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LETTER TO THE EDITOR

Aspirin for those at high risk: when to stop?

Dear Dr. Papageorghiou,

Bonacina et al. report the results of a post-hoc analysis of the StopPRE trial.[1,2] In the trial, women identified by screening at 11–13 weeks of gestation as being at high risk for preterm pre-eclampsia (PE) were treated with aspirin (150 mg/day). Participants were reassessed at 24–28 weeks of gestation and, if the results of biomarkers of impaired placentation were normal, they were randomly assigned, in a 1:1 ratio, to either continue aspirin treatment until 36 weeks of gestation (control group) or to discontinue aspirin treatment (intervention group). The objective was to determine whether aspirin discontinuation was non-inferior to aspirin continuation in the prevention of preterm PE. The non-inferiority margin was set at a difference of 1.9% for the incidence of preterm PE and a sample size of 540 women in each group was calculated, assuming an expected incidence of preterm PE of 1.6%. In the primary study, the criterion for enrolment to the trial was a normal ratio (≤38) of soluble fms-like tyrosine kinase-1 to placental growth factor (sFlt-1:PlGF); the incidence of preterm PE was 1.48% (7/473) in the intervention group and 1.73% (8/463) in the control group (absolute difference, −0.25%; 99% CI −1.86 to 1.36), indicating non-inferiority.[1]

In the secondary analysis of the trial (in the subgroup with low sFLT-1:PlGF), the incidence of preterm PE in women with normal uterine artery pulsatility index (≤90th percentile) at 24–28 weeks of gestation was compared between the discontinuation and the control groups; the incidence in the discontinuation group was 0.7% (3/409) versus 1.3% (5/395) in the control group (absolute difference −0.53; 95% CI −1.91 to 0.85), indicating the non-inferiority of aspirin discontinuation. The authors concluded that aspirin discontinuation at 24–28 weeks of gestation was non-inferior to aspirin continuation in the prevention of preterm PE in pregnant individuals at high risk of preterm PE and with normal sFlt-1:PlGF ratio or uterine artery Doppler at 24–28 weeks of gestation.

We challenge the conclusion of the authors because the equivalence margin of 1.9% is too big and the study has insufficient power to conclude non-inferiority. Based on the ASPRE trial, it is supposed that aspirin prevents 62% of preterm PE.[3] An incidence of 1.6% in a treated group would correspond to an incidence without treatment of 4.2%; 62% of the 4.2% (i.e. 2.6%) would be prevented, and the incidence would be reduced to 1.6%. If the treatment effect were halved to 31%, then the incidence of treatment would be reduced by 31% of 4.2% (1.3%–2.9%). A 50% reduction in the effectiveness of aspirin therefore corresponds to a difference in incidence of 2.9% – 1.6%, which is 1.3%. With this non-inferiority margin, 1463 women would be needed in each group to get a power of 80% with a two-tailed type 1 error rate of 5%. More conservatively, a 20% reduction in efficacy equates to a non-inferiority margin of 0.522% and a sample size of 9070 in each group.

We conclude that there is a need for a much larger study to establish the effect of the discontinuation of treatment with aspirin and whether this should apply to all women at high risk or to a targeted subgroup.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated for this letter.

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