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LOW-DOSE ASPIRIN TO PREVENT PREECLAMPSIA IN WOMEN AT HIGH RISK

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ABSTRACT

Background Whether low-dose aspirin prevents preeclampsia is unclear. It is not recommended as prophylaxis in women at low risk for preeclampsia but may reduce the incidence of the disease in women at high risk.

Methods We conducted a double-blind, randomized, placebo-controlled trial in four groups of pregnant women at high risk for preeclampsia, including 471 women with pregestational insulin-treated diabetes mellitus, 774 women with chronic hypertension, 688 women with multifetal gestations, and 606 women who had had preeclampsia during a previous pregnancy. The women were enrolled between gestational weeks 13 and 26 and received either 60 mg of aspirin or placebo daily.

Results Outcome data were obtained on all but 36 of the 2539 women who entered the study. The incidence of preeclampsia was similar in the 1254 women in the aspirin group and the 1249 women in the placebo group (aspirin, 18 percent; placebo, 20 percent; $P=0.23$). The incidences in the aspirin and placebo groups for each of the four high-risk categories were also similar: for women with pregestational diabetes mellitus, the incidence was 18 percent in the aspirin group and 22 percent in the placebo group ($P=0.38$); for women with chronic hypertension, 26 percent and 25 percent ($P=0.66$); for those with multifetal gestations, 12 percent and 16 percent ($P=0.10$); and for those with preeclampsia during a previous pregnancy, 17 percent and 19 percent ($P=0.47$). In addition, the incidences of perinatal death, preterm birth, and infants small for gestational age were similar in the aspirin and placebo groups.

Conclusions In our study, low-dose aspirin did not reduce the incidence of preeclampsia significantly or improve perinatal outcomes in pregnant women at high risk for preeclampsia. (*N Engl J Med* 1998; 338:701-5.)

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PROPHYLAXIS with low-dose aspirin has been recommended to prevent preeclampsia, the rationale being that hypertension and abnormalities of coagulation in this disease are caused in part by an imbalance between vasodilating and vasoconstricting prostaglandins. Low-dose aspirin therapy inhibits thromboxane production more than prostacyclin production and therefore should protect against vasoconstriction and pathologic blood coagulation in the placenta. Initially, several single-center trials, mostly among women at increased risk for preeclampsia, demonstrated a substantial reduction in the risk of proteinuric hypertension as well as reductions in the incidences of preterm birth, infants small for gestational age, and perinatal death.¹⁻⁵ These reports led to the widespread use of prophylactic aspirin to prevent preeclampsia. Subsequently, several larger trials revealed no beneficial effects of aspirin.⁶⁻¹¹ Although the women in these large trials were thought to be at increased risk for preeclampsia, it developed in only 2.5 percent to 7.6 percent of the women who

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*The members of the network are listed in the Appendix.

received placebo. Therefore, the failure of the large trials to detect any major effects of low-dose aspirin may in fact have been due to the inclusion of women at low risk for preeclampsia.¹²

We therefore designed a double-blind, randomized, placebo-controlled trial to determine whether aspirin therapy reduces the incidence of preeclampsia in women at increased risk for the disease.

METHODS

Study Subjects

We screened 6941 pregnant women at 13 centers for entry into the study. Among them we identified 2539 women who qualified for entry into one of four high-risk groups: women with pregestational, insulin-treated diabetes mellitus, women with chronic hypertension, women with multifetal gestations, and women who had had preeclampsia in a previous pregnancy. The diagnosis of chronic hypertension required documentation of antihypertensive-drug therapy by medical records or a blood pressure while sitting of 140/90 mm Hg or higher taken on two occasions at least four hours apart, either before pregnancy or during pregnancy but before entry into the study. Multifetal gestation was documented by ultrasound examination before enrollment. Previous preeclampsia was defined as new-onset proteinuric hypertension as determined by medical records or, in the absence of a record, an oral history of preeclampsia that resulted in delivery before the 37th gestational week. At the screening visit, all the women underwent urinary-protein testing by dipstick. If the test was 1+ or greater, a 24-hour urine sample was collected; women with values of ≥ 300 mg of protein per 24 hours were considered to have proteinuria. Women with multifetal gestations were ineligible for the study if they also had diabetes mellitus, chronic hypertension, or proteinuria as defined above, as were women with a history of preeclampsia and current proteinuria. Women with both diabetes and hypertension were included in the diabetes group. The protocol was approved by the institutional review board at each center, and all the women gave written informed consent.

