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ORIGINAL ARTICLES

Prevention of fetal growth retardation with low-dose aspirin: findings of the EPREDA trial

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The efficacy of low-dose aspirin in preventing fetal growth retardation was tested in a randomised, placebo-controlled, double-blind trial. A secondary aim was to find out whether dipyridamole improves the efficacy of aspirin. 323 women at 15–18 weeks' amenorrhoea were selected at twenty-five participating centres on the basis of fetal growth retardation and/or fetal death or abruptio placentae in at least one previous pregnancy. They were randomly allocated to groups receiving placebo, 150 mg/day aspirin, or 150 mg/day aspirin plus 225 mg/day dipyridamole, for the remainder of the pregnancy. In the first phase of the trial all actively treated patients (n=156) were compared with the placebo group (n=73). Mean birthweight was significantly higher in the treated than in the placebo group (2751 [SD 670] *vs* 2526 [848] g; difference 225 g [95% CI 129–321 g], p=0·029) and the frequency of fetal growth retardation in the placebo group was twice that in the treated group (19 [26%] *vs* 20 [13%]; p<0·02). The frequencies of stillbirth (4 [5%] *vs* 2 [1%]) and abruptio placentae (6 [8%] *vs* 7 [5%]) were also higher in the placebo than in the treated group. The benefits of aspirin treatment were greater in patients with two or more previous poor outcomes than in those with only one. In the second analysis, of aspirin only (n=127) *vs* aspirin plus dipyridamole (n=119), no significant differences were found. There was no excess of maternal or neonatal side-effects in the aspirin-treated patients.

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Introduction

Fetal growth retardation remains a substantial cause of fetal and neonatal mortality. It is commonly associated with pre-eclampsia, but it can occur without any maternal hypertension or proteinuria. Fetal growth retardation is related to chronic fetal hypoperfusion, in most cases due to placental dysfunction. Pathophysiological studies have concentrated on pre-eclampsia, which appears more and more clearly to be an early disease of the trophoblast,[1,2] characterised by early maladaptation of spiral arteries, endothelial injury, and secondary thrombosis. An imbalance of prostacyclin/thromboxane production by various tissues is also a characteristic of the disease.[3] The same defective placentation is found in pre-eclampsia and in "idiopathic" fetal growth retardation,[4] which suggests a common pathogenesis and pathophysiology.

In our pilot randomised trial of early low-dose aspirin and dipyridamole in 100 women on the basis of poor previous obstetric history,[5] patients who received the drugs had significantly less pre-eclampsia and fewer severe outcomes (fetal death, small-for-gestational age babies, and abruptio placentae) than those who did not. Several studies (with aspirin only) tended to confirm this beneficial effect;[6–10] they were all, however, small studies.

We undertook a second study, called EPREDA (Essai Pre-eclampsie Dipyridamole Aspirine). Its aims were to ascertain the efficacy of treatment by means of a larger sample in a multicentre trial with improved methods, to determine whether dipyridamole improves the efficacy of aspirin, and to see if patients with different estimated levels of risk (based on past obstetric history) respond differently to treatment.

Patients and methods

Twenty-five centres took part between 1985 and 1989 in this randomised, placebo-controlled trial. The coordinating committee wrote this report. An advisory committee of independent experts in coagulation, obstetrics, or paediatrics carried out a survey of the trial independent of the coordinating committee to give technical and/or ethical advice. The protocol was approved by the ethics committee of CHU Saint Antoine, Paris.

Criteria for inclusion of patients were: a poor outcome during the two previous pregnancies, at least one being fetal growth retardation,

