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ASPIRIN VERSUS PLACEBO IN PREGNANCIES AT HIGH RISK FOR PRETERM PREECLAMPSIA

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Abstract:
Objective*: To compare the effects of Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia*
Design: *double-blind randomization, placebo-controlled trial*

Patient(s): *The study comprised a total of 121 singleton pregnant women with high risk of preterm preeclampsia*
Intervention(s): *start either aspirin 100 mg/day or placebo, which were continued until 35 weeks of gestation or delivery, whichever occurred first.*
Main Outcome Measure(s): *preterm preeclampsia*
Result(s): *Preterm preeclampsia occurred in 13 participants 1.5% in the aspirin group, as compared with 4.6% in the placebo group (odds ratio in the aspirin group, 0.38; 95% confidence interval, 0.20 to 0.74; P=0.004).*
Conclusion: *The administration of aspirin at a dose of 150 mg per day from 12 to 13 +6 weeks of gestation until delivery resulted in a significantly lower incidence of preterm preeclampsia than that with placebo.*
Key words: *aspirin, placebo, pregnancy, preterm preeclampsia.*

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INTRODUCTION:

Pre-eclampsia remains one of the most important challenges in obstetrics. The disorder affects 3–5% of pregnancies and is defined according to new-onset hypertension and proteinuria, which appear after 20 weeks of gestation. [1] it is a multisystem disease with adverse short-term and long-term outcomes to both the mother and the fetus. In total, pre-eclampsia and related complications account for 63 000 maternal deaths worldwide every year, 12% of all maternal deaths. [2] The onset and clinical course are unpredictable, and there is a strong need for tools to predict and prevent the disorder. The etiology of pre-eclampsia remains unknown, although placental dysfunction, which is due to early placental developmental abnormality, is central in the disease process. The early placental disease is followed months later by the clinical manifestations of pre-eclampsia, which reflect widespread endothelial dysfunction, resulting in vasoconstriction, end-organ ischemia and increased vascular permeability. [3] many of the proposed prediction and prevention strategies are based on processes involved in placental development in early pregnancy, although none of these has been established in clinical practice.

Antiplatelet agents, such as aspirin (acetylsalicylic acid), are among the most promising candidates for prevention of pre-eclampsia. They have a positive effect on the balance between prostacyclin, a vasodilator, and thromboxane, a vasoconstrictor and stimulant of platelet aggregation. This process plays a key role in the development of the disease and is believed to result from shallow placental invasion and ischemia that occur shortly after implantation. A recent meta-analysis, based on 27 trials on 31 678 women, concluded that aspirin is effective in preventing pre-eclampsia, although the effect was too modest to warrant routine use in all women.[4] However, if started early in pregnancy, in high-risk women, the treatment may be effective, [5,6] although studies are few and results are inconsistent. [7-9]

A recent multicenter placebo-controlled trial by Rolnick et al. has indicated that taking 150 mg aspirin nocte in women at high risk of pre-eclampsia reduced the prevalence of preterm pre-eclampsia in comparison with placebo from 4.3 to 1.5%. [10] This journal watch article discusses the paper in more detail as well as a separate subgroup analysis of the data, published by Poon et al., specifically assessing the benefit in certain patient groups. [11] Pre-eclampsia is a pregnancy-specific multisystem condition, associated with significant morbidity for both the mother and fetus. Delivery is currently the only definitive treatment; however, previous studies have indicated that its incidence can be reduced by 10% [12] –50% [13,14] by administration of prophylactic low-dose aspirin early in pregnancy to high-risk women. The maximum benefit of aspirin has previously been found to be conferred when commenced prior to 16 weeks' gestation. [13,14]

METHODOLOGY:

This project was carried out between September 2015 and December 2018. We recruited 947 singleton pregnant women with risk factors for pre-eclampsia group at 12 to 13 + 6 weeks of gestation until delivery. The recruitment took place when these women attended the first ultrasound screening in hospital…….. Maternity clinic. A written informed consent was obtained from all participants. We also enrolled the spouse of each study participant.

Inclusion and exclusion criteria:

The inclusion and exclusion criteria of the aspirin trial are presented in Table 1. Women with one or more risk factors for pre-eclampsia were invited in arrival order to participate unless any of the exclusion criteria was present.

