Prevention of Preeclampsia and Intrauterine Growth Restriction With Aspirin Started in Early Pregnancy

A Meta-Analysis

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OBJECTIVE: To estimate the effect of low-dose aspirin started in early pregnancy on the incidence of preeclampsia and intrauterine growth restriction (IUGR).

DATA SOURCES: A systematic review and meta-analysis were performed through electronic database searches (PubMed, Cochrane, Embase).

METHODS OF STUDY SELECTION: Randomized controlled trials of pregnant women at risk of preeclampsia who were assigned to receive aspirin or placebo (or no treatment) were reviewed. Secondary outcomes included IUGR, severe preeclampsia and preterm birth. The effect of aspirin was analyzed as a function of gestational age at initiation of the intervention (16 weeks of gestation or less, 16 weeks of gestation or more).

TABULATION, INTEGRATION, AND RESULTS: Thirty-four randomized controlled trials met the inclusion criteria, including 27 studies (11,348 women) with follow-up for the outcome of preeclampsia. Low-dose aspirin started at 16 weeks or earlier was associated with a significant reduction in preeclampsia (relative risk [RR] 0.47, 95% confidence interval [CI] 0.34–0.65, prevalence in 9.3% treated compared with 21.3% control) and IUGR (RR 0.44, 95% CI 0.30–0.65, 7% treated compared with 16.3% control), whereas aspirin started after 16 weeks was not (preeclampsia: RR 0.81, 95% CI 0.63–1.03, prevalence in 7.3% treated compared with 8.1% control; IUGR: RR 0.98, 95% CI 0.87–1.10, 10.3% treated compared with 10.5% control). Low-dose aspirin started at 16 weeks or earlier also was associated with a reduction in severe preeclampsia (RR 0.09, 95% CI 0.02–0.37, 0.7% treated compared with 15.0% control), gestational hypertension (RR 0.62, 95% CI 0.45–0.84, 16.7% treated compared with 29.7% control), and preterm birth (RR 0.22, 95% CI 0.10–0.49, 3.5% treated compared with 16.9% control). Of note, all studies for which aspirin had been started at 16 weeks or earlier included women identified to be at moderate or high risk for preeclampsia.

CONCLUSION: Low-dose aspirin initiated in early pregnancy is an efficient method of reducing the incidence of preeclampsia and IUGR.

(Obstet Gynecol 2010;116:402–14)

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Dr. Emmanuel Bujold holds a Clinician Scientist Award and Dr. François Audibert holds a New Investigator Award from the Canadian Institutes of Health Research (CIHR). Dr. Yves Giguère holds a Clinician-Scientist Award from Fonds de la recherche en santé du Québec (FRSQ). Supported by the Jeanne and Jean-Louis Levesque Perinatal Research Chair at Université Laval.

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Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/10

Preeclampsia and intrauterine growth restriction (IUGR) are important causes of maternal and perinatal morbidity and mortality.[1,2] Preeclampsia affects about 2–5% of pregnancies and leads to over 100,000 maternal deaths worldwide each year.[2] In developed countries, it remains responsible for severe maternal complications such as coagulopathy, renal and liver failure, stroke, and maternal death.[3] Pre-

eclampsia also is associated with a fourfold increase in the risk of IUGR, which is linked to both short-term and long-term health consequences.[4] Those affected by IUGR are at high risk of obesity, cardiovascular disease, hypertension, and diabetes later in life.[5,6]

Although the original causes of preeclampsia and IUGR are still unclear, both entities typically are characterized by defective placentation eliciting inadequate uteroplacental blood perfusion and ischemia.[7] Normal placentation comprises trophoblast cell invasion of the spiral arteries, which results in reversible changes in the normal arterial wall architecture.[8] Physiological trophoblastic invasion of the spiral arteries develops from 8 weeks of gestation and is believed to be mostly completed by 16 to 20 weeks of gestation.[7,9,10] Recent studies have shown that abnormal uterine artery Doppler and serum markers of defective placentation can identify women at high risk of preeclampsia and IUGR, as early as the first trimester.[11,12]

Inadequate perfusion and placental ischemia evoke endothelial dysfunction, with platelet and clotting system activation.[13,14] Therefore, the hypothesis that antiplatelet agents might prevent preeclampsia and IUGR held considerable interest for the last 30 years.[15,16] It was thought that low-dose aspirin could inhibit thromboxane-mediated vasoconstriction and thereby protect against vasoconstriction and pathological blood coagulation in the placenta.[17,18] Its use was expected to prevent failure of physiological spiral artery transformation and, thus, the development of preeclampsia and IUGR. However, the results from randomized trials are contradictory.[16,19,20] Several large, prospective, multicenter studies failed to demonstrate the clinical efficacy of low-dose aspirin in preventing preeclampsia.[20–23] On the other hand, late initiation of treatment (after 18 to 20 weeks) and the inclusion of low-risk patients may represent potential reasons for the negative or weakly-positive results obtained. Indeed, we recently found that prophylactic low-dose aspirin started before 16 weeks of gestation in women with abnormal uterine artery Doppler was associated with a 50% reduction of preeclampsia.[24]

In this review, we aim to assess and compare the influence of gestational age at the introduction of aspirin therapy on the incidence of preeclampsia and IUGR by performing a systematic review and meta-analysis of all women identified as being at risk of preeclampsia.

