finally, we found similar effects of early aspirin prophylaxis in women who received ≤80 mg daily and those who received ≥100 mg daily (Table 2) and in women who were selected using abnormal uterine artery Doppler as an inclusion criterion as compared with those selected using anamnesis factors only (Table 3).

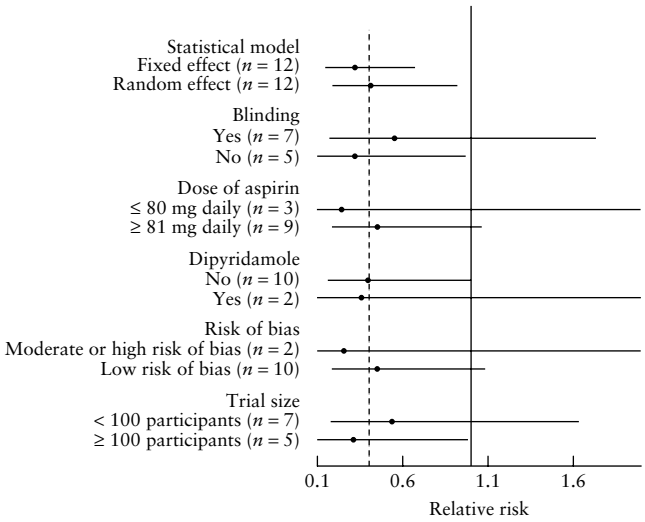

Figure 5 Sensitivity analysis of relative risk for perinatal death for studies in which aspirin treatment was initiated at ≤16 weeks. The dashed vertical line shows the relative risk obtained from random effects meta-analysis of all included studies.

DISCUSSION

Our meta-analysis suggests that the prophylactic use of low-dose aspirin is associated with a significant decrease in perinatal death, provided the treatment is initiated at or before 16 weeks of gestation. Low-dose aspirin initiated at or before 16 weeks is also associated with a significant and greater reduction of pre-eclampsia, FGR and preterm birth than is low-dose aspirin started after 16 weeks of gestation. This finding is in agreement with a similar meta-analysis published in 2010[7]. Since then, four additional randomized trials that recruited high-risk women prior to 16 weeks' gestation were published and their findings were consistent with our previous results[29,30,36,37,41]. Moreover, the addition of two trials changed the conclusion regarding the effect of aspirin

Table 2 Perinatal outcomes associated with aspirin started before 16 weeks according to dose of aspirin prescribed

Outcome/ dose of aspirin	*Trials* (n)	*Participants* (n)	*Prevalence*		*Relative risk (95% CI) (random effect)*	P	P *(between subgroups)*
			Treated (%)	*Controls (%)*			
Perinatal death							
≤80 mg	3	255	0	2.4	0.24 (0.03 to 2.14)	NS	NS
≥100 mg	9	1053	1.3	4.4	0.45 (0.19 to 1.06)	NS	
Pre-eclampsia							
≤80 mg	5	401	14.1	31.8	0.35 (0.16 to 0.76)	<0.001	NS
≥100 mg	8	1078	5.2	12.9	0.46 (0.30 to 0.71)	<0.01	
Severe pre-eclampsia							
≤80 mg	2	222	0.9	10.4	0.12 (0.02 to 0.65)	0.01	NS
≥100 mg	4	427	1.8	13.2	0.20 (0.08 to 0.53)	0.02	
Fetal growth restriction							
≤80 mg	4	301	12.2	22.8	0.52 (0.32 to 0.87)	0.01	NS
≥100 mg	6	763	6.2	15.6	0.41 (0.26 to 0.64)	<0.001	
Preterm birth							
≤80 mg	2	169	4.4	17.7	0.27 (0.09 to 0.77)	0.01	NS
≥100 mg	4	735	4.9	13.7	0.38 (0.20 to 0.69)	<0.01	
Placental abruption							
≤80 mg	0	—	—	—	—	—	N/A
≥100 mg	4	592	2.3	5.1	0.55 (0.21 to 1.47)	NS	
			Mean difference (95% CI)			P	
Birth weight (g)							
≤80 mg	4	321	104 (−47 to 254)			NS	NS
≥100 mg	6	740	278 (114 to 442)			0.001	
GA at delivery (weeks)							
≤80 mg	2	119	2.00 (−1.61 to 5.62)			NS	NS
≥100 mg	6	719	1.09 (0.28 to 1.89)			<0.001	

GA, gestational age; N/A, not applicable; NS, not significant.