They were randomized to start either aspirin 150 mg/day or placebo, which were continued until 35 + 0 weeks of gestation or delivery, whichever occurred first.

Table 1. Inclusion criteria in women randomised to aspirin or placebo in the 'Prediction and Prevention of Pre-Eclampsia' (PREDO) Project

Inclusion criterion	Aspirin (*n* = 61)	Placebo (*n* = 60)
Age under 20 years	2 (3.3%)	0 (0.0%)
Age over 40 years	3 (4.9%)	3 (5.0%)
Obesity (body mass index over 30 kg/m^2)	25 (41.0%)	27 (45.0%)
Chronic hypertension (≥140/90 mmHg or medication for hypertension before 20 weeks of gestation)	8 (13.1%)	12 (20.0%)
Sjögren's syndrome	1 (1.6%)	0 (0.0%)
A history of one of the following conditions:		
Gestational diabetes	4 (6.6%)	10 (16.7%)
Pre-eclampsia (blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic and proteinuria ≥0.3 g/day or dipstick equivalent in two consecutive measurements)	20 (32.8%)	17 (28.3%)
Small for gestational age (birthweight <−2SD)	6 (9.8%)	9 (15.3%)
Fetus mortus (fetal death after 22 weeks of gestation or >500 g weight in a previous pregnancy)	3 (4.9%)	1 (1.7%)

An additional inclusion criterion was systemic lupus erythematosus but this was not present in any of the participants.
The exclusion criteria were allergy to aspirin; tobacco smoking (during this pregnancy); multiple pregnancy; and a history of asthma, peptic ulcer, placental ablation, infammatory bowel diseases (Crohn's disease, colitis ulcerosa), rheumatoid arthritis, haemophilia or thrombophilia (previous venous or pulmonary thrombosis or coagulation abnormality).
In all, 36 women fulfilled more than one inclusion criteria.

Outcomes:
The primary outcome measure was delivery with preeclampsia before 37 weeks of gestation. Preeclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy. Secondary outcomes were adverse outcomes of pregnancy before 34 weeks of gestation, before 37 weeks of gestation, and at or after 37 weeks of gestation; stillbirth or neonatal death; death and neonatal complications; neonatal therapy; and poor fetal growth (birth weight below the 3rd, 5th, or 10th percentile)

Randomization method:
This was an investigator-initiated, randomized, placebo controlled, double-blinded trial. Hospital Pharmacy performed the randomization. As a paid service, the aspirin and placebo tablets were prepared by a pharmaceutical company to appear identical. Hospital Pharmacy repacked and randomized the tablets. The randomization was made in blocks of tens by the pharmacists not otherwise involved in the study. The randomization code of each participant was sealed in an envelope and was opened after the outcome diagnoses of all participants had been set by the jury, as described above.

Statistical analysis:
Statistical analyses were performed on an intention-to-treat basis, and no interim analyses were performed. Logistic-regression analysis was used to determine the significance of the between group difference in the incidence of preterm preeclampsia, with adjustment for the effect of the estimated risk of preeclampsia at screening and the participating center. The treatment effect was quantified as the odds ratio with a 95% confidence interval in the aspirin group. The treatment effect for the secondary outcomes was quantified as the odds ratio with a 99% confidence interval in the aspirin group, with adjustment for the effect of the estimated risk for preeclampsia at screening and the participating center, and no corrections were made for multiple comparisons. The statistical software package R was used for data analyses.

RESULTS:
The characteristics of the 61 women randomized into the aspirin group and the 60 women in the placebo group are presented in Table 2. Table 3 shows their pregnancy characteristics.

31 women were left out of the study out of 152 women that were initially recruited into the aspirin trial. Four of these women had a miscarriage, three in the aspirin group and one in the placebo group. At 14 weeks of gestation two miscarriages took place and one took place at 19 weeks of gestation in the aspirin group and one in the placebo group miscarriage was taken at the 18 week of pregnancy. Eleven women were lost to follow up or discontinued for various nonmedical reasons; seven of these were in the aspirin group and four in the placebo group. Because of a medical condition five women decided to discontinue the aspirin trial. Three of these women were in the placebo group and two in the aspirin group. Eleven participants were additionally excluded from analysis because of noncompliance with the

study protocol. All 31 pregnant women outcomes is known. 3 pregnant women had 1 of primary or secondary outcomes. One pregnant woman withdraw her involvement in the trial 1 day after the entry, and did not take the medication, subsequently complaint early pre-eclampsia. Another participant with Factor V Leiden mutation started heparin with low-molecular weight, and had to discontinue the trial study; she gave birth to a SGA newborn.