SOURCES

Relevant citations were extracted from Embase, PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) from 1965 to July 2008. Keywords and MeSH terms were combined to generate lists of studies: "pregn*," "pregnancy," "pregnancy-complication," "aspirin," "antiplatelet," "salicy*," "preeclam*," "pre-eclam*," "hypertension," "hypertens*," "blood press*," "PIH," "toxaemi*," "toxemi*," "eclamp*." No language restriction was imposed. The search strategy was sorting by a first reviewer (S.R.) of articles by title for more detailed evaluation. The second sort was made by two reviewers (S.R., E.B.) for abstracts categorized as relevant, not relevant or possibly relevant. All relevant and possibly relevant trials were entirely reviewed, classified, and approved by the same two reviewers. Disagreement was resolved by discussion with a third reviewer (M.B.). Quality and integrity of this review were validated with PRISMA (preferred reporting items for systematic reviews and meta-analyses).[25]

STUDY SELECTION

Only prospective, randomized, controlled trials were included. Quasi-randomized trials were excluded. The selected population was constituted of pregnant women at risk of preeclampsia. No restrictions were applied to risk criteria for preeclampsia but we evaluated the trials according to the prevalence of preeclampsia in each study. Women in the treatment group had to receive low-dose aspirin (50 to 150 mg of acetylsalicylic acid daily, alone or in combination with less than 300 mg of dipyridamole, another antiplatelet agent). The control group had to be allocated to placebo or no treatment. Studies were excluded if more than 20% of women were lost to follow-up or excluded from analysis after randomization to prevent possibility of attrition bias.[26] Studies with inappropriate allocation concealment, such as numbered tables or nonsealed envelopes, also were excluded to prevent the possibility of selection bias.[26] The quality of each study was reported.[27]

The primary outcome was the occurrence of preeclampsia. Secondary outcomes were IUGR, severe preeclampsia, gestational hypertension, placental abruption, preterm birth, low birth weight and gestational age at delivery (Table 1). Data were extracted in duplicate from all included studies by two independent reviewers (S.R., M.B.). Each outcome was stratified according to gestational age at the beginning of aspirin treatment: 16 completed weeks of gestation or less, more than 16 weeks. The threshold in gestational age was 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 of gestation.[7,9]

Table 1. Definition of Outcomes and Enrollment Characteristics

Outcomes and Enrollment Characteristics	Definition
Preeclampsia	Chronic or gestational hypertension combined with proteinuria detected after 20 wk of gestation
Gestational hypertension	Systolic BP 140 mmHg or higher or diastolic BP 90 mmHg or higher, or both detected after 20 wk of gestation[9]
Proteinuria	300 mg of protein or more in a 24-h urine specimen or a positive reaction (+1) on a midstream urine specimen[10]
Severe preeclampsia	Recorded according to the following criteria: severe hypertension (BP of at least 160 mmHg systolic or 110 mmHg diastolic or 105 mmHg diastolic), severe proteinuria (at least 2, 3, or 5 g of protein in 24 h or 3+ on dipstick), reduced urinary volume (less than 400 to 500 mL in 24 h), neurologic disturbances such as headache and visual perturbations, upper abdominal pain, pulmonary edema, impaired liver function tests, high serum creatinine, low platelet count
IUGR	Birth weight less than the 10th percentile (IUGR, less than the 10th percentile) or birth weight less than the 5th or birth weight less than the 3rd percentile or reported as small for gestational age (IUGR, any definition)
Preterm birth	Birth before 37 wk of gestation or, when not available, before 36, 35, or 34 wk of gestation
Placental abruption	Abruption of the placenta or antepartum hemorrhage
Birth weight	Weight of neonate at birth in grams
Gestational age	Gestational age at delivery in weeks
Population risk of preeclampsia	Prevalence of preeclampsia reported in the control group
Low	7% or less
Moderate or high	More than 7%

BP, blood pressure; IUGR, intrauterine growth restriction.

Continuous and dichotomous variables were analyzed with Review Manager 5.0.12 software (Cochrane IMS, www.cc-ims.net/revman), and SAS 9.1 (SAS Institute Inc., Cary, NC) was used to calculate agreement between reviewers and to compare subgroup relative risks (RR).[28] The analyses included data on all randomized participants followed up until the end of pregnancy on an intention-to-treat basis. Within each trial, for dichotomous variables, individual RR with 95% confidence intervals (CIs) was calculated according to the Mantel-Haentszel method to compare the effectiveness of treatment over placebo. RR were pooled according to DerSimmonian and Laird random effect models.[29] For continuous variables, mean differences were weighted by the inverse of population variance and combined according to random effect models and 95% CI. Heterogeneity between studies was analyzed by Higgins' I^2.[30,31] The distribution of trials was examined with funnel plots and analyzed with Egger test to assess publication bias.[32] Sensitivity analysis was performed to evaluate the robustness of the findings.[31,33]

Relative risks of subgroups stratified according to gestational age at entry were compared for primary and secondary outcomes using mixed regression weighted by the size of each study.[34] Finally, analyses were repeated for studies categorized according to prevalence in the control group in each study: those with a prevalence equal or less than 7% of preeclampsia being considered at low risk and those with prevalence greater than 7% being considered a moderate-risk or high-risk population for preeclampsia. *P* values less than 0.05 were considered significant.