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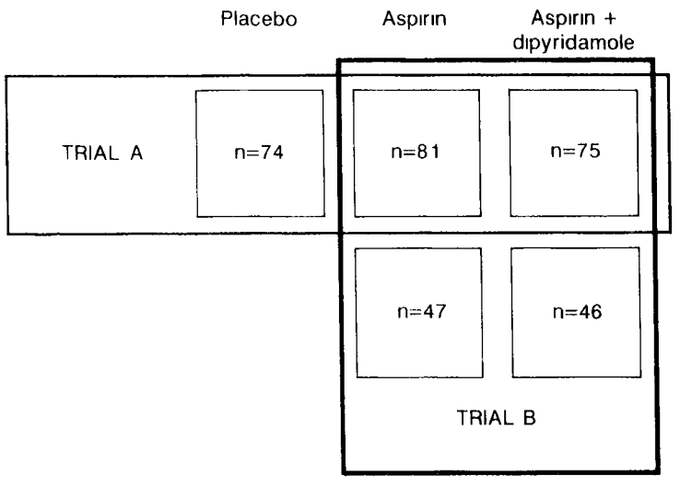

Design of patient inclusions and analysis for trials A and B.

or fetal growth retardation during the one preceding pregnancy; 15–18 weeks since the last menstrual period; and delivery in a trial centre. Poor outcomes were defined as either severe fetal growth retardation (below 10th percentile of Lubchenco et al[11]), fetal death, or abruptio placentae.

Exclusion criteria were twin pregnancy, uterine malformation, renal disease, secondary hypertension, any disorder which could have a specific effect on pregnancy outcome (diabetes, cardiac disease, systemic lupus erythematosus); early fetal death (before 24 weeks) or fetal death of known or probable cause (traumatic, cord abnormality, malformation) in a previous pregnancy; contraindication to use of aspirin or dipyridamole, and current use of anti-inflammatory drugs or anticoagulants.

Patients were first evaluated in the antenatal clinics before 18 weeks of amenorrhea. After giving informed consent, those who met the inclusion criteria were randomly allocated to one of the treatment or placebo groups. Whatever group, all patients ingested three tablets per day, and all were instructed not to take any aspirin-containing compound. They were followed by the same physician, and clinical and biological assessments were done at least monthly. Frequency of ultrasound and doppler assessments depended upon the physician's habits, as did other investigations, such as plasma volume measurement. Birthweights were classified as percentiles for term according to Lubchenco et al.[11] Each baby was evaluated at birth and on hospital discharge by a paediatrician.

The study was divided into two double-blind trials (figure). Trial A was designed to assess the efficacy of treatment compared with placebo, and trial B to test for a difference between two treatment regimens. Therefore, the survey was conducted in two phases: in the first phase there were three groups—placebo, aspirin (150 mg/day), and aspirin (150 mg/day) plus dipyridamole (225 mg/day). There was no placebo group in the second phase. No intermediate analysis was done, and the last patient in trial A delivered her baby about the time the last patient was included in the second phase.

The patients were stratified by centre and by whether they had one or two previous poor outcomes. The randomisation was balanced every 3 subjects for the first phase, every 2 subjects for the second. The randomisation by centre allowed the ratio between treated and placebo patients to be the same in each centre, and precluded a bias introduced by centre differences. The primary endpoint was birthweight. Secondary endpoints were the incidence of poor outcomes defined as above, and evolution of blood pressure and proteinuria.

All patients for whom the endpoint was known were included in the analysis, even if treatment was withdrawn. The two trials were analysed separately. The difference between placebo and the pooled therapeutic groups was assessed for patients included during the first phase (trial A). Subsequently, the active treatment groups were compared with each other for patients included in both phases (trial B). Thus, patients receiving active treatment during the first phase were included in both analyses (figure).

From the results of our previous study,[5] the sample necessary to observe a 250 g difference in birthweight between treatment and placebo groups was 225 patients (75 in each group) with a type I (false-positive) and type II (false-negative) error risk of 0·05. The calculated sample for a 175 g difference in birthweight between treatments was 80 patients more (40 per group). Thus, a total of 305 patients was needed. Differences were assessed by Student's t test for quantitative data, and chi-square tests for qualitative data. The 95% confidence intervals for frequency differences were computed from the formula:

$$95\%\ CI = \Delta \pm \Sigma_{\alpha}\sqrt{\frac{pq}{n_a} + \frac{pq}{n_b}}$$

Results

323 patients entered the study, 230 in the first phase, 93 in the second. The endpoint is not known for 5 patients (3 spontaneous abortions before 20 weeks, 1 therapeutic abortion because of ultrasonographically diagnosed malformations, and 1 lost to follow-up). Treatment was withdrawn from 22 patients. The reasons for withdrawal were: adverse effects in 9 cases (2 placebo, 3 aspirin, 4 combination), patient's decision without defined reason in 11 cases; patient moving (1 case); and discovery of a circulating anticoagulant after inclusion (1 case). 8 patients included did not completely satisfy the inclusion criteria (6 would have been excluded for obstetric and 2 for non-obstetric reasons). 5 patients were misclassified for the number of previous poor outcomes in either direction. Thus, 284 patients (88%) strictly conformed with the requirements of the protocol. Since there were no major inclusion errors, all patients whose endpoint was known were considered eligible for analysis.

Trial A: treatment vs *placebo*

The study groups were comparable for ethnic origin, social and professional status, parity (average 2·2 to 2·4), and other characteristics (table I). A detailed analysis of the number and nature of previous poor outcomes (not shown) revealed no differences between the groups.

The effect of treatment on the primary endpoint (birthweight) is shown in table II. The mean birthweight was significantly higher in the treated group (difference 225 g [95% CI 129–321 g]; $p = 0·029$). The difference between placebo and treated groups' mean birthweight was greater for boys than for girls (277 [183–371] *vs* 146 [21–271] g).

High blood pressure was slightly more common in the placebo group than in the treated group, but the difference was not significant. Proteinuria was significantly more common in the placebo group ($p < 0·02$). The frequency of poor outcomes in the treated group was about half that in the placebo group and most of the difference was due to the different rates of fetal growth retardation. Frequencies of fetal death and abruptio placentae were also lower in the treated group but the numbers were small. The mean duration of pregnancy was 6 days longer in the treated group than in the placebo group ($p = 0·05$).

TABLE I—PATIENTS' CHARACTERISTICS AT ENTRY

	Mean (SD) or No *(%)*	
—	Placebo (n=73)	Treated (n=156)
Age (yr)	28·8 (4·6)	29·7 (4·3)
Body weight (kg)	57·9 (8·3)	59·6 (11·0)
Height (cm)	161 (7)	160 (6)
Gestational age (days)	114 (14)	114 (10)
No (%) with SBP >140 mm Hg	6 *(8%)*	9 *(6%)*
No (%) with DBP >90 mm Hg	1 *(1%)*	6 *(4%)*

SBP and DBP = systolic and diastolic blood pressure.

The only significant difference between the groups for other biological variables was in the frequency of proteinuria ($p < 0.02$).

All 6 stillbirths occurred before 30 weeks' gestation (25–29 weeks) and all were severely growth-retarded babies (birthweight 360–985 g). Maternal diastolic blood pressure at this time ranged between 70 mm Hg and 100 mm Hg; only 1 had proteinuria (0·35 g/l).

There was 1 maternal death, in an aspirin-treated patient. 1 month before delivery, she was lost to follow-up. We found out later that she had abandoned the aspirin treatment and decided to attend a private clinic. She died there at the induction of anaesthesia for caesarean section. A live baby was delivered; there was no abnormal bleeding. The presumed cause of death was embolisation of amniotic fluid.

The benefit of treatment was greatest in patients with two or more previous poor outcomes. The gain in birthweight with treatment was 156 g (95% CI 55–257 g) for patients with one previous poor outcome and 346 g (152–539 g) for those with two or more poor outcomes. The treatment-placebo difference in the frequency of any poor outcome was 10% (26% − 16%; not significant) in patients with one previous poor outcome and 20% (46% − 16%; $p < 0.01$) for patients with two or more. In the patients with two or more poor outcomes there was also a significant difference between treated and placebo groups for fetal growth retardation (42% *vs* 13%; $p < 0.01$) and a borderline significant difference for stillbirth and abruptio placentae (12% *vs* 2%; $p = 0.054$).

The frequencies of unfavourable features of the babies at birth and during the first days of life were all slightly lower in the treated than in the placebo group, but no difference reached statistical significance (table II).