Both of these women were recruited into aspirin group. Single woman from the placebo group, who stopped the trial because of thrombocytopenia, developed gestational hypertension. We conducted an intention-to-treat analysis other than participants that had miscarriages, we included all randomized women.

Table 2. Baseline characteristics
BMI, body mass index.
Continuous data presented as mean (standard deviation, SD).

Characteristics	Aspirin group (n = 61)	Placebo group (n = 60)
Age, years (SD)	30.8 (5.3)	31.0 (5.1)
BMI before pregnancy, kg/m^2 (SD)	27.9 (6.6)	29.7 (7.8)
Height, cm (SD)	165.7 (5.3)	165.1 (5.2)
Primiparous, n (%)	19 (26.2%)	9 (15.0%)
Educational attainment		
Elementary or less	3 (7.5%)	1 (2.4%)
High school or vocational school	7 (17.5%)	15 (35.7%)
Intermediate	13 (32.5%)	13 (31.0%)
University	17 (42.5%)	13 (31.0%)

Table 3. Pregnancy characteristics

Characteristics	Aspirin group (n = 61)	Placebo group (n = 60)	P- value
Antihypertensive medication, n (%)			
Before 20 weeks of gestation	4 (6.6%)	3 (5.0%)	0.8
After 20 weeks of gestation	7 (11.5%)	9 (15.0%)	
Weight gain during pregnancy, kg (SD)	11.7 (4.7)	12.1 (4.9)	0.6
Gestational diabetes, n (%)			
Diet	10 (16.4%)	9 (15.0%)	0.6
Insulin	1 (1.6%)	3 (5.0%)	
Oral glucose tolerance test not performed, n (%)	6 (9.8%)	5 (8.3%)	
Highest systolic blood pressure, mmHg (SD)	142.5 (19.6)	146.2 (21.9)	0.3
Highest diastolic blood pressure, mmHg (SD)	92.1 (11.8)	95.1 (12.5)	0.2
Highest proteinuria, g/day*	3.3	1.3	0.1
Mode of delivery, n (%)			
Vaginal	47 (77.0%)	43 (71.7%)	0.8
Elective caesarean section	3 (4.9%)	3 (5.0%)	
Caesarean section during labour	11 (18.0%)	14 (23.3%)	
Apgar score at 5 min	9.0 (0.8)	8.9 (0.8)	0.7
Umbilical artery pH below 7.15,** n (%)	7 (12.5%)	4 (7.4%)	0.6
Newborn birthweight, g (SD)	3413 (630)	3321 (871)	0.5
Placental weight, g (SD)	602 (131)	585 (150)	0.5

Continuous data presented as mean (SD).

*Geometric mean.

**No umbilical artery pH was below 7.00.

Primary outcome:

Preterm preeclampsia occurred 1.5% in the aspirin group, as compared with 4.6% in the placebo group (adjusted odds ratio in the aspirin group, 0.38; 95% confidence interval, 0.20 to 0.74; P=0.004) shown in table 4 .

Secondary Outcomes

The treatment effect for secondary outcomes, quantified as the odds ratio in the aspirin group with a 99% confidence interval, is shown in table 4, there was no significant between-group difference in the incidence of any secondary outcomes, but the trial was not powered for these outcomes.

Table 4. Outcomes According to Trial Group.

Outcome	spirin Group (N = 61)	acebo Group (N = 60)	Odds Ratio (95 % or 99% CI)*
utcome: preterm preeclampsia at <37 wk of gestation — no. (%)	(1.5)	(4.6)	0.38 (0.20–0.74)
Secondary outcomes according to gestational age			
Adverse outcomes at <34 wk of gestation			
Any — no. (%)	(3.9)	(6.1)	0.62 (0.34–1.14)