Protocol

Eligible women were enrolled between the 13th and 26th week of pregnancy. They were given a package containing 10 placebo tablets, which they were to take once daily, and were asked to return in one week. The women who took at least five tablets were randomly assigned according to risk group to receive 60 mg of aspirin or a lactose-containing placebo tablet identical in appearance to the aspirin tablet (both prepared by Sterling Winthrop, New York) once daily. The aspirin and placebo packets were prepared and labeled at a central location with the use of a computer-generated permuted-block randomization sequence stratified according to clinical center and risk group. The packets were shipped to the 13 clinical centers, each woman receiving the next labeled packet.

The women were instructed to continue taking the tablets until delivery but to discontinue the medication if told that preeclampsia had developed. They also received a list of aspirin-containing products to be avoided and acetaminophen if they needed an analgesic drug. Their prenatal care was dictated by the standard schedule at each participating center. Visits usually occurred every 4 weeks until the 28th week of pregnancy, every 2 weeks from then until the 36th week, and then weekly until delivery. Weight, qualitative urinary protein excretion (measured by dipstick), and blood pressure were measured at each visit. Blood pressure was measured with the woman seated quietly; the fifth Korotkoff sound was used to determine diastolic blood pressure. If the result of a qualitative protein test was 2+ or more, a 24-hour urine sample was usually collected to measure protein excretion. Compliance was determined by direct questioning and by tablet

counts. In addition, a research nurse contacted the women periodically to survey and reinforce compliance.

Outcome Variables

The primary outcome variable was preeclampsia, defined in the women who did not have hypertension or proteinuria at base line as the development of hypertension plus one of the following: proteinuria, thrombocytopenia, or pulmonary edema. Hypertension was defined as either a systolic blood pressure ≥ 140 mm Hg or a diastolic blood pressure ≥ 90 mm Hg on two occasions at least four hours apart. Proteinuria was defined as excretion of 300 mg of protein in a 24-hour urine collection, or two dipstick-test results of $\geq 2+$ (≥ 100 mg per deciliter), the values recorded at least 4 hours apart, with no evidence of urinary tract infection. Thrombocytopenia was defined as a platelet count of less than 100,000 per cubic millimeter.

In women who had normal blood pressure but proteinuria at base line, the diagnosis of preeclampsia required the presence of thrombocytopenia, a serum aspartate aminotransferase concentration of ≥ 70 U per liter, or hypertension accompanied by either severe headaches, epigastric pain, or a sudden increase in proteinuria (either five times the base-line value or twice base line if the base-line value exceeded 5 g per 24 hours). In the women who had hypertension but no proteinuria at base line, a diagnosis of preeclampsia required the development of proteinuria or thrombocytopenia. In the women who had both hypertension and proteinuria at base line, the diagnosis of preeclampsia required any one of the following: thrombocytopenia, an elevated serum concentration of aspartate aminotransferase (≥ 70 U per liter), or worsening hypertension (as shown by two diastolic readings ≥ 110 mm Hg taken four hours apart in the week before delivery) combined with either exacerbation of proteinuria (see above), severe headaches, or epigastric pain.

A woman was deemed to have preeclampsia if she had an eclamptic convulsion or the HELLP syndrome, defined as hemolysis (serum total bilirubin concentration, ≥ 1.2 mg per deciliter [$20 \mu\text{mol}$ per liter]), a serum lactate dehydrogenase concentration of ≥ 600 U per liter, or hemolytic anemia as determined by peripheral smear), elevated serum concentration of aspartate aminotransferase (≥ 70 U per liter), and thrombocytopenia.