RESULTS

Through our literature search, 773 articles were identified as potentially eligible, and 337 of them were deemed to be potentially relevant. Of these, 290 were eliminated because they did not follow the inclusion criteria (Fig. 1). For this review, 34 trials were analyzed, including 27 for primary outcome (preeclampsia), for a total of 11,348 women.[20,21,23,35–66] Interreviewer agreement for the second selection of 337 articles was associated with a weighted kappa of 0.88. In addition to electronic searches, other recent meta-analyses permitted us to confirm the completeness of our literature search.[16,67–69] All selected articles were published between 1985 and 2005 and included participants from more than 20 countries. Twelve studies report data from women randomized at or before 16 weeks of gestation, and 22 studies report data from women randomized after 16 weeks of gestation. Table 2 shows the characteristics of all included studies, and Table 3 shows the aggregated quality of the studies (randomization method, blinding, intention-to-treat and completeness of follow-up) in each subgroup. Women were identified at risk for preeclampsia based

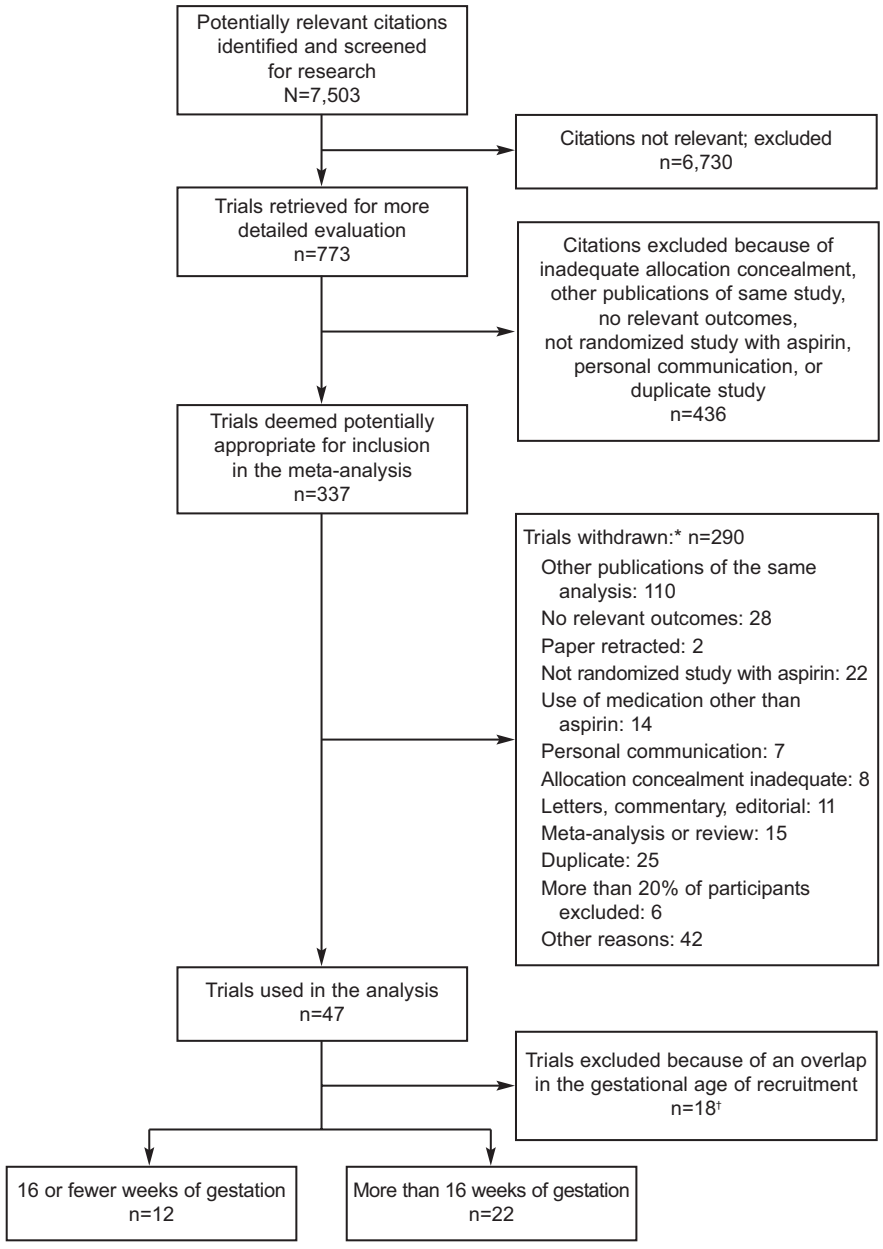

Fig. 1. Selection process. Summary of selection process for systematic review of aspirin to prevent preeclampsia. *A study could be in more than one category. †Partial data from five trials that reported the results for women recruited at 20 weeks of gestation or more were included in our analysis.

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on heterogeneous criteria including nulliparity, previous history of preeclampsia or other hypertensive disorders, abnormal uterine artery Doppler, among others.

The diminution of preeclampsia was significant in the subgroup of women who began the intervention at 16 weeks of gestation or less (RR 0.47, 95% CI 0.34–0.65), whereas it was not in the subgroup of women who began the intervention at more than 16 weeks (RR 0.81, 95% CI 0.63–1.03) (Fig. 2). The difference of treatment's effect on the risk of preeclampsia between the two groups was significant (mixed regression analysis for comparison between subgroups: 16 weeks or less compared with more than 16 weeks, $P=.01$). A significant decrease of severe preeclampsia, gestational hypertension and preterm birth was also observed in the subgroup of women who started the intervention at 16 weeks of gestation or less (Table 4). Moreover, the mean gestational age at delivery (weighted mean difference 1.4 weeks, 95% CI 0.4–2.3 weeks) was greater when aspirin was started at 16 weeks or less, whereas it was not when started at more than 16 weeks (weighted mean difference 0.0 weeks; 95% CI -0.7 to 0.7 weeks). The rate of