There were 7 neonatal deaths. 5 of these babies were born after 27 to 30 weeks' gestation: 4 were also growth retarded;

TABLE II—OUTCOME OF PREGNANCIES IN TRIAL A

—	No *(%)* or mean (SD)		95% CI for difference
	Placebo (n=73)	Treated (n=156)	
Mean (SD) birthweight (g)			
All babies	2526 (848)	2751 (670)	129, 321
Boys	2583 (768)	2860 (312)	183, 371
Girls	2510 (910)	2656 (521)	21, 271
SBP > 140 mm Hg	25 *(34%)*	40 *(26%)*	−3·9, 21
DBP > 90 mm Hg	25 *(34%)*	35 *(22%)*	−0·4, 24
Proteinuria	8 *(11%)*	5 *(3%)*	1·4, 14
Serum uric acid > 350 μmol/l	15 *(21%)*	17 *(11%)*	0·01, 19·3
Platelet count < 150 × 10⁹/l	7 *(10%)*	11 *(7%)*	−4·9, 10·0
Poor outcomes			
Any	24 *(33%)*	25 *(16%)*	5·6, 28
FGR	19 *(26%)*	20 *(13%)*	2·8, 23
Stillbirth	4 *(5%)*	2 *(1%)*	−0·2, 9·0
Abruptio placentae	6 *(8%)*	7 *(5%)*	−2·7, 10
CS before 34 wk	7 *(10%)*	11 *(7%)*	−4·9, 10
Mean (SD) duration (days)	258 (27)	264 (19)	3·1, 8·6

FGR = fetal growth retardation; CS = caesarean section.

TABLE III—PRINCIPAL EVENTS IN NEONATAL PERIOD, TRIAL A

—	No *(%)*	
	Placebo	Treated
Live babies	69	154
Apgar <7 at 5 min	6 *(9%)*	5 *(3%)*
Primary transfer in ICU	17 *(25%)*	29 *(19%)*
Secondary transfer	7 *(10%)*	12 *(8%)*
Artificial ventilation	10 *(15%)*	13 *(8%)*
Neonatal death	2 *(3%)*	5 *(2%)*
Mean (SD) duration hospital stay (days)	20 (24)	18 (24)

TABLE IV—OUTCOME OF PREGNANCIES IN TRIAL B

—	Aspirin (n=127)	Aspirin and dipyridamole (n=119)
Mean (SD)		
Birthweight (g)	2766 (614)	2763 (671)
Gestational age (days)	266 (18)	264 (18)
No (%) with poor outcomes		
Any	20 *(16%)*	20 *(17%)*
FGR	16 *(13%)*	17 *(14%)*
Stillbirth	1 *(1%)*	2 *(2%)*
Abruptio placentae	6 *(5%)*	3 *(3%)*

None of the differences was significant.

and 4 were born by caesarean section (2 abruptio placentae, 2 acute fetal distress on cardiotocogram). 1 baby, born at 38 weeks' gestation weighing 2800 g, died shortly after an operation for diaphragmatic hernia. The remaining death was in a 4060 g fetus during caesarean section for uterine rupture during labour at 40 weeks' gestation.

Trial B: comparison of treatments

In this trial, there were no significant differences between the aspirin alone and aspirin plus dipyridamole groups in age (30·4 [4·5] *vs* 29·6 [4·4] years), body weight (58·3 [9·4] *vs* 61·1 [12·0] kg), height (160 [7] *vs* 161 [6] cm), or gestational age (115 [11] *vs* 114 [12] days) at entry. 6% and 7%, respectively, had systolic blood pressure above 140 mm Hg (not significant) and 6% and 3%, respectively, a diastolic blood pressure above 90 mm Hg.

No difference was apparent between the treatment groups, for either main or secondary endpoints of the study. Similarly, the distributions of birthweights and gestational ages did not differ. Separate analysis for patients with one or two previous poor outcomes showed no differences. Frequencies of high blood pressure, proteinuria, serum uric acid over 350 μmol/l, and thrombocytopenia were similar in both groups.

1 more stillbirth occurred during this phase of the study. The mother received aspirin and dipyridamole, her highest diastolic blood pressure recorded was 80 mm Hg, and there had been no proteinuria. Fetal death occurred very near term; the baby weighed 2300 g.

