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ASPRE trial: influence of compliance on beneficial effect of aspirin in prevention of preterm preeclampsia

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ASPRE trial: influence of compliance on beneficial effect of aspirin in prevention of preterm preeclampsia

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Condensation

The beneficial effect of aspirin in the prevention of preterm preeclampsia appears to depend with compliance.

Short version of article title

Compliance with aspirin treatment determines efficacy in the reduction of preeclampsia

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ABSTRACT

Objective: To examine the influence of compliance on the beneficial effect of aspirin in prevention of preterm preeclampsia in the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial.

Study design: This was a secondary analysis of data from the ASPRE trial. In this multicenter-study women with singleton pregnancies had screening by means of an algorithm that combines maternal factors and biomarkers (mean arterial pressure, uterine-artery pulsatility index, and maternal serum pregnancy-associated plasma protein A and placental growth factor) at 11-13 weeks' gestation. Those with an estimated risk for preterm preeclampsia of >1 in 100 were invited to participate in a double-blind trial of aspirin (150 mg per day) vs. placebo from 11 to 14 until 36 weeks' gestation. Preterm preeclampsia with delivery at <37 weeks' gestation, which was the primary outcome, occurred in 1.6% (13/798) participants in the aspirin group, as compared with 4.3% (35/822) in the placebo group (odds ratio in the aspirin group, 0.38; 95% confidence interval, 0.20 to 0.74). The proportion of prescribed tablets taken was used as an overall measure of compliance. Logistic-regression analysis was used to estimate the effect of aspirin on the incidence of preterm preeclampsia according to compliance of <90% and ≥90%, after adjustment for the estimated risk of preterm preeclampsia at screening and the participating center. The choice of cut-off of 90% was based on an exploratory analysis of the treatment effect. Logistic regression analysis was used to investigate predictors of compliance ≥90%

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among maternal characteristics and medical history.

Results: Preterm preeclampsia occurred in 5/555 (0.9%) participants in the aspirin group with compliance ≥90%, in 8/243 (3.3%) of participants in the aspirin group with compliance <90%, in 22/588 (3.7%) of participants in the placebo group with compliance ≥90%, and in 13/234 (5.6%) of participants in the placebo group with compliance <90%. The odds ratio in the aspirin group for preterm preeclampsia was 0.24 (95% confidence interval, 0.09 to 0.65) for compliance ≥90% and 0.59 (95% confidence interval, 0.23 to 1.53) for compliance <90%. Compliance was positively associated with family history of preeclampsia and negatively associated with smoking, maternal age <25 years, Afro-Caribbean and South Asian racial origin, and history of preeclampsia in a previous pregnancy.

Conclusions: The beneficial effect of aspirin in the prevention of preterm preeclampsia appears to depend on compliance.

Key words: First trimester screening, Aspirin, ASPRE trial, Preeclampsia, Pyramid of pregnancy care, Compliance, Uterine artery Doppler, Mean arterial blood pressure, Placental growth factor, Pregnancy associated plasma protein-A, Prediction, Treatment effect.

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Introduction

Several trials have examined the potential value of aspirin in the prevention of preeclampsia (PE) in women at high-risk of developing this disease. These trials provided inconsistent results, possibly because of heterogeneity in entry criteria, gestational age at onset of treatment, dosage of aspirin and outcome measure being total-PE or preterm-PE with delivery at <37 weeks' gestation.[1,2] In the recent ASPRE trial (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) women with singleton pregnancies had screening by means of an algorithm that combines maternal factors, mean arterial pressure (MAP), uterine-artery pulsatility index (UTPI), and maternal serum pregnancy-associated plasma protein A (PAPP-A) and placental growth factor (PLGF) at 11-13 weeks' gestation.[3,4] Those with an estimated risk for preterm PE of >1 in 100 were invited to participate in a double-blind trial of aspirin (150 mg/day) vs. placebo from 11 to 14 until 36 weeks' gestation. Preterm-PE, which was the primary outcome, occurred in 1.6% (13/798) participants in the aspirin group, as compared with 4.3% (35/822) in the placebo group (odds ratio in the aspirin group with adjustment for the effect of the estimated risk for preterm-PE at screening and participating center 0.38; 95% confidence interval, 0.20 to 0.74).[3] The trial showed that aspirin had no significant effect in reducing the risk of term-PE.