Table 3 Perinatal outcomes associated with aspirin started before 16 weeks according to whether abnormal uterine artery (UtA) Doppler was used as an inclusion criterion

Outcome/ inclusion criterion	*Trials* (n)	*Participants* (n)	*Prevalence*		*Relative risk (95% CI) (random effect)*	P	P *(between subgroups)*
			Treated (%)	*Controls (%)*			
Perinatal death							
Abnormal UtA Doppler	3	343	0.6	1.8	0.45 (0.06 to 3.41)	NS	NS
Anamnesis factors only	9	965	1.2	4.8	0.41 (0.17 to 0.97)	0.04	
Pre-eclampsia							
Abnormal UtA Doppler	4	423	16.6	34.0	0.46 (0.26 to 0.82)	<0.01	NS
Anamnesis factors only	9	1056	4.0	11.6	0.39 (0.24 to 0.64)	<0.001	
Severe pre-eclampsia							
Abnormal UtA Doppler	3	343	2.3	11.4	0.25 (0.09 to 0.68)	<0.01	NS
Anamnesis factors only	3	306	0.6	13.2	0.10 (0.02 to 0.40)	0.001	
Fetal growth restriction							
Abnormal UtA Doppler	3	343	9.0	18.1	0.49 (0.28 to 0.84)	0.01	NS
Anamnesis factors only	7	721	7.4	13.3	0.44 (0.29 to 0.67)	<0.001	
Preterm birth							
Abnormal UtA Doppler	2	257	6.0	13.0	0.44 (0.10 to 1.91)	NS	NS
Anamnesis factors only	4	647	4.3	14.9	0.29 (0.17 to 0.52)	<0.001	
Placental abruption							
Abnormal UtA Doppler	0	—	—	—	—	—	N/A
Anamnesis factors only	4	592	2.3	5.1	0.55 (0.21 to 1.47)	NS	
			Mean difference (95% CI)			P	
Birth weight (g)							
Abnormal UtA Doppler	3	343	46 (−115 to 206)			NS	NS
Anamnesis factors only	7	718	274 (137 to 411)			<0.001	
GA at delivery (weeks)							
Abnormal UtA Doppler	1	86	0.30 (−0.48 to 1.08)			NS	NS
Anamnesis factors only	7	752	1.32 (0.51 to 2.12)			0.001	

GA, gestational age; N/A, not applicable; NS, not significant.

started after 16 weeks from insufficient evidence of effect to evidence of modest, but significant, reduction of the risk of pre-eclampsia[7,53,57].

In the Cochrane review, low-dose aspirin was associated with an 18% reduction (RR = 0.82; 95% CI, 0.69–0.98) of fetal and neonatal death in women recruited before 20 weeks, but not in women recruited after 20 weeks of gestation (RR = 0.91; 95% CI, 0.73–1.13)[14]. However, the difference between those subgroups was not significant. In a meta-analysis of individual patient data, Askie *et al.* did not find a significant reduction of perinatal death (RR = 0.91; 95% CI, 0.81–1.03) with the use of low-dose aspirin[13]. However, they did not report the data stratified according to gestational age at entry for this outcome. Askie *et al.* did not find a significant impact of gestational age at initiation of aspirin on the risk of pre-eclampsia but the meta-analysis did not include several trials that recruited prior to 16 weeks[26,33,35,39]. As most large trials recruited women at around 20 weeks of gestation, we suggest that this cut-off cannot discriminate the effect of gestational age at initiation of low-dose aspirin.

