Pre-eclampsia screening studies - overcoming intervention bias

Howard Cuckle[1]

[1]Tel Aviv University

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HS Cuckle

Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

The ASPRE trial established beyond doubt the efficacy of aspirin prophylaxis in women with positive multi-marker first trimester preeclampsia (PE) screening test results (Rolnik et al. N Eng J Med 2017;50:613-22). Screening combined maternal characteristics, blood pressure, uterine artery Doppler, maternal serum pregnancy associated plasma protein (PAPP)-A and placental growth factor (PlGF). Screen-positive women were randomised to aspirin or placebo and there was a 62% reduction of pre-term PE in the aspirin arm.

Subsequently, a practical question has arisen regarding the maternal serum markers: which is superior, PlGF or PAPP-A? This is best answered by non-intervention studies of PE screening when all markers are measured prospectively. There are four such studies and all show that the detection rate for a fixed 10% false-positive rate was higher when PlGF was included compared with PAPP-A; the increase ranged from 5% to 7% (Cuckle. Ultrasound Obstet Gynecol 2022;??:??-??).

However, a non-intervention study, despite not revealing the PE screening test report to clinicians and patients, does not preclude the use of aspirin in some women; for example, those with high risk characteristics are likely to be recommended treatment. Moreover, these occasional interventions might bias the PlGF versus PAPP-A comparison. This would occur as a consequence of simultaneous Down syndrome screening using the Combined Test, since that test report includes the PAPP-A level. If this marker was low, treatment might be recommended, leading to the prevention of some pre-term PE cases, a proportion of which are screen-positive. In the absence of intervention these screen-positive cases would be true-positive but actually become false-positive, hence reducing the detection-rate and slightly increasing the false-positive rate. These effects will be stronger for PAPP-A combinations. The standard Combined Test does not include PlGF yielding a bias towards superior PE screening performance for PlGF combinations.

In the current analysis, data from two of the four non-intervention studies are reanalysed to adjust for this potential bias (Wright et al. BJOG 2022;??:??-??). In both combined 4.2% (1066/25,226) had taken aspirin, although for nearly all the treatment was sub-optimal compared with the ASPRE regimen of 150mg/night at <16-36 weeks. The reanalysis was by statistical modeling using the original 'competing risks' method. But additionally superimposed were simulations from an 'imputation' model, which re-assigned false-positives among the 1066 treated women to true- or false-positive according to the probability of reduction in pre-term PE found in ASPRE.

The model predicted that the increase in detection rate for a 10% false-positive rate when PlGF was included compared with PAPP-A was 7.0% and this reduced to 6.4% following imputation. Hence, even adopting the extreme assumption that intervention was at an optimal level, the bias in favour of PlGF was small. The authors also modeled combinations without blood pressure or uterine artery Doppler and the bias was proportionally similar or smaller.

Clinical studies are often marred by subtle bias, and once discovered it is vital to assess whether the results were materially affected. The current publication is exemplary in using imputation modeling to confirm the superiority of PlGF over PAPP-A.

(500 words)