To ensure consistency in the diagnosis of preeclampsia, the records of all the women with apparent preeclampsia, worsening hypertension, new-onset proteinuria, or proteinuria at base line of 1+ or more were reviewed independently by three physicians unaware of the treatment-group assignments. They had to agree unanimously on the validity of the designated outcomes. Forty-three percent (1089) of the women's charts were reviewed in this way.

Secondary outcome variables included abruptio placentae, preterm birth, infants small for gestational age, neonatal intraventricular hemorrhage, postpartum hemorrhage, and neonatal bleeding. An infant was considered small for gestational age if its weight was below the 10th percentile of normative birth weights for singletons¹³ and twins.¹⁴ Preterm birth was defined as delivery before the completion of 37 weeks' gestation. Intraventricular hemorrhage was defined according to ultrasound criteria¹⁵; all films that suggested intraventricular hemorrhage as well as an equal number of films considered normal were reviewed in a blinded fashion by two radiologists. Abruptio placentae was diagnosed according to clinical criteria (vaginal bleeding and uterine tenderness) and examination of the placenta. The medical records of all the women with suspected abruption were reviewed by two physician members of the protocol committee who had no knowledge of the treatment assignments.

Statistical Analysis

Comparisons of the aspirin and placebo groups were performed with the use of chi-square tests, Fisher's exact tests, Wilcoxon rank-sum tests, or Mantel-Haenszel tests. Overall relative-risk estimates were calculated with stratification according to risk group.

An overall sample size of 2600 was chosen to allow us to detect

a reduction of 50 percent in the incidence of preeclampsia within each of the four risk groups separately, with a type I error of 0.05, two-sided, and 80 percent power.

RESULTS

Of the 2539 women enrolled in the study between May 1, 1991, and June 30, 1995, 1273 were assigned to the aspirin group and 1266 to the placebo group. Outcome data could not be obtained on 19 women in the aspirin group and on 17 in the placebo group. All the women with outcome data were included in the treatment group to which they were assigned. The base-line characteristics of the women and the distribution according to risk group are shown in Table 1. Within each risk group, there were no significant differences between the aspirin and placebo groups. Thirteen percent of the women with diabetes had vascular disease, and 79 percent of the women with chronic hypertension were taking antihypertensive drugs at base line.

The effect of aspirin on the incidence of preeclampsia according to the risk category and status at the time of entry is shown in Table 2. The incidence of preeclampsia was similar in the aspirin and placebo groups, both within each risk group and in the aggregate. This absence of a difference between the aspirin and placebo groups, within each risk group and in the aggregate, persisted even when the criterion for proteinuria was changed from 300 to 500 mg of protein per 24 hours.

The effects of aspirin on the incidence of preeclampsia according to the characteristics at base line, specifically the absence or presence of hypertension, proteinuria, or both, are also shown in Table 2. Regardless of status at entry, the incidence of pre-

eclampsia was similar in the aspirin and placebo groups. The effect of aspirin and placebo in several subgroups of women in whom antiplatelet treatment either has been reported to have a distinct benefit or might conceivably have a benefit is shown in Table 3.^{7,8} In none of these subgroups did aspirin significantly reduce the incidence of preeclampsia as compared with placebo. This conclusion pertains to the individual risk groups as well as to the aggregate group. There was also no significant effect of aspirin on the frequency of certain maternal and perinatal outcomes (Table 4).

The median numbers of tablets taken were 100 in the aspirin group and 99 in the placebo group, and only 2 percent of the women reported having taken other aspirin-containing medications. Compliance, measured on the basis of tablet counts and interviews, was high; 93 percent of the women in both groups took half or more of their pills, and 79 percent took at least 80 percent of the tablets. The incidence of preeclampsia did not differ significantly between the groups regardless of the percentage of tablets taken.