We selected the 16th week of gestation as the gestational age cut-off because placental implantation and transformation of uterine spiral arteries are mostly complete by 16–20 weeks of gestation[12]. More specifically, histological studies suggest that endovascular trophoblastic invasion of uterine spiral arteries starts at around 8–10 weeks of gestation and continues until 22 weeks of gestation[12,70,71]. Some authors suggest a 'two-wave' process: the initial decidual phase being completed by around 10 weeks and the later myometrial phase starting at around 14–15 weeks[72,73], while others suggest a continuous process[71]. We propose that the beneficial effect of aspirin is a consequence of an improvement in the transformation of uterine spiral arteries. This is based on two facts. First, low-dose aspirin is associated with a greater reduction of the preterm and severe forms of pre-eclampsia, which are typically associated with poor placentation[5,6,74–77]. Second, abnormal uterine artery blood flow is present as early as 12 weeks' gestation in women who will subsequently develop pre-eclampsia, and low-dose aspirin improves uterine artery blood flow between the first and the second trimesters[10,78,79]. With these facts in mind, one could suggest that low-dose aspirin should probably be initiated at around 8–12 weeks' gestation in high-risk women. An individual patients' meta-analysis should be used to establish the benefits of aspirin in specific gestational-age subgroups (≤ 16 weeks', 17–20 weeks' and 21–24 weeks' gestation) and could estimate the benefits of initiating aspirin prophylaxis in women who are first seen after 16 weeks.

This meta-analysis has some limitations. First, none of the included trials was designed to evaluate perinatal death and few reported the reasons for perinatal death. Second, small studies without effect were missing, as seen in the funnel plot, raising the possibility of publication bias.

Third, the definition of perinatal death was heterogeneous between studies. Fourth, we found that the six largest trials that could have had the power to examine the impact of low-dose aspirin on perinatal death recruited women mostly after 16 weeks of gestation[43,44,46,50,51,59]. Finally, our finding was limited by the small size of the studies that recruited at ≤ 16 weeks' gestation: each of them individually was underpowered to address perinatal death, which can lead to a lack of precision. However, we found that the effect of low-dose aspirin started at ≤ 16 weeks of gestation was significant and homogeneous according to the I^2 test and the sensitivity analysis, and remained significant with the exclusion of the trials at high risk of bias.

In 1979, Crandon and Isherwood found that women taking aspirin for other reasons were less likely to develop pre-eclampsia, and Masotti *et al*. demonstrated a different inhibition of cyclo-oxygenase in platelets and vessel walls by low doses of aspirin[80,81]. Six years later, Beaufils *et al*. published the first randomized controlled trial which demonstrated the beneficial effect of low-dose aspirin, starting at 12–14 weeks of gestation, for the prevention of pre-eclampsia and FGR[27]. Of note, they found a significant reduction in perinatal death. Unfortunately, most subsequent randomized trials evaluating low-dose aspirin recruited women at around 20 weeks of gestation and demonstrated little or no beneficial effect. Such late recruitment is likely to be the consequence of the traditional approach to pregnancy care, where the first hospital visit was delayed to 16 weeks of gestation or later[82].

Extensive research in the last 20 years has identified a series of early biophysical and biochemical markers of impaired placentation[83]. A combination of maternal characteristics and obstetric and medical history with the measurement of mean arterial pressure, uterine artery pulsatility index and serum pregnancy-associated plasma protein-A and placental growth factor at 11–13 weeks can identify a high proportion of pregnancies at high risk for severe, early-onset pre-eclampsia, FGR, miscarriage and stillbirth[84–86]. The extent to which the administration of low-dose aspirin to such high-risk pregnancies can substantially reduce perinatal death, as suggested by the results of our meta-analysis, remains to be determined.

In conclusion, women at high risk for pre-eclampsia or other placenta-mediated adverse pregnancy outcomes should be offered low-dose aspirin daily starting before 16 weeks of gestation. The benefits of low-dose aspirin initiated after 16 weeks appear to be modest.