Table 2. Characteristics of Included Studies

First Author, Year	Participants	Inclusion Criteria	Intervention	Outcome
16 wk of gestation or less				
August, 1994[35]	54 women at 13–15 wk	Chronic HTN or previous severe PE	ASA 100 mg vs placebo	PE, severe PE, IUGR, AP
Azar, 1990[37]	91 women at 16 wk	Previous early onset PE, severe IUGR, or fetal death due to placental insufficiency	ASA 100 mg + dipyridamole 300 mg vs no treatment	PE, GH, BW, GA at birth
Beaufils, 1985[38]	102 women from 14 wk	Had several previous complicated pregnancies or vascular risk factors such as essential HTN (BP higher than 160/95 or a family history of HTN)	ASA 150 mg + dipyridamole 300 mg vs no treatment	PE, GH, severe PE, BW, GA at birth, IUGR, AP
Benigni, 1989[39]	33 women at 12 wk	Essential HTN or a significant previous obstetric history	ASA 60 mg vs placebo	PE, GH, BW, PTB, GA at birth, IUGR
Chiaffarino, 2004[41]	40 women at less than 14 wk	Chronic HTN with or without nephropathy or history of severe PE, eclampsia, IUGR, or stillbirth	ASA 100 mg vs no treatment	GH, BW, GA at birth, SGA
Dasari, 1998[36]	50 women at 12 wk	Primiparous women	ASA 100 mg vs placebo	SGA, BW, GA at birth
Ebrashy, 2005[43]	139 women at 14–16 wk	Abnormal uterine artery Doppler and risk factors for PE and IUGR	ASA 75 mg vs no treatment	PE, severe PE, BW, IUGR, PTB
Hermida, 1997[50]	107 women at 12–16 wk	Family or own history of PIH, PE, chronic HTN, cardiovascular or endocrine problem, spontaneous abortion, multiple pregnancy, or obesity or nulliparous (younger than 18 or older than 35)	ASA 100 mg vs placebo	PE, GH, BW, GA at birth, IUGR, PTB, AP
Hermida, 1999[49]	255 women at 12–16 wk	Family or own history of PIH, PE, chronic HTN, cardiovascular or endocrine problem, spontaneous abortion, multiple pregnancy, or obesity or nulliparous (younger than 18 or older than 35)	ASA 100 mg vs placebo	IUGR, PTB, AP
Michael, 1992[52]	110 women at 16 wk	HTN in early pregnancy, DBP 90 mmHg or higher or SBP 140 mmHg or higher or a history of severe PE	ASA 100 mg vs placebo	PE, GH
Tulppala, 1997[59]	66 women around 7 wk	Previous consecutive miscarriage	ASA 50 mg vs placebo	PE, IUGR, BW
Vainio, 2002[60]	90 women at 12–14 wk	Anamnestic risk factor with abnormal uterine Doppler	ASA 0.5 mg/kg/d vs placebo	PE, GH, severe PE, IUGR, SGA, BW, GA at birth
More than 16 wk				
Byaruhanga, 1998[66]	250 women at 20–28 wk	History of PE or chronic HTN	ASA 75 mg vs placebo	PE, GH, severe PE, IUGR, PTB, AP
Caritis, 1998[21]*	2,539 women at 13–26 wk	Insulin-treated diabetes, chronic HTN, multiple pregnancy, or previous PE	ASA 60 mg vs placebo	PE, IUGR, BW, PTB, AP
CLASP, 1994[20]*	9,364 women at 12–32 wk	Risks for PE based on history of HTN, renal disease, AMA, family history, multiple pregnancy, established PE, or IUGR	ASA 60 mg vs placebo	PE, IUGR, PTB
Davies, 1995[42]	122 women at 18 wk	Nulliparous, Hb higher than 13.2 g/dL at 12–19 wk of gestation, DBP lower than 90 mmHg, and no proteinuria	ASA 75 mg vs placebo	PE, severe PE, GH, BW, GA at birth, PTB, AP
ECPPA, 1996[44]*	1,009 women at 12–32 wk	Chronic HTN, primigravidity, diabetes, renal disease, history of PE or IUGR	ASA 60 mg vs placebo	PE, severe PE, preterm birth, IUGR, BW, GH, GA at birth, AP

(*continued*)

Table 2. Characteristics of Included Studies (*continued*)