Extensive evidence suggests that in many medical conditions patients who are compliant with drug therapy have better outcomes than those with poor

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compliance and in randomized trials the results could be influenced by the level of compliance.[5-11]

The objectives of this study, which is a secondary analysis of data from the ASPRE trial, are to examine the factors affecting compliance and the influence of compliance on the beneficial effect of aspirin in prevention of preterm-PE.

Methods

Study population

This was a prospective, multicenter study in consecutive singleton pregnancies at 11^{+0} -13^{+6} weeks' gestation in women booking for routine pregnancy care at 13 maternity hospitals in the United Kingdom, Spain, Italy, Belgium, Greece, and Israel.[3] Maternal demographic characteristics and medical and obstetric history were recorded,[12] MAP was measured by validated automated devices and standardized protocol,[13] transabdominal color Doppler ultrasound was used to measure the left and right UTPI and the average value was recorded,[14] serum PAPP-A and PLGF concentrations were measured by an automated device (PAPP-A and PlGF 1-2-3™ kits, DELFIA® Xpress random access platform; PerkinElmer Inc. Wallac Oy, P.O.Box 10, 20101 Turku, Finland). All operators undertaking the Doppler studies had received the appropriate Certificate of Competence from the Fetal Medicine Foundation. Measured values of MAP, UTPI, PAPP-A and PLGF were expressed as a MoM adjusting for those characteristics found to provide a substantive contribution to the $\log_{10}$ transformed value including the maternal factors in the prior model.[15-18] Gestational age was

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determined from the measurement of fetal crown-rump length.[19] The patient-specific risk for preterm-PE was estimated from a combination of maternal factors and biomarkers.[4]

The eligibility criteria were maternal age ≥18 years, no serious mental illness or learning difficulties, singleton pregnancy with live fetus with no major abnormality demonstrated on the 11-13 weeks scan. Eligible women with an estimated risk for preterm-PE of >1 in 100 were invited to participate in a double-blind trial of aspirin (150 mg per day) vs. placebo from 11 to 14 until 36 weeks' gestation.[3] The placebo tablets were identical to the aspirin tablets with respect to variables such as size, thickness, physical properties, and appearance. Approval for the trial was obtained from the relevant research ethics committee and competent authority in each country in which the trial was conducted.

Primary outcome

The primary outcome measure was delivery with PE at <37 weeks' gestation. Preeclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy.[20] The systolic blood pressure should be ≥140 mmHg and/or the diastolic blood pressure should be ≥90 mmHg on at least two occasions four hours apart developing after 20 weeks of gestation in previously normotensive women. Hypertension should be accompanied by proteinuria of ≥300 mg in 24 hours or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available. In PE superimposed on chronic hypertension significant proteinuria (as defined above)

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should develop after 20 weeks of gestation in women with known chronic hypertension.

Compliance

We assessed compliance by counting the tablets that were returned by participants at each visit and by the participants' reporting of tablet counts during each telephone interview. The total number of tablets taken was calculated by subtracting the number of tablets returned from the number of tablets prescribed. Compliance was calculated as a percentage of the reported intake of tablets to the total number that participants were expected to have taken between the date of randomization and the date of the visit at 36 weeks' gestation or the date of delivery if delivery occurred before 36 weeks.

Statistical analyses

Logistic-regression analysis was used to test the difference in the incidence of preterm-PE between the aspirin and placebo groups. The estimated risk of preterm-PE at screening and the participating center were included as covariates. The treatment effect was quantified as the odds ratio (aspirin/placebo) with a 95% confidence interval (CI). We analysed the aspirin effects in subgroups with compliance cut-offs of 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, and 95%. On the basis of these analyses we chose to dichotomise compliance using a cut-off of 90%. Logistic regression analysis was used to estimate the effect of aspirin on the incidence of preterm-PE stratified according to compliance of <90%

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and ≥90%, adjusting for the estimated risk of preterm-PE at screening and the participating center.