ACKNOWLEDGMENTS

Emmanuel Bujold holds a Clinician Scientist Award and Stéphanie Roberge holds a PhD Study Award (Réseau de formation en recherche périnatale du Quebec) from the Canadian Institutes of Health Research and from the Fond de Recherche du Québec – Santé. This study was supported by the Jeanne and Jean-Louis Lévesque Perinatal Research Chair at Université Laval, Quebec, QC, Canada.

REFERENCES

1. Geographic variation in the incidence of hypertension in pregnancy. World Health Organization International Collaborative Study of Hypertensive Disorders of Pregnancy. *Am J Obstet Gynecol* 1988; **158**: 80–83.
2. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009; **33**: 130–137.
3. Bukowski R, Carpenter M, Conway D, Coustan D, Dudley DJ, Goldenberg RL, Hogue CJ, Koch MA, Parker CB, Pinar H, Reddy UM, Saade GR, Silver RM, Stoll BJ, Varner MW, Willinger M; Stillbirth Collaborative Research Network Writing Group. Causes of death among stillbirths. *JAMA* 2011; **306**: 2459–2468.
4. Leitich H, Egarter C, Husslein P, Kaider A, Schemper M. A meta-analysis of low dose aspirin for the prevention of intrauterine growth retardation. *Br J Obstet Gynaecol* 1997; **104**: 450–459.
5. Roberge S, Giguere Y, Villa P, Nicolaides K, Vainio M, Forest JC, von Dadelzen P, Vaiman D, Tapp S, Bujold E. Early administration of low-dose aspirin for the prevention of severe and mild preeclampsia: a systematic review and meta-analysis. *Am J Perinatol* 2012; **29**: 551–556.
6. Roberge S, Villa P, Nicolaides K, Giguere Y, Vainio M, Bakthi A, Ebrashy A, Bujold E. Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis. *Fetal Diagn Ther* 2012; **31**: 141–146.
7. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, Forest JC, Giguere Y. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol* 2010; **116**: 402–414.
8. Lyall F. Priming and remodelling of human placental bed spiral arteries during pregnancy – a review. *Placenta 2005*; **26 Suppl A**: S31–S36.
9. Vainio M, Kujansuu E, Koivisto AM, Maenpaa J. Bilateral notching of uterine arteries at 12–14 weeks of gestation for prediction of hypertensive disorders of pregnancy. *Acta Obstet Gynecol Scand* 2005; **84**: 1062–1067.
10. Haapsamo M, Martikainen H, Rasanen J. Low-dose aspirin reduces uteroplacental vascular impedance in early and mid gestation in IVF and ICSI patients: a randomized, placebo-controlled double-blind study. *Ultrasound Obstet Gynecol* 2008; **32**: 687–693.
11. Espinoza J, Romero R, Mee Kim Y, Kusanovic JP, Hassan S, Erez O, Gotsch F, Than NG, Papp Z, Jai Kim C. Normal and abnormal transformation of the spiral arteries during pregnancy. *J Perinat Med* 2006; **34**: 447–458.
12. Pijnenborg R, Dixon G, Robertson WB, Brosens I. Trophoblastic invasion of human decidua from 8 to 18 weeks of pregnancy. *Placenta* 1980; **1**: 3–19.
13. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet* 2007; **369**: 1791–1798.
14. Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev* 2007; CD004659.
15. Coomarasamy A, Honest H, Papaioannou S, Gee H, Khan K. Aspirin for prevention of preeclampsia in women with historical risk factors: a systematic review. *Obstet Gynecol* 2003; **101**: 1319–1332.
16. Bujold E, Morency AM, Roberge S, Lacasse Y, Forest JC, Giguere Y. 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. *J Obstet Gynaecol Can* 2009; **31**: 818–826.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097.