First Author, Year	Participants	Inclusion Criteria	Intervention	Outcome
Ferrier, 1996[45]	43 women at 22–24 wk	Nulliparous women with a placental side uterine artery resistance index higher than the 90th centile or a diastolic notch	ASA 60 mg vs placebo	PE, GH
Gallery, 1997[46]	120 women at 17–19 wk	Preexisting chronic HTN, renal disease, or previous early PE	ASA 100 mg vs placebo	PTB, SGA, AP
Grab, 2000[47]	43 women at 20 wk	Singleton with early IUGR, impaired uteroplacental flow, chronic HTN, or previous IUGR, stillbirth, or PE	ASA 100 mg vs placebo	PE
Golding, 1998[23]*	6,275 women at 12–32 wk	Primiparous women	ASA 60 mg vs placebo	PE, severe PE, GH, BW, GA at birth, PTB, SGA, AP
Hauth, 1993[48]	606 women at 24 wk	Nulliparous, healthy, singleton gestation	ASA 60 mg vs placebo	PE, GH, severe PE, BW, PTB, IUGR,
McParland, 1990[51]	106 women at 24 wk	Nulliparous women with persistent abnormal Doppler waveform	ASA 75 mg vs placebo	PE, GH, SGA, IUGR, GA at birth, BW,
Morris, 1996[53]	104 women at 17–19 wk	Nulliparous with abnormal uterine Doppler flow at 18 wk (S/D higher than 3.3 or higher than 3 with early diastolic notch)	ASA 100 mg vs placebo	PE, GH, PTB, IUGR, BW
Newnham, 1995[54]	51 women at 28–36 wk	IUGR, umbilical artery, Doppler S/D higher than the 95th centile	ASA 100 mg vs placebo	BW, IUGR, GA at birth
Rogers, 1999[55]	215 women at 22 wk	Normotensive, primigravid with MAP 80 or higher and lower than 106 mmHg early in 2nd trimester and MAP higher than 60	ASA 80 mg vs no treatment	PE, GH, BW, GA at birth
Rotchell, 1998[56]*	3,697 women at 12–32 wk	All pregnant women without contraindications	ASA 75 mg vs placebo	PE, GH, severe PE, BW, SGA, PTB, AP, GA at birth
Schiff, 1989[57]	65 women at 28–29 wk	Twin pregnancy, a history of PE, nulliparity, and a positive rollover test at 28–29 wk of gestation	ASA 100 mg vs placebo	PE, GH, severe PE, BW, GA at birth, PTB, IUGR
Schrocksnadel, 1992[58]	41 women at 28–32 wk	Primigravid women with positive rollover test	ASA 80 mg vs placebo	PE, GH, severe PE, IUGR, BW, GA at birth, PTB
Wallenburg, 1986[61]	46 women at 28 wk	Angiotensin II–sensitive primigravid, no history of HTN, cardiovascular or renal disease, DBP lower than 80 mmHg	ASA 60 mg vs placebo	PE, GH, severe PE, PTB, IUGR
Wang, 1996[62]	84 women at 28–34 wk	Mainly nulliparous with a singleton pregnancy at high risk for IUGR	ASA 75 mg vs placebo	GH, BW, IUGR, PTB, GA at birth,
Wu, 1996[63]	104 women at 30–32 wk	Old nulliparous, multiparous with history of severe PIH, obesity, MAP higher than 12 kPa, Hb less than 8, PCV more than 0.37 family history of HTN or PIH	ASA 50 mg vs placebo	GH, BW
Yu, 2003[64]	560 women at 22–24 wk	Singleton pregnancy and Doppler pulsatility index more than 1.6 (95th centile)	ASA 150 mg vs placebo	PE, severe PE, IUGR, PTB, AP,
Zimmermann, 1997[65]	26 women at 22–24 wk	Uterine artery bilateral notches on Doppler	ASA 50 mg vs no treatment	PE, GH, BW, GA at birth, PTB, IUGR, AP

HTN, hypertension; PE, preeclampsia; ASA, acetyl salicylic acid; IUGR, intrauterine growth restriction; AP, abruptio placenta; GH, gestational hypertension; BW, birth weight; GA, gestational age; BP, blood pressure; PTB, preterm birth; SGA, small for gestational age; PIH, pregnancy-induced hypertension; DBP, diastolic blood pressure; SBP, systolic blood pressure; AMA, advanced maternal age; Hb, hemoglobin concentration; S/D, systolic/diastolic ratio; MAP, mean arterial blood pressure; PCV, packed cell volume.

* Data for these trials could be extracted for more than 20 wk.

Table 3. Aggregated Results for the Quality of the 34 Studies Included in the Meta-Analysis

Outcome	16 wk or Less (n=12)	More Than 16 wk (n=22)
Method of randomization		
Computer-generated	3 (25)	11 (50)
Sealed envelopes	—	2 (9)
Others	3 (25)	4 (18)
Not reported	6 (50)	5 (23)
Intention-to-treat		
Yes	4 (33)	10 (46)
Not reported	8 (67)	12 (55)
Blinding		
Double	4 (33)	16 (73)
Single	1 (8)	2 (9)
None	3 (25)	2 (9)
Not reported	4 (33)	2 (9)

Data are n (%).

placental abruption was not modified by low-dose aspirin in any subgroups.

The reduction of IUGR, defined as birth weight less than the 10th percentile, or based on any definition used by the different studies, was significant only in the subgroup of women who started low-dose aspirin at 16 weeks of gestation or less (Fig. 3) (mixed regression analysis for comparison between subgroups: 16 weeks or less compared with more than 16 weeks, $P<.001$). The increase in mean birth weight was 196 g (95% CI 107–285 g) when aspirin was started at 16 weeks of gestation or less compared with 70 g (95% CI 15–124 g) when aspirin was started at more than 16 weeks.

We found that the heterogeneity within each subgroup was lower than the heterogeneity present in all studies taken together, and it was almost absent in the 16-weeks-or-less subgroup (I^2 for preeclampsia: 16 weeks or less 0%, more than 16 weeks 48%, overall 52%; I^2 for IUGR: 16 weeks or less 0%, more than 16 weeks 1%, overall 28%). This finding supports the hypothesis that the effect of low-dose aspirin vary with gestational age. Analysis of the funnel plot revealed the possibility of a publication bias because small studies showing no benefits are missing (Fig. 4).[33] This finding is confirmed by the Egger test that indicates asymmetry and publication bias that was significant in the 16-weeks-or-less subgroup. Such finding suggests a possible overestimation of the size effect. Because other variations could exist between the trials, we performed a sensitivity analysis to examine the robustness of our findings (Fig. 5). In this analysis, we found a very small amount of variation in the 16-weeks-or-less subgroup: no significant differ-

Table 4. Relative Risk of Outcomes Associated With the Use of Low-Dose Aspirin According to Gestational Age at Initiation of Intervention