DISCUSSION

We found that low-dose aspirin did not prevent preeclampsia in pregnant women at risk for the disease. We limited our study to women whose risk of preeclampsia was known to be higher than that of the general population — i.e., women with pregestational insulin-treated diabetes mellitus, chronic hypertension, multifetal gestations, or preeclampsia during a previous pregnancy. Our approach seems to have been justified, because preeclampsia developed

TABLE 1. BASE-LINE CHARACTERISTICS OF THE WOMEN AT HIGH RISK FOR PREECLAMPSIA.*

CHARACTERISTIC	WOMEN WITH DIABETES (N=471)	WOMEN WITH CHRONIC HYPERTENSION (N=774)	WOMEN WITH MULTIFETAL GESTATIONS (N=688)	WOMEN WITH PREVIOUS PREECLAMPSIA (N=606)
Mean age (yr)	26±6	30±6	25±6	25±5
Mean wk of gestation at entry (wk)	18±4	20±4	22±4	20±4
Primigravida (%)	31	18	27	—
Race or ethnic group (%)				
Black	39	61	50	71
Hispanic	7	12	18	4
White	53	27	32	25
Other	1	1	0	0
Blood pressure (mm Hg)				
Systolic	114±14	128±15	110±11	112±11
Diastolic	69±11	78±12	63±9	66±10
Body-mass index†	28±7	33±9	27±7	28±8
Smoked during pregnancy (%)	22	17	14	15

*Plus-minus values are means ±SD.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

TABLE 2. EFFECT OF ASPIRIN ON THE INCIDENCE OF PREECLAMPSIA IN HIGH-RISK WOMEN ACCORDING TO RISK GROUP AND ENTRY STATUS.

VARIABLE	INCIDENCE OF PREECLAMPSIA		RELATIVE RISK (95% CONFIDENCE LIMITS)
	ASPIRIN	PLACEBO	
	percent		
Risk group			
Pregestational diabetes mellitus (n = 462)	18	22	0.9 (0.6, 1.2)
Hypertension (n = 763)	26	25	1.1 (0.8, 1.4)
Multifetal gestation (n = 678)	12	16	0.7 (0.5, 1.1)
Previous preeclampsia (n = 600)	17	19	0.9 (0.6, 1.2)
All groups (n = 2503)	18	20	0.9 (0.8, 1.1)
Entry status			
No proteinuria, no hypertension (n = 1613)	15	18	0.8 (0.7, 1.0)
Proteinuria, hypertension (n = 119)	32	22	1.4 (0.8, 2.6)
Proteinuria, no hypertension (n = 48)	25	33	0.8 (0.3, 1.8)
No proteinuria, hypertension (n = 723)	25	25	1.0 (0.8, 1.3)

TABLE 3. EFFECT OF ASPIRIN ON THE INCIDENCE OF PREECLAMPSIA IN HIGH-RISK WOMEN ACCORDING TO RISK FACTOR.

Risk Factor	INCIDENCE OF PREECLAMPSIA		RELATIVE RISK (95% CONFIDENCE LIMITS)
	ASPIRIN	PLACEBO	
	percent		
Week of gestation at entry			
<20 (n = 1214)	20	22	0.9 (0.8, 1.2)
≥20 (n = 1289)	17	19	0.9 (0.7, 1.1)
Week of gestation at delivery			
<32 (n = 279)	29	20	1.4 (0.9, 2.2)
≥32 (n = 2224)	17	20	0.9 (0.7, 1.0)
Systolic blood pressure at entry*			
<120 mm Hg (n = 1151)	11	14	0.8 (0.6, 1.1)
120–134 mm Hg (n = 435)	22	26	0.8 (0.6, 1.2)
Parity			
Nullipara (n = 668)	25	27	0.9 (0.7, 1.2)
Para (n = 1835)	16	18	0.9 (0.7, 1.1)
Race			
White (n = 814)	18	22	0.8 (0.6, 1.1)
Nonwhite (n = 1689)	18	20	0.9 (0.8, 1.2)

*Excludes women with hypertension at base line.

in 20 percent of the women in the placebo group. Aspirin was ineffective in preventing preeclampsia in all four risk groups, regardless of parity, race, base-line blood pressure, gestational age at base line or delivery, or degree of compliance. Our data also demonstrate that aspirin prophylaxis had no effect on the incidence of preterm birth, infants small for gestational age, or perinatal death. On a positive note, aspirin prophylaxis was not associated with ad-

TABLE 4. MATERNAL AND PERINATAL OUTCOMES IN THE ASPIRIN AND PLACEBO GROUPS.