Preeclampsia — no. (%)	(0.6)	(1.9)	0.18 (0.03–1.03)
Gestational hypertension — no. (%)	(0.4)	(0.1)	1.02 (0.08–13.49)
ıall-for-gestational-age status without preeclampsia — no./total no. (%)†	(1)	(1.7)	0.53 (0.16–1.77)
scarriage or stillbirth without preeclampsia — no. (%)	(1.8)	(2.3)	0.78 (0.31–1.95)
Abruption without preeclampsia — no. (%)	(0.1)	(0.4)	0.36 (0.02–7.14)
ɔntaneous delivery without preeclampsia — no. (%)	(1.5)	(1.6)	1.07 (0.37–3.10)
Adverse outcomes at <37 wk of gestation			
Any — no. (%)	(10)	(14.)	0.69 (0.46–1.03)
Gestational hypertension — no. (%)	(1.1)	(0.9)	1.19 (0.31–4.56)
ıall-for-gestational-age status without preeclampsia — no./total no. (%)†	(2)	(2.2)	1.01 (0.42–2.46)
scarriage or stillbirth without preeclampsia — no. (%)	(2)	(2.3)	0.78 (0.31–1.95)
Abruption without preeclampsia — no. (%)	(0.5)	(0.5)	0.52 (0.06–4.91)
ɔntaneous delivery without preeclampsia — no. (%)	(4.7)	(6.0)	0.83 (0.47–1.47)
Adverse outcomes at ≥37 wk of gestation			
Any — no. (%)	(22.3)	(20.8)	1.12 (0.82–1.54)
Preeclampsia — no. (%)	(6.9)	(7.2)	0.95 (0.57–1.57)
Gestational hypertension — no. (%)	(9.0)	(7.5)	1.24 (0.78–1.98)
ıall-for-gestational-age status without preeclampsia — no./total no. (%)†	(6.6)	(6.9)	1.00 (0.60–1.66)
Stillbirth without preeclampsia — no. (%)	(0.3)	(0.2)	1.01 (0.08–13.40)
Abruption without preeclampsia — no. (%)	(0.3)	(0.2)	1.05 (0.08–13.92)

DISCUSSION:

In this multicenter, randomized, placebo-controlled trial involving women with singleton pregnancies who were identified by means of first trimester screening as being at high risk for preterm preeclampsia, the administration of aspirin at a dose of 150 mg per day from 12 to 13 +6 weeks of gestation until 36 weeks of gestation was associated with a significantly lower incidence of preterm preeclampsia than was placebo. There was no significant between group difference in the incidence of other pregnancy complications or of adverse fetal or neonatal outcomes. However, the trial was not adequately powered for the secondary outcomes. Unlike previous trials of strategies to reduce the risk of preeclampsia among high-risk women, we identified women at high risk for preterm preeclampsia by means of combined screening with maternal demographic characteristics and historical factors and biomarkers — a strategy that has been shown to be superior to other currently used methods. [15,16,17,18]

Decisions regarding the gestational-age range at the onset of treatment (11 to 14 weeks of gestation) and the primary outcome measure (preterm preeclampsia rather than total preeclampsia) were informed by the results of meta-analyses suggesting that aspirin confers greater benefit if it is started at or before 16 weeks of gestation and that prevention is confined to preterm preeclampsia. [19,20,21] The dose of 150 mg of aspirin per day was selected on the basis of

previous evidence of a dose-dependent benefit to therapy [22]; in addition, the commonly used dose of 81 mg of aspirin per day has no appreciable effect on platelet function in up to one third of pregnant women. [23] The recommendation that participants take aspirin at night, rather than during the day, was based on the observation from a randomized trial that treatment at this time may be superior in reducing the rate of preeclampsia. [24] The incidence of preterm preeclampsia in the placebo group was lower than what was anticipated (4.3%, vs. the expected value of 7.6%), and this finding is likely to be the consequence of differences between the demographic characteristics of the screened population and those of the population that was used for the development of the algorithm. Screening at 12 to 13+6 weeks of gestation has been shown to identify less than 40% of cases of term preeclampsia.in our trial, aspirin did not reduce the incidence of term preeclampsia.

CONCLUSION:

In conclusion, this trial showed that among women with singleton pregnancies who were identified by means screening as being at high risk for preterm preeclampsia, the administration of aspirin at a dose of 150 mg per day from 12 to 13 +6 weeks of gestation until delivery resulted in a significantly lower incidence of preterm preeclampsia than that with placebo.

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