Outcome	No. of Trials	No. of Participants	Prevalence in Treated (%)	Prevalence in Controls (%)	RR (95% CI)	NNT (95% CI)
Preeclampsia						
16 wk or less	9	764	9.3	21.3	0.47 (0.34–0.65)*	9 (6–25)
more than 16 wk	18	10,584	7.3	8.1	0.81 (0.63–1.03)	
Severe preeclampsia						
16 wk or less	3	278	0.7	15.0	0.09 (0.02–0.37)*	7 (5–13)
more than 16 wk	2	669	0.6	2.4	0.26 (0.05–1.26)	
Gestational hypertension						
16 wk or less	7	548	16.7	29.7	0.62 (0.45–0.84)†	8 (5–17)
more than 16 wk	14	4,303	11.6	15.0	0.63 (0.47–0.85)†	29 (17–50)
Preterm birth						
16 wk or less	4	387	3.5	16.9	0.22 (0.10–0.49)*	8 (6–15)
more than 16 wk	16	10,398	18.6	20.8	0.90 (0.83–0.97)†	46 (25–100)
IUGR (any definition)						
16 wk or less	9	853	7	16.3	0.44 (0.30–0.65)*	11 (8–20)
more than 16 wk	15	7,027	10.3	10.5	0.98 (0.87–1.10)	
IUGR ([less than the 10th centile)						
16 wk or less	5	414	10.7	23.0	0.47 (0.30–0.74)†	9 (5–17)
more than 16 wk	10	1,381	13.4	16.0	0.92 (0.78–1.10)	
Placental abruption						
16 wk or less	4	360	1.1	3.3	0.62 (0.08–5.03)	
more than 16 wk	6	3,583	2.3	1.4	1.56 (0.96–2.55)	

RR, relative risk; CI, confidence interval; NNT, number needed to treat; IUGR, intrauterine growth restriction.
* $P<.001$.
† $P<.05$.

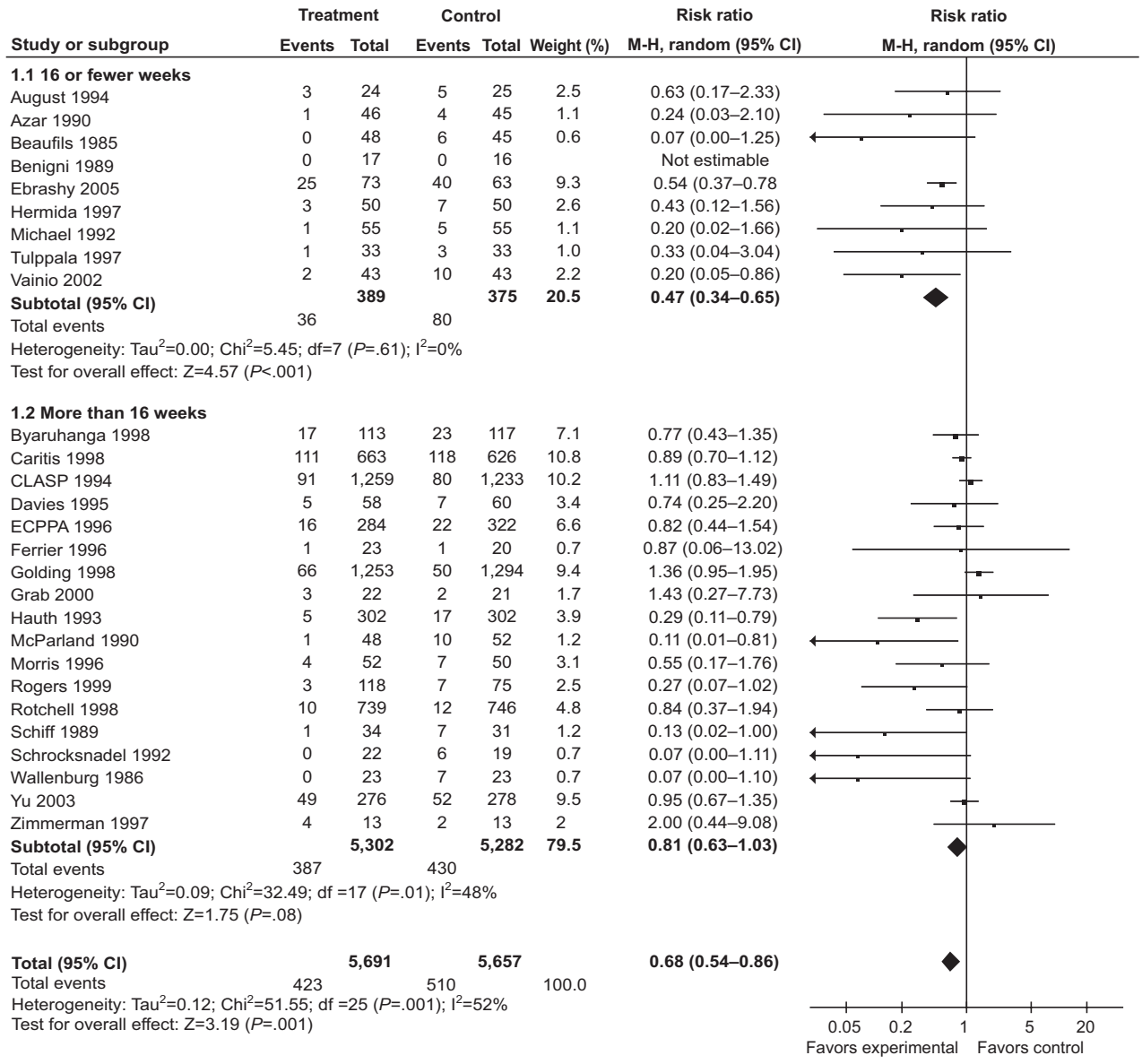

Fig. 2. Forest plot of trials studying preeclampsia. Aspirin treatment to prevent preeclampsia according to gestational age at the initiation of intervention. CI, confidence interval; M-H, Mantel-Haentszel.