OUTCOME	INCIDENCE		RELATIVE RISK (95% CONFIDENCE LIMITS)
	ASPIRIN (N = 1254)	PLACEBO (N = 1249)	
	percent		
Postpartum hemorrhage	6	6	0.9 (0.7, 1.3)
Abruptio placentae	1	2	0.7 (0.4, 1.3)
Preterm delivery	40	43	0.9 (0.9, 1.0)
Infant small for gestational age	10	9	1.2 (0.9, 1.5)
Perinatal death	3	5	0.8 (0.5, 1.1)
Neonatal intraventricular hemorrhage	2	1	1.5 (0.8, 2.8)

verse consequences to either the mothers or the neonates, there being no evidence of any increase in abruptio placentae, postpartum hemorrhage, or neonatal intraventricular hemorrhage. Despite the large number of women studied, a small aspirin effect leading to a reduced incidence of preeclampsia might still have been present. Similarly, we cannot exclude the possibility of some small adverse effect of aspirin.

The effect of antiplatelet therapy on the incidences of preeclampsia, preterm birth, and perinatal death in the more than 28,000 women in this and other trials of preeclampsia prevention is shown in Table 5.^{9-11,16,17} A disparity between the small trials (less than 200 women) and the large trials (200 or more women) is evident. Antiplatelet therapy was associated with a reduction of 82 percent (from 17.6 to 3.1 percent) in the risk of preeclampsia in the small trials but with a reduction of only 9 percent (from 7.5 to 6.8 percent) in the large trials. What might account for these differences? One possibility is publication bias, because small trials with positive findings are more likely to be submitted and published than are small trials with ambiguous or negative findings.¹⁸ The results of this and other large trials tend to support this possibility. When the large and small trials are combined, aspirin is found to have reduced the incidence of preeclampsia by 13 percent (6.7 percent vs. 7.7 percent), a difference that is statistically significant but of questionable clinical importance, because 100 women would have to be treated to prevent one case of preeclampsia. Even in the high-prevalence groups we studied (incidence of preeclampsia, 20.3 percent), 38 women would have to be treated to prevent one case of preeclampsia — a benefit that we believe is too small to justify routine use of aspirin prophylaxis. The cumulative results indicate that antiplatelet therapy also does not reduce the incidence of perinatal death,

TABLE 5. RESULTS OF PREECLAMPSIA-PREVENTION TRIALS.

OUTCOME	INCIDENCE		RELATIVE RISK (95% CONFIDENCE LIMITS)
	ASPIRIN	PLACEBO	
	no./no. at risk (%)		
Preeclampsia			
Small trials*	10/319	50/284	0.2 (0.1, 0.4)
Large trials†	949/13,928	1032/13,765	0.9 (0.8, 1.0)
Total	959/14,247 (6.7)	1082/14,049 (7.7)	0.9 (0.8, 1.0)
Preterm delivery	2404/13,729 (17.5)	2540/13,645 (18.6)	0.9 (0.9, 1.0)
Perinatal death	418/14,407 (2.9)	450/14,253 (3.2)	0.9 (0.8, 1.0)

*Data are from Viinikka et al.¹⁶ and Collins.¹⁷

†Data are from the Estudo Colaborativo para Prevenção da Pré-eclampsia com Aspirina,⁹ Rotchell et al.,¹⁰ Golding,¹¹ and Collins.¹⁷

but it is associated with a reduction in the incidence of preterm birth (from 18.6 to 17.5 percent). Although statistically significant, the clinical importance of this reduction is also debatable.