18. *Cochrane Handbook for Systematic Reviews of Interventions*, version 5.1.0 (updated March 2011). Higgins JPT, Green S (eds). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
19. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; **273**: 408–412.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–188.
21. Chevalier P, van Driel M, Vermeire E. Hétérogénité dans les synthèses méthodiques et méta-analyses. *Minerva* 2007; **6**: 160.
22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.
23. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods* 2006; **11**: 193–206.
24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–634.
25. August P, Helseth G, Edersheim T, Hutson J, Druzin M. Sustained relase, low-dose aspirin ameliorates but does not prevent preeclampsia (PE) in a high risk population. Proceedings of the 9th International Congress, International Society for the Study of Hypertension, March 15–18, 1994, Sydney, Australia. Hypertension in Pregnancy, p. 72.
26. Azar R, Turpin D. Effect of antiplatelet therapy in women at high risk for pregnancy-induced hypertension. Proceedings of the 7th World Congress of Hypertension in Pregnancy. October 1990, Perugia, Italy, p. 257.
27. Beaufils M, Uzan S, Donsimoni R, Colau JC. Prevention of pre-eclampsia by early antiplatelet therapy. *Lancet* 1985; **1**: 840–842.
28. Benigni A, Gregorini G, Frusca T, Chiabrando C, Ballerini S, Valcamonico A, Orisio S, Piccinelli A, Pinciroli V, Fanelli R, Gastaldi A, Remuzzi G. Effect of low-dose aspirin on fetal and maternal generation of thromboxane by platelets in women at risk for pregnancy-induced hypertension. *N Engl J Med* 1989; **321**: 357–362.
29. Bakhti A, Vaiman D. Prevention of gravidic endothelial hypertension by aspirin treatment administered from the 8th week of gestation. *Hypertens Res* 2011; **34**: 1116–1120.
30. Bakhti A, Vaiman D. Erratum: prevention of gravidic endothelial hypertension by aspirin treatment administered from the 8th week of gestation (2012; **34**: 1116). *Hypertens Res* 2012; **35**: 244.
31. Chiaffarino F, Parazzini F, Paladini D, Acaia B, Ossola W, Marozio L, Facchinetti F, Del Giudice A. A small randomised trial of low-dose aspirin in women at high risk of pre-eclampsia. *Eur J Obstet Gynecol Reprod Biol* 2004; **112**: 142–144.
32. Dasari R, Narang A, Vasishta K, Garewal G. Effect of maternal low dose aspirin on neonatal platelet function. *Indian Pediatr* 1998; **35**: 507–511.
33. Ebrashy A, Ibrahim M, Marzook A, Yousef D. Usefulness of aspirin therapy in high-risk pregnant women with abnormal uterine artery Doppler ultrasound at 14–16 weeks pregnancy: randomized controlled clinical trial. *Croat Med J* 2005; **46**: 826–831.
34. Hermida RC, Ayala DE, Iglesias M, Mojon A, Silva I, Ucieda R, Fernandez JR. Time-dependent effects of low-dose aspirin administration on blood pressure in pregnant women. *Hypertension* 1997; **30**: 589–595.
35. Hermida RC, Ayala DE, Fernandez JR, Mojon A, Alonso I, Silva I, Ucieda R, Codesido J, Iglesias M. Administration time-dependent effects of aspirin in women at differing risk for preeclampsia. *Hypertension* 1999; **34**: 1016–1023.
36. Ayala DE, Ucieda R, Hermida RC. Chronotherapy with low-dose aspirin for prevention of complications in pregnancy. *Chronobiol Int* 2012 Sep 24. [Epub ahead of print].
37. Mesdaghinia E, Talari H, Abedzadeh-Kalahroudi M. Effect of aspirin for prevention of preeclampsia in women with abnormal ultrasonic findings in uterine artery. *Feyz, J Kashan University Med Sci* 2011; **15**: 98–104.