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ence was found between the trials in regards with the statistical model used, the blinding, the size of the trials, the dose of aspirin, and the addition of dipyridamole. Of note, only one large trial was included in this subgroup and it included only women identified to be at moderate or high risk for preeclampsia (rate of preeclampsia greater than 7% in the control group).

CONCLUSION

We determined that daily low-dose aspirin initiated before 16 weeks of gestation was associated with a significant decrease in the incidence of preeclampsia, severe preeclampsia, IUGR and preterm birth in women identified to be at risk for preeclampsia. Our observations are in complete agreement with previous meta-analyses which demonstrated an overall preeclampsia reduction of approximately 20% with low-dose aspirin started any time during pregnancy.[16,68] The results also concur with the recent retrospective study of Baschat et al who reported that first-trimester, low-dose aspirin decreases placental blood flow resistance and most likely prevents pre-

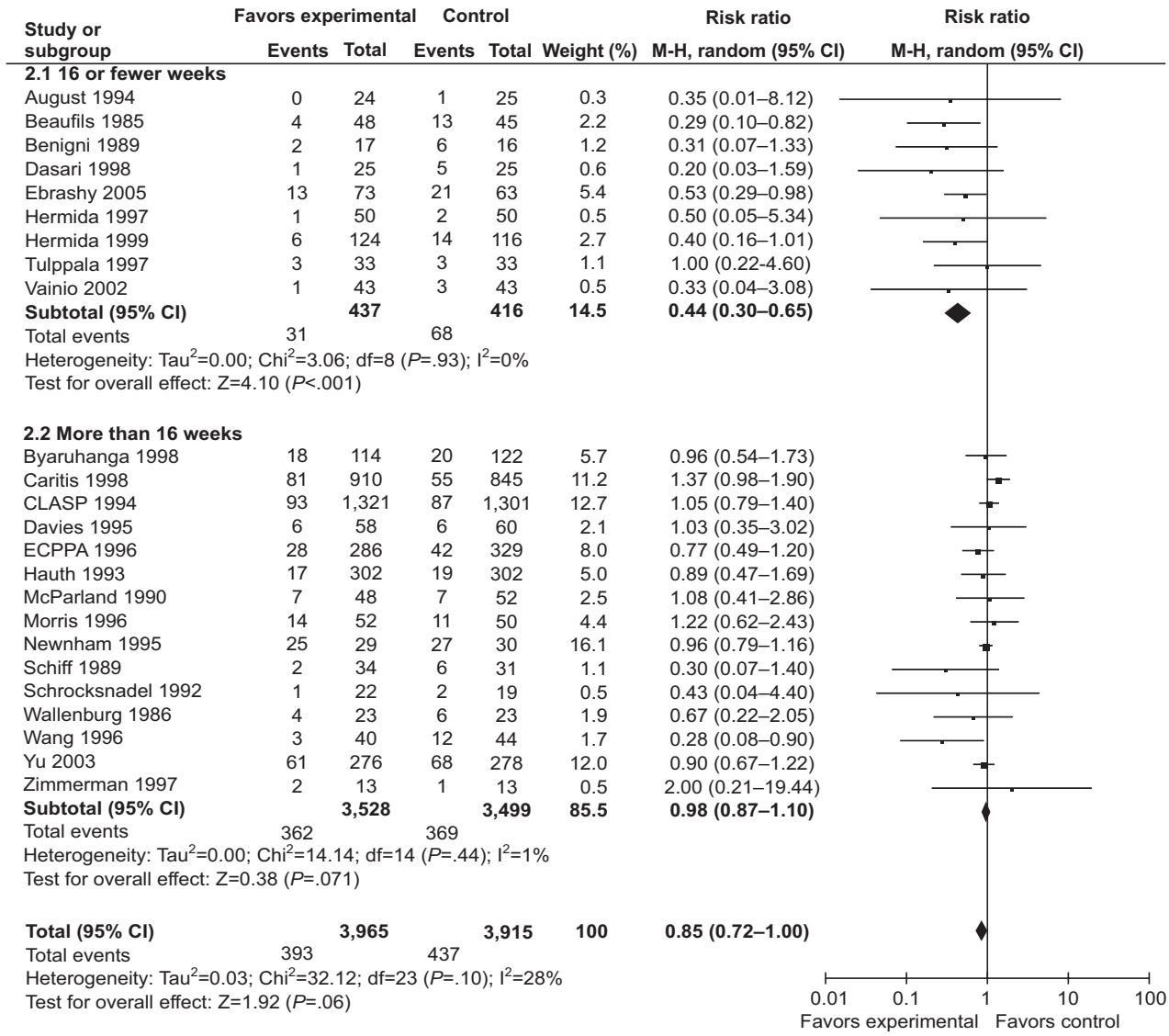

Fig. 3. Forest plot of trials studying intrauterine growth restriction. Aspirin treatment to prevent intrauterine growth restriction according to gestational age at the initiation of intervention. CI, confidence interval; M-H, Mantel-Haentszel.
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eclampsia.[70] Furthermore, it is also in agreement with a recent randomized trial that showed a lower incidence of hypertensive complications with low-dose aspirin given throughout in vitro fertilization treatment and the first trimester of pregnancy in infertile women.[71] The novelty of our study resides in subgroup analysis according to gestational age at the initiation of therapy. In a previous meta-analysis, Duley et al reported no significant difference in the incidence of preeclampsia with low-dose aspirin in women recruited in studies where mean gestational age at randomization was less than 20 weeks compared with studies where mean gestational age at randomization was greater than 20 weeks.[68] In this scenario, the mean gestational age of women recruited in the less-than-20-week subgroup was most likely between 16 and 18 weeks. Taken together, these results suggest that: 1) women at moderate or high risk for preeclampsia benefit from daily low-dose aspirin for the prevention of preeclampsia and IUGR, and 2) the earlier low-dose aspirin is started in pregnancy, the greater the benefits. It remains unclear if there is a gestational age threshold beyond which low-dose aspirin becomes inefficient, and whether or not pursuing treatment until the end of pregnancy is beneficial.