Logistic regression analysis was used to quantify predictors of compliance ≥90% among maternal characteristics and medical history (age, body mass index, method of conception, racial origin, smoking, family history of PE, parity with and without previous PE, medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome).

The statistical software package R was used for data analyses.[21]

Results

There were no significant differences between the aspirin and placebo groups with regard to the characteristics of the participants at baseline.[3] Preterm-PE occurred in 13 of 798 participants (1.6%) in the aspirin group, as compared with 35 of 822 (4.3%) in the placebo group (adjusted odds ratio in the aspirin group, 0.38; 95% confidence interval, 0.20 to 0.74; P = 0.004).[3] The size of the treatment effect was consistent across estimated risk groups at the time of screening, across groups defined according to obstetrical history, and across countries of the participating centers.[3]

Compliance, as pre specified in the trial protocol, was considered to be good if it was ≥85%, moderate if 50-84.9% and poor if <50% and according to the results it was good in 80% of participants, moderate in 15% and poor in 5%.[3] The results of subgroup analysis on the aspirin effects according to different compliance cut-offs are shown in Figure 1. The aspirin effect was substantially increased in

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the subgroup of compliance of ≥90% with no further increase in the ≥95% compliance subgroup. We dichotomized compliance using a cut-off of 90%. After adjustment for the estimated risk of preterm-PE at screening and the participating center, both aspirin (odds ratio 0.37, 95% CI 0.19 to 0.72) and compliance (odds ratio 0.49, 95% CI 0.27 to 0.91) were independent predictors of preterm-PE. Although the interaction between treatment and compliance was not statistically significant (P = 0.19), the estimated aspirin effect was smaller with compliance <90% than with compliance ≥90% (Figure 2).

Logistic regression analysis demonstrated that compliance ≥90% was positively associated with family history of PE and negatively associated with smoking, maternal age <25 years, Afro-Caribbean and South Asian racial origin, and multiparity with history of PE in a previous pregnancy; there were no significant effects of body mass index, method of conception, multiparity with no PE in a previous pregnancy or history of pre-existing medical condition (Figure 3).

Comment

Principal findings of this study

The ASPRE trial demonstrated that, in women with singleton pregnancies identified by means of first trimester screening as being at high risk for preterm-PE, the administration of aspirin at a dose of 150 mg per day from 11 to 14 weeks until 36 weeks' gestation reduces the incidence of preterm-PE by approximately 60%.[3] The results of the secondary analysis suggest that the beneficial effect of aspirin depends on compliance and the reduction in incidence

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of preterm-PE may be about 75% in those with compliance of ≥90% and only 40% in those with compliance of <90%. The trial was powered for a 50% reduction in the incidence of preterm-PE and had the overall compliance been <90% the trial may have failed to demonstrate a significant benefit of aspirin in reducing the incidence of preterm PE.

High compliance was positively associated with family history of PE and negatively associated with smoking, maternal age <25 years, Afro-Caribbean and South Asian racial origin, and multiparity with history of PE in a previous pregnancy. A possible explanation for the surprising finding of low compliance in those with previous history of PE is that poor compliance is associated with an unknown trait that is also associated with PE. A good example of such a trait that we know about is Afro-Caribbean racial origin which is associated with poor compliance and with increased risk for PE.[12] Consequently, the observed dependence of the beneficial effect of aspirin on compliance may at least in part be due to differences in the characteristics of the highly compliant subjects compared to those with lower compliance.