38. Michael CA, Walters BNJ. Low-dose aspirin in the prevention of pre-eclampsia: current evaluation. In *Maternal Physiology and Pathology*. The Current Status of Gynaecology and Obstetrics Series. Teoh ES, Ratnam SS, Macnaughton MC (eds). Parthenon Publishing Group Limited: Carnforth, 1992; 183–189.
39. Tulppala M, Marttunen M, Soderstrom-Anttila V, Foudila T, Ailus K, Palosuo T, Ylikorkala O. Low-dose aspirin in prevention of miscarriage in women with unexplained or autoimmune related recurrent miscarriage: effect on prostacyclin and thromboxane A2 production. *Hum Reprod* 1997; **12**: 1567–1572.
40. Vainio M, Kujansuu E, Iso-Mustajarvi M, Maenpaa J. Low dose acetylsalicylic acid in prevention of pregnancy-induced hypertension and intrauterine growth retardation in women with bilateral uterine artery notches. *BJOG* 2002; **109**: 161–167.
41. Villa PM, Kajantie E, Raikkonen K, Pesonen AK, Hamalainen E, Vainio M, Taipale P, Laivuori H. Aspirin in the prevention of pre-eclampsia in high-risk women: a randomised placebo-controlled PREDO Trial and a meta-analysis of randomised trials. *BJOG* 2013; **120**: 64–74.
42. Byaruhanga RN, Chipato T, Rusakaniko S. A randomized controlled trial of low-dose aspirin in women at risk from pre-eclampsia. *Int J Gynaecol Obstet* 1998; **60**: 129–135.
43. Caritis S, Sibai B, Hauth J, Lindheimer MD, Klebanoff M, Thom E, VanDorsten P, Landon M, Paul R, Miodovnik M, Meis P, Thurnau G. Low-dose aspirin to prevent preeclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med* 1998; **338**: 701–705.
44. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. *Lancet* 1994; **343**: 619–629.
45. Davies N, Gazvani M, Farquharson R, Walkinshaw S. Low-dose aspirin in the prevention of hypertensive disorders of pregnancy in relatively low-risk nulliparous women. *Hypertens Pregnancy* 1995; **14**: 49–55.
46. ECPPA: randomised trial of low dose aspirin for the prevention of maternal and fetal complications in high risk pregnant women. ECPPA (Estudo Colaborativo para Prevencao da Pre-eclampsia com Aspirina) Collaborative Group. *Br J Obstet Gynaecol* 1996; **103**: 39–47.
47. Ferrier C, North R, Kincaid-Smith P. Low dose aspirin delays the onset of pre-eclampsia in pregnancies with abnormal uteroplacental circulation. Proceedings of the 10th World Congress of the International Society for the Study of Hypertension in Pregnancy, August 4–8, 1996, Seattle, WA, USA, p. 151.
48. Gallery E, Ross M, Hawkins M, Leslie G, Gyory A. Low-dose aspirin in high-risk pregnancy. *Hypertens Pregnancy* 1997; **16**: 229–238.
49. Grab D, Paulus WE, Erdmann M, Terinde R, Oberhoffer R, Lang D, Muche R, Kreienberg R. Effects of low-dose aspirin on uterine and fetal blood flow during pregnancy: results of a randomized, placebo-controlled, double-blind trial. *Ultrasound Obstet Gynecol* 2000; **15**: 19–27.
50. Golding J. A randomised trial of low dose aspirin for primiparae in pregnancy. The Jamaica Low Dose Aspirin Study Group. *Br J Obstet Gynaecol* 1998; **105**: 293–299.
51. Hauth JC, Goldenberg RL, Parker CR Jr, Philips JB 3rd, Copper RL, DuBard MB, Cutter GR. Low-dose aspirin therapy to prevent preeclampsia. *Am J Obstet Gynecol* 1993; **168**: 1083–1091.
52. Kim HS, Kim KS, Kim TY, Cho JS, Park YW, Song CH. Clinical efficacy of doppler ultrasound for low dose aspirin therapy in high risk pregnancy. *Korean J Obstet Gynecol* 1997; **40**: 71–77.
53. McCowan LM, Harding J, Roberts A, Barker S, Ford C, Stewart A. Administration of low-dose aspirin to mothers with small for gestational age fetuses and abnormal umbilical Doppler studies