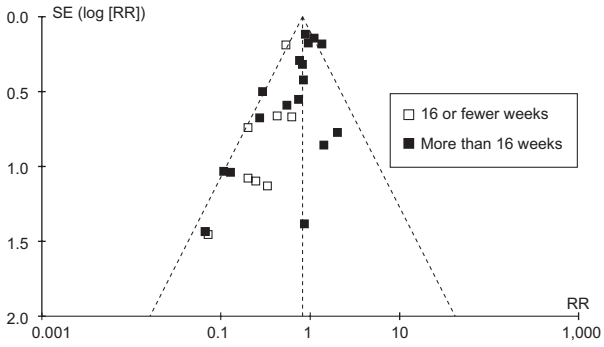

Fig. 4. Funnel plot of trials studying preeclampsia. Funnel plot of the risk ratio (RR) against its standard error (SE) (*empty square,* 16 weeks or fewer; *filled square,* more than 16 weeks). This visual evaluation of the funnel plot suggests the possibility of publication bias because small studies showing no benefits are missing, mainly in the 16 weeks or fewer subgroup (there is no study from the 16 weeks or fewer subgroup in the right lower quadrant of the graph). This finding is confirmed by the Egger test (16 weeks or fewer: $P=.03$; more than 16 weeks: $P=.06$).

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The limitations of our meta-analysis include the reduction of power by stratification of the population into subgroups. Such limitations could lead to false-negative results. We found that studies within the 16-week-or-less subgroups were mostly small studies, included only those women at moderate or high risk for preeclampsia, and were more likely to use higher doses of aspirin. However, the fact that we noted a stronger homogeneity in the subgroups (16 weeks or less and more than 16 weeks) suggests a definitive role for the gestational age at initiation of the treatment in the effects of low-dose aspirin in prevention of preeclampsia and IUGR. The very strong homogeneity in the results between studies included in the 16-weeks-or-less subgroup suggests a real effect in this specific subgroup of women. On the other hand the funnel plot and the sensitivity analysis suggest a potential publication bias.

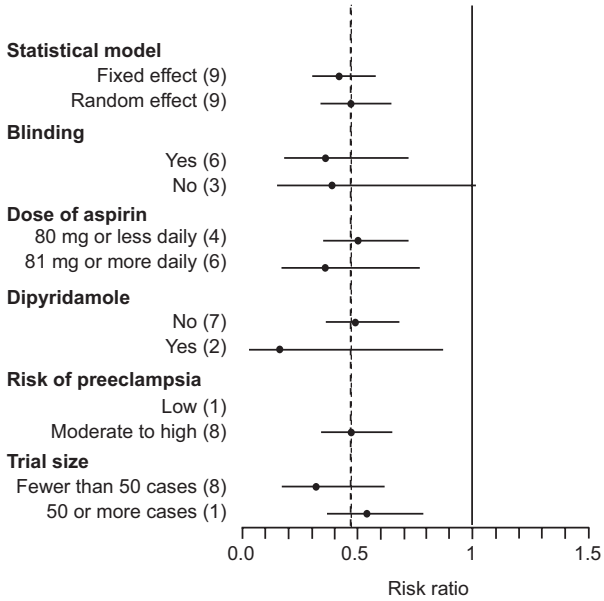

Fig. 5. Sensitivity analysis. The sensitivity analysis examines the robustness of the effect on preeclampsia of low-dose aspirin started at 16 weeks of gestation or before. The *dotted vertical line* corresponds to the combined risk ratio from the random effects model.

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The clinical implications of our results are important. A growing body of evidence suggests that a significant proportion of women at moderate or high risk for preeclampsia, and mainly early-onset preeclampsia, severe preeclampsia and IUGR, can be identified as early as the first trimester of pregnancy by a combination of factors, such as mean arterial blood pressure, body mass index, ethnicity, serum biomarkers and uterine artery Doppler.[72] Moreover, recent data indicate that 3-dimensional analysis of first-trimester placenta could also predict very early placental insufficiency.[73,74] Therefore, we hypothesized that it is possible to identify women at moderate or high risk for preeclampsia or IUGR or both and to prevent these outcomes with low-dose aspirin started in early pregnancy. Issues that should be considered in future randomized trials should include the optimal dose of aspirin or platelet aggregation tests for dosage adjustments.[75,76] Moreover, with the recent publication of a randomized controlled trial showing that low-molecular weight heparin can also decrease the recurrence of severe preeclampsia, future studies should compare low-dose aspirin to heparin in high-risk populations.[77]

Based on the results of this review, current evidence indicates that low-dose aspirin started in early pregnancy may reduce the incidence of preeclampsia, IUGR and preterm birth in women identified at moderate or high risk for preeclampsia. Of note, because most studies in the 16-weeks-or-less subgroup were small and included women at high risk for preeclampsia, and because we found a potential publication bias, we believe that a large randomized controlled trial should be carrying out to validate our results. With the development of better tools to spot women at high risk for preeclampsia, it will become possible to perform randomized trials combining the tracking of high-risk women early in pregnancy and

the prevention of preeclampsia and IUGR with low-dose aspirin in early pregnancy.

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