Limitations of the study

The data of this study suggest that the beneficial effect of aspirin in the prevention of preterm-PE, demonstrated in the ASPRE trial,[3] is dependent on compliance, but the trial was not adequately powered for such secondary analysis. Another limitation of the study relates to the method of ascertainment of compliance which relied on the counting of tablets rather than a more objective measurement of

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biomarkers. There is a wide range of platelet activation and function assays that have been used to assess responsiveness to aspirin, but these assays suffer from limited reproducibility and poor agreement between them; additionally, suboptimal suppression of platelet activation does not necessarily reflect poor compliance but may be the consequence of interacting physiological, pharmacokinetic and pharmacodynamics factors.[22]

Clinical implications of the study

In clinical practice the importance of compliance to therapy is widely appreciated for healthcare outcomes but in the case of clinical trials regulators have been reluctant to acknowledge its importance, often hiding behind the use of intention-to-treat analysis of data which masks the problem.[23] In the ASPRE trial if the compliance was <90% the effect of aspirin in reducing the incidence of preterm-PE may not have achieved significance. High compliance is an essential prerequisite of a successful clinical trial and poor compliance could lead to the erroneous conclusion that effective therapy may be ineffective.

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Figure legends

Figure 1. Odds ratio for preterm preeclampsia in the aspirin group with 95% confidence intervals in different subgroups according to compliance expressed as percentage of intake of the required number of tablets.

Figure 2. Odds ratio for preterm preeclampsia in the aspirin group with 95% confidence intervals in the total population and the subgroups with compliance of <90% and ≥90%.

Figure 3. Effect of maternal characteristics and obstetric and medical history on compliance of ≥90%.

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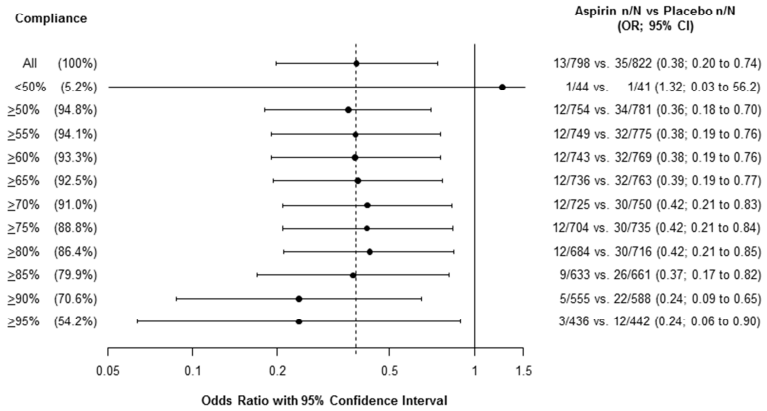

Figure 1

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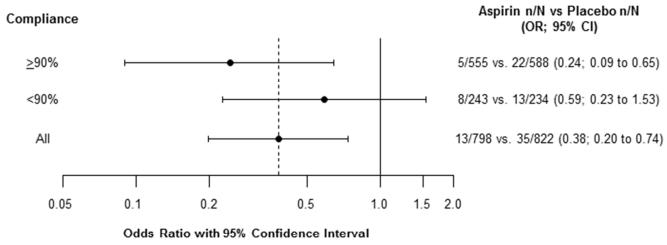

Figure 2

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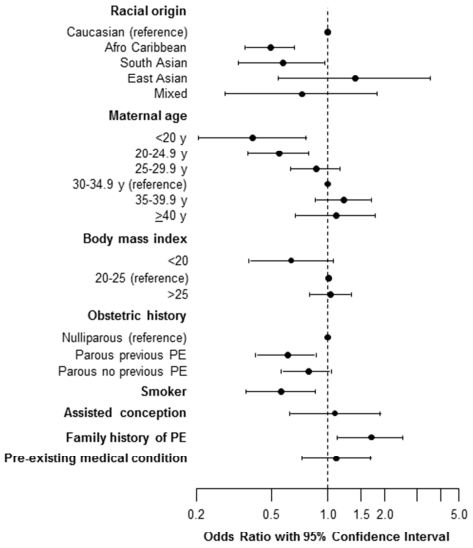

Figure 3

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