In summary, low-dose aspirin did not reduce the incidence of preeclampsia in women with pregestational insulin-treated diabetes mellitus, chronic hypertension, multifetal gestations, or a history of preeclampsia. It also did not significantly reduce the incidence of perinatal death, preterm birth, or small-for-gestational-age infants. However, aspirin did not affect the mothers or neonates adversely. We conclude that aspirin should not be given to prevent preeclampsia in women with pregestational insulin-treated diabetes, chronic hypertension, multifetal gestation, or preeclampsia in a previous pregnancy.

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APPENDIX

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REFERENCES

1. Beaufils M, Uzan S, Donsimoni R, Colau JC. Prevention of pre-eclampsia by early antiplatelet therapy. *Lancet* 1985;1:840-2.
2. Wallenburg HCS, 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.
3. Schiff E, Peleg E, Goldenberg M, et al. 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;321:351-6.
4. Uzan S, Beaufils M, Breart G, Bazin B, Capitant C, Paris J. Prevention of fetal growth retardation with low-dose aspirin: findings of the EPREDA trial. *Lancet* 1991;337:1427-31.
5. Hautz JC, Goldenberg RL, Parker CR Jr, et al. Low-dose aspirin therapy to prevent preeclampsia. *Am J Obstet Gynecol* 1993;168:1083-91.
6. Italian Study of Aspirin in Pregnancy. Low-dose aspirin in prevention and treatment of intrauterine growth retardation and pregnancy-induced hypertension. *Lancet* 1993;341:396-400.
7. Sibai BM, Caritis SN, Thom E, et al. Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. *N Engl J Med* 1993;329:1213-8.
8. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. *Lancet* 1994;343:619-29.
9. ECPPA (Estudo Colaborativo para Prevenção da Pré-eclampsia com Aspirina) Collaborative Group. ECPPA: randomised trial of low dose aspirin for the prevention of maternal and fetal complications in high risk pregnant women. *Br J Obstet Gynaecol* 1996;103:39-47.
10. Rotchell YE, Cruickshank JK, Phillips-Gay M, et al. Barbados Low-dose Aspirin Study in Pregnancy (BLASP): a randomised trial for the prevention of pre-eclampsia and its complications. *Br J Obstet Gynaecol* (in press).
11. Golding J. A randomised trial of low dose aspirin for primiparae in pregnancy. *Br J Obstet Gynaecol* (in press).
12. Grant J. Multicentre trials in obstetrics and gynaecology: smaller explanatory trials are required. *Br J Obstet Gynaecol* 1996;103:599-602.
13. Brenner WE, Edelman DA, Hendricks CH. A standard of fetal growth for the United States of America. *Am J Obstet Gynecol* 1976;126:555-64.
14. Naeye RL, Benirschke K, Hagstrom JW, Marcus CC. Intrauterine growth of twins as estimated from liveborn birth-weight data. *Pediatrics* 1966;37:409-16.
15. Intracranial hemorrhage: germinal matrix — intraventricular hemorrhage of the premature infant. In: Volpe JJ. *Neurology of the newborn*. 3rd ed. Philadelphia: W.B. Saunders, 1995:403-63.
16. Viinikka L, Hartikainen-Sorri AL, Lumme R, Hiilesmaa V, Ylikorkala O. Low dose aspirin in hypertensive pregnant women: effect on pregnancy outcome and prostacyclin-thromboxane balance in mother and newborn. *Br J Obstet Gynaecol* 1993;100:809-15.
17. Collins R. Antiplatelet agents for IUGR and preeclampsia. Revised May 4, 1994. In: Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C, eds. *Pregnancy and childbirth module*. In: *The Cochrane pregnancy and childbirth database: the Cochrane Collaboration*, issue 2. Oxford, England: Update Software, 1995 (software).
18. Pipkin B, Crowther C, de Swiet M, et al. Where next for prophylaxis against pre-eclampsia? *Br J Obstet Gynaecol* 1996;103:603-7.