to increase birthweight: a randomised double-blind controlled trial. *Br J Obstet Gynaecol* 1999; **106**: 647–651.
54. McParland P, Pearce JM, Chamberlain GV. Doppler ultrasound and aspirin in recognition and prevention of pregnancy-induced hypertension. *Lancet* 1990; **335**: 1552–1555.
55. Morris JM, Fay RA, Ellwood DA, Cook CM, Devonald KJ. A randomized controlled trial of aspirin in patients with abnormal uterine artery blood flow. *Obstet Gynecol* 1996; **87**: 74–78.
56. Newnham J, Godfrey M, Walters B, Philips J, Evans S. Low dose aspirin for the treatment of fetal growth restriction: a randomised controlled trial. *Aust N Z J Obstet Gynaecol* 1995; **35**: 370–374.
57. Omrani GR, Karimi MM, Zareh F. Prevention of pregnancy-induced hypertension by low dose aspirin. *Iran J Med Sci* 1992; **17**: 131–136.
58. Rogers MS, Fung HY, Hung CY. Calcium and low-dose aspirin prophylaxis in women at high risk of pregnancy-induced hypertension. *Hypertens Pregnancy* 1999; **18**: 165–172.
59. Rotchell YE, Cruickshank JK, Gay MP, Griffiths J, Stewart A, Farrell B, Ayers S, Hennis A, Grant A, Duley L, Collins R. Barbados Low Dose Aspirin Study in Pregnancy (BLASP): a randomised trial for the prevention of pre-eclampsia and its complications. *Br J Obstet Gynaecol* 1998; **105**: 286–292.
60. Schiff E, Peleg E, Goldenberg M, Rosenthal T, Ruppin E, Tamarkin M, Barkai G, Ben-Baruch G, Yahal I, Blankstein J, Goldman B, Mashiach S. The use of aspirin to prevent pregnancy-induced hypertension and lower the ratio of thromboxane A2 to prostacyclin in relatively high risk pregnancies. *N Engl J Med* 1989; **321**: 351–356.
61. Schrocksnadel H, Sitte B, Alge A, Stechel-Berger G, Schwegel P, Pastner E, Daxenbichler G, Hansen H, Dapunt O. Low-dose aspirin in primigravidae with positive rollover test. *Gynecol Obstet Invest* 1992; **34**: 146–150.
62. Trudinger B, Cook CM, Thompson R, Giles W, Connelly A. Low-dose aspirin improves fetal weight in umbilical placental insufficiency. *Lancet* 1988; **2**: 214–215.
63. Wallenburg HC, Dekker GA, Makovitz JW, Rotmans P. Low-dose aspirin prevents pregnancy-induced hypertension and pre-eclampsia in angiotensin-sensitive primigravidae. *Lancet* 1986; **1**: 1–3.
64. Wallenburg HC, Dekker GA, Makovitz JW, Rotmans N. Effect of low-dose aspirin on vascular refractoriness in angiotensin-sensitive primigravid women. *Am J Obstet Gynecol* 1991; **164**: 1169–1173.
65. Wang Z, Li W. A prospective randomized placebo-controlled trial of low-dose aspirin for prevention of intra-uterine growth retardation. *Chin Med J (Engl)* 1996; **109**: 238–242.
66. Wu J, Yang W, Shen W, He Y. Small dosage aspirin in the prevention of hypertension of pregnancy. *Acta Academiae Medicinae Suzhou* 1996; **16**: 551–553.
67. Yu CK, Papageorghiou AT, Parra M, Palma Dias R, Nicolaides KH. Randomized controlled trial using low-dose aspirin in the prevention of pre-eclampsia in women with abnormal uterine artery Doppler at 23 weeks' gestation. *Ultrasound Obstet Gynecol* 2003; **22**: 233–239.
68. Zimmermann P, Eirio V, Koskinen J, Niemi K, Nyman R, Kujansuu E, Ranta T. Effect of low-dose aspirin treatment on vascular resistance in the uterine, uteroplacental, renal and umbilical arteries – A prospective longitudinal study on a high risk population with persistent notch in the uterine arteries. *Eur J Ultrasound* 1997; **5**: 17–30.
69. Sterne JA, Egger M, Smith GD. Systematic 7 in health care: investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001; **323**: 101–105.