Side-effects

The most frequent side-effect was headache; the incidence (7–15%) did not differ significantly between the groups. Minor side-effects, such as stomach-aches, were observed occasionally. Epistaxis and other minor bleeding occurred in 8 patients receiving aspirin and none on placebo, but the difference was not significant.

Unusually profuse bleeding during delivery or caesarean section and post-partum haemorrhage were no more frequent in the treated than in the placebo group. It is unlikely that the maternal death was related to aspirin treatment, which had been withdrawn 1 month previously. Among the babies, there was gastrointestinal bleeding in 1 in each group (placebo and treated). There were 2 cases of intraventricular haemorrhage in the placebo group. Minor bleeding disorders (petechiae, cephalhaematoma) were seen in similar frequency in both groups.

Discussion

The efficacy of aspirin in the prevention of arterial thrombosis has been known for many years.[12,13] Several studies have suggested that low-dose aspirin can prevent

pre-eclampsia and/or fetal growth retardation. In our open, randomised trial[5] we gave aspirin with dipyridamole, because of its possible potentiation of aspirin action, though its efficacy has been questioned.[14] There were significant reductions in the frequencies of pre-eclampsia, fetal growth retardation, and fetal death.[5] Other controlled[6-10] and uncontrolled[15-17] studies supported such an effect of aspirin. Meta-analysis of controlled studies shows a highly significant reduction of proteinuric pre-eclampsia and of fetal growth retardation (unpublished). However, these small trials used differing selection criteria and gave treatment at various gestational ages.

This study is the largest so far on this subject, since it included more than 300 patients. Inclusion criteria were based, as in our previous trial, on previous obstetric history, since this selection had proved to be efficient, and moreover afforded us the standard deviations allowing a calculation of the necessary sample. In this trial, stratification was done on the number of previous poor outcomes, which seemed to reflect the risk level, and emphasis was placed in the selection on fetal growth retardation, which was chosen as primary endpoint of the study. The results in the placebo group show clearly that this was indeed a high-risk population: the incidence of intrauterine growth retardation was 17% and 42% in patients with one or two previous poor outcomes, respectively, compared with about 3% in the French population. There were similar excesses of fetal death and abruptio placentae.

Trial A showed a beneficial effect of treatment on fetal weight. An increased duration of pregnancy was also observed. The distribution of fetal weights showed a significant reduction in the number of small-for-dates babies in the treated group. No significant reduction was found in the incidence of high blood pressure, but there was a significant reduction in that of proteinuric hypertension as already found in other studies.[5,6,9] The incidence of severe outcomes was also greatly reduced (more than halved) in the treatment group. The benefits of treatment were much greater in patients with the greater risk of recurrence. Trial B showed no difference between aspirin alone and aspirin plus dipyridamole. This finding could mean that dipyridamole, at the dose given here has little effect on platelet aggregation or that the observed effect of aspirin is due less to its effects on aggregation than to its action on vasoactive eicosanoids.

The effect of aspirin is linked to an action on prostaglandins. Low-dose aspirin greatly inhibits thromboxane production in human placental arteries in vitro, but has no effect on production of prostacyclin.[18,19] In vivo,[8,20] low-dose aspirin selectively reduces urinary excretion of thromboxane B_2, without changing that of 6-keto-prostaglandin $F_{1\alpha}$. Some studies[8,20] have found reductions in fetal thromboxane with aspirin, and others[21] have not. Sanchez-Ramos et al[22] reported a significant decrease in angiotensin II pressor responsiveness 2 h after ingestion of 80 mg acetylsalicylic acid by pregnant women in the third trimester. Spitz et al[23] showed that the same treatment greatly increased the pressor dose of angiotensin II, mirroring a reduction of thromboxane B_2, in pregnant patients with a positive angiotensin test.

Despite its potential benefits, aspirin use has been discouraged in pregnant women because of a possible risk of abnormal bleeding in the mother or the newborn infant, and because of some doubts about congenital defects in babies. Since no study of prevention of pre-eclampsia has given aspirin in the first trimester, and there is no reason to do so, the question of congenital defects is not relevant. In any case, aspirin does not increase the overall risk of malformations, and cardiac defects are not associated with aspirin use.[24] The risk of bleeding, especially in the infant, has been emphasised when mothers ingested high doses of acetylsalicylic acid.[25,26] No study of low-dose aspirin has reported abnormal bleeding in babies. Moreover, Sibai et al[21] showed good clinical and biological tolerance in babies whose mothers ingested 60–80 mg aspirin. Those infants also had patent ductus arteriosus and a normal right ventricular systolic time interval ratio. Thus, there is as yet no evidence of a definite risk associated with low-dose aspirin in pregnant women. However, data are still scarce and great caution remains necessary.

In conclusion, this study confirms the efficacy of early low-dose aspirin in preventing fetal growth retardation and maternal proteinuria. Its effects on fetal death and abruptio placentae have not been proved here, and would need to be tested by specific trials. Thus, it now seems justifiable to propose aspirin treatment for any patient considered at high risk, even if in her first pregnancy. On the other hand, massive use of aspirin by millions of pregnant women yearly certainly cannot be recommended. Early, reliable, and inexpensive markers of risk need to be found urgently. Although preliminary data are reassuring, only the very large scale clinical trials going on in several countries can prove the safety of aspirin. Meanwhile, indication and the benefit versus risk ratio should be weighed with great caution for each patient.

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Propranolol in prevention of recurrent bleeding from severe portal hypertensive gastropathy in cirrhosis

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The two main causes of gastrointestinal bleeding in cirrhosis are oesophageal varices and portal hypertensive gastropathy (PHG). Rebleeding from varices can be prevented by beta-blockers, but it is not clear whether these drugs effectively reduce rebleeding from PHG. 54 cirrhotic patients with acute or chronic bleeding from severe PHG took part in a randomised, controlled trial to investigate the efficacy of propranolol in prevention of rebleeding from PHG. 26 patients were randomised to receive propranolol daily at a dose that reduced the resting heart rate by 25% or to 55 bpm (20–160 mg twice daily), throughout mean follow-up of 21 (SD 11) months. 28 untreated controls were followed-up, with the same examinations, for 18 (13) months. The actuarial percentages of patients free of rebleeding from PHG were significantly higher in the propranolol-treated patients than in the untreated controls at 12 months (65% *vs* 38%; $p < 0.05$) and at 30 months of follow-up (52% *vs* 7%; $p < 0.05$). Propranolol-treated patients had fewer episodes of acute bleeding than controls (0·010 [0·004] *vs* 0·120 [0·040] per patient per month). Multivariate analysis showed that absence of propranolol treatment was the only predictive variable for rebleeding. Actuarial survival was slightly higher in the propranolol group than in the controls, but the difference was not significant. Thus, long-term propranolol treatment significantly reduces the frequency of rebleeding from severe PHG, and may improve the prognosis of cirrhotic patients with this disorder.

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Introduction

Portal hypertensive gastropathy (PHG) in patients with cirrhosis is histologically characterised by dilatation of the capillaries and veins of the gastric mucosa.[1-3] It is now accepted that this disorder includes several endoscopic lesions, ranging from a mucosal mosaic pattern or diffuse hyperaemia, which may indicate a mild gastropathy,[4] to multiple gastric red spots, which indicate severe vascular gastropathy. The pathogenesis is not completely understood, but high portal pressure, increased splanchnic blood flow, and local disturbances in vascular tone regulation are thought to be involved.[5-10]

Severe gastropathy probably accounts for most non-variceal bleeding episodes in patients with cirrhosis.[11,12] The treatment of this complication has been very unsatisfactory. The increased pressure and blood flow in the portal venous system can be modified by drugs reducing cardiac output and splanchnic blood flow, such as propranolol.[13] Such drugs have been used successfully to prevent bleeding from gastro-oesophageal varices.[14-16] Two open studies in cirrhotic patients bleeding from PHG suggested that propranolol may be an effective treatment for this lesion.[17,18] However, no randomised, controlled trial has been done to assess its efficacy in preventing bleeding from PHG.

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