70. Lyall F, Bulmer JN, Duffie E, Cousins F, Theriault A, Robson SC. Human trophoblast invasion and spiral artery transformation: the role of PECAM-1 in normal pregnancy, preeclampsia, and fetal growth restriction. *Am J Pathol* 2001; **158**: 1713–1721.
71. Robson S, Ball E, Lyall F, Simpson H, Ayis H, Bulmer J. Endovascular trophoblast invasion and spiral artery transformation: the "two wave" theory revisited. *Placenta* 2001; **22**: A25.
72. Pijnenborg R, Bland JM, Robertson WB, Brosens I. Uteroplacental arterial changes related to interstitial trophoblast migration in early human pregnancy. *Placenta* 1983; **4**: 397–413.
73. Robertson WB, Khong TY, Brosens I, De Wolf F, Sheppard BL, Bonnar J. The placental bed biopsy: review from three European centers. *Am J Obstet Gynecol* 1986; **155**: 401–412.
74. Kim YM, Chaiworapongsa T, Gomez R, Bujold E, Yoon BH, Rotmensch S, Thaler HT, Romero R. Failure of physiologic transformation of the spiral arteries in the placental bed in preterm premature rupture of membranes. *Am J Obstet Gynecol* 2002; **187**: 1137–1142.
75. Ogge G, Chaiworapongsa T, Romero R, Hussein Y, Kusanovic JP, Yeo L, Kim CJ, Hassan SS. Placental lesions associated with maternal underperfusion are more frequent in early-onset than in late-onset preeclampsia. *J Perinat Med* 2011; **39**: 641–652.
76. Dolitzky M, Inbal A, Segal Y, Weiss A, Brenner B, Carp H. A randomized study of thromboprophylaxis in women with unexplained consecutive recurrent miscarriages. *Fertil Steril* 2006; **86**: 362–366.
77. Kim YM, Bujold E, Chaiworapongsa T, Gomez R, Yoon BH, Thaler HT, Rotmensch S, Romero R. Failure of physiologic transformation of the spiral arteries in patients with preterm labor and intact membranes. *Am J Obstet Gynecol* 2003; **189**: 1063–1069.
78. Plasencia W, Maiz N, Bonino S, Kaihura C, Nicolaides KH. Uterine artery Doppler at 11+0 to 13+6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2007; **30**: 742–749.
79. Baschat AA, Poon LY, Blitzer M, Nicolaides KH, Harman C. Impact of 1st trimester aspirin on population prevalence of preeclampsia. *Ultrasound Obstet Gynecol* 2009; **34**: 14.
80. Crandon AJ, Isherwood DM. Effect of aspirin on incidence of pre-eclampsia. *Lancet* 1979; **1** (8130): 1356.
81. Masotti G, Galanti G, Poggesi L, Abbate R, Neri Serneri GG. Differential inhibition of prostacyclin production and platelet aggregation by aspirin. *Lancet* 1979; **2** (8154): 1213–1217.
82. Ministry of Health Report. 1929 *Memorandum on Antenatal Clinics: Their Conduct and Scope*. His Majesty's Stationery Office: London, 1930.
83. Nicolaides KH. Turning the pyramid of prenatal care. *Fetal Diagn Ther* 2011; **29**: 183–196.
84. Akolekar R, Syngelaki A, Sarquis R, Zvanca M, Nicolaides KH. Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11–13 weeks. *Prenat Diagn* 2011; **31**: 66–74.
85. Poon LC, Akolekar R, Lachmann R, Beta J, Nicolaides KH. Hypertensive disorders in pregnancy: screening by biophysical and biochemical markers at 11–13 weeks. *Ultrasound Obstet Gynecol* 2010; **35**: 662–670.
86. Poon LC, Volpe N, Muto B, Yu CK, Syngelaki A, Nicolaides KH. Second-trimester uterine artery doppler in the prediction of stillbirths. *Fetal Diagn Ther* 2013; **33**: 28–35.

SUPPORTING INFORMATION ON THE INTERNET

Table S1 Characteristics of included studies according to gestational age at entry

This article is included in this month's Journal Club.

A slide presentation, prepared by Dr Leona Poon, one of UOG's Editors for Trainees, is available online.