ASPRE trial: performance of screening for preterm pre-eclampsia

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Short title: ASPRE trial screening performance

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ABSTRACT

Objective: To examine the performance of screening for preterm and term preeclampsia (PE) in the study population participating in the ASPRE (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) trial.

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Methods: This was a prospective first-trimester multicenter study of screening for preterm-PE in 26,941 singleton pregnancies by means of an algorithm that combines maternal factors, mean arterial pressure, uterine-artery pulsatility index, and maternal serum pregnancy-associated plasma protein A and placental growth factor at 11-13 weeks' gestation. 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. In the aspirin group the incidence of preterm-PE was reduced by 62%. In the screened population the detection rates (DR) and false positive rates (FPR) for delivery with PE at <37 and ≥37 weeks were estimated after adjustment for the effect of aspirin in those receiving this treatment. We excluded 1,144 (4.2%) of pregnancies because of loss to follow-up (n=716), miscarriage (n=243) or termination (n=185).

Results: The study population of 25,797 pregnancies, included 180 (0.7%) cases of preterm-PE, 450 (1.7%) of term-PE and 25,167 (97.6%) without PE. In combined first-trimester screening for preterm-PE and risk cut-off of 1 in 100 the DR was 76.7% (138/180) for preterm-PE and 43.1% (194/450) for term-PE, at screen positive rate of 10.5% (2,707/25,797) and FPR of 9.2% (2,375/25,797).

Conclusion: The performance of screening in the ASPRE study was compatible with that of a study of approximately 60,000 singleton pregnancies used for development of the algorithm; in that study combined screening detected 76.6% of cases of preterm-PE and 38.3% of term-PE at FPR of 10%.

INTRODUCTION

The ASPRE (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) trial was a prospective first-trimester multicenter study of screening for preterm-PE in 26,941 singleton pregnancies 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.[1] The algorithm was developed from a study of approximately 60,000 singleton pregnancies; in that study combined screening detected 76.6% of cases of preterm-PE and 38.3% of term-PE at false positive rate (FPR) of 10%.[2]

In the ASPRE study, 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.[1] In the aspirin group the incidence of preterm-PE was reduced by 62%.

The objective of this study is to report the accuracy of the previously reported first-trimester model of screening for PE [2] in the screened population of the ASPRE study. The hypothesis is that the performance of screening would be similar to that estimated from the original model.

The Standards for Reporting Diagnostic accuracy studies (STARD) [3] were adhered to.

METHODS

Study design and participants

This was a prospective, multicenter study in 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.[1] Approval for the trial was

obtained from the relevant research ethics committee and competent authority in each country in which the trial was conducted.

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. We excluded pregnancies with no follow up and those ending in termination or miscarriage.

Test methods

The index test, or test whose accuracy has been evaluated, is the previously reported algorithm for first-trimester assessment of risk for PE by maternal factors, MAP, UTPI, PAPP-A and PLGF.[2] Maternal factors were recorded,[4] MAP was measured by validated automated devices and standardized protocol,[5] transabdominal color Doppler ultrasound was used to measure the left and right UTPI and the average value was recorded,[6] 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.[7-10]

The index test was carried out prospectively in consecutive singleton pregnancies at 11^{+0} - 13^{+6} weeks' gestation; gestational age was determined from the measurement of fetal crown-rump length.[11]

The target condition was PE, as defined by the International Society for the Study of Hypertension in Pregnancy.[12] The systolic blood pressure should be ≥140 mm Hg 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) should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks' gestation in the absence of trophoblastic disease).

Data on pregnancy outcome were collected from the hospital maternity records of the women. The obstetric records of all women with pre-existing or pregnancy associated hypertension were examined to determine if the condition was PE.

Analysis

The previously described algorithm was used for the calculation of patient-specific risk of delivery with PE at <37 weeks' gestation.[2] 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.[1] In the aspirin group the incidence of preterm-PE was reduced by 62%. In the screened population the FPR and detection rates (DR) for delivery with PE at <37 and ≥37 weeks were estimated after adjustment for the effect of aspirin in those receiving this treatment.

RESULTS

Participants

A total of 26,941 women with singleton pregnancies underwent screening for PE (Figure 1). For the purpose of this study we excluded 1,144 (4.2%) of pregnancies because of loss to follow-up (n=716), miscarriage (n=243) or termination (n=185). The loss to follow-up group included 152 high-risk pregnancies that participated in the trial but subsequently withdrew consent; 78 allowed reporting of their screening data; the baseline characteristics of the women who withdrew consent were similar between those assigned to receive aspirin and those assigned to receive placebo.[1]

In the study population of 25,797 pregnancies, the risk for preterm-PE was >1 in 100 in 2,707 (10.5%) and ≤1 in 100 in 23,090 (89.5%). In the group with a risk of >1 in 100, 806 participated in the trial and were assigned to receive placebo, 785 participated in the trial and were assigned to receive aspirin and 1,116 did not participate in the trial, either because they did not want to do so (n=806) or they did not fulfill the eligibility criteria (n=310) due to hypersensitivity to aspirin, peptic ulceration or bleeding disorder, treatment with aspirin within 28 days before screening, or participation in another drug trial within 28 days before screening.

Test results

The incidence of preterm-PE and term-PE in the screen positive and screen negative groups is shown in Figure 1. In the group assigned to receive aspirin there were 13 cases of preterm-PE and 53 cases of term-PE. The ASPRE trial demonstrated that administration of aspirin, compared to placebo, resulted in a 62% reduction in the incidence of preterm-PE but had no significant effect on the incidence of term-PE. Consequently, the observed number of 13 cases of preterm-PE in the aspirin group was adjusted to the expected number of 34 had these patients not received aspirin (Figure 1).

The study population of 25,797 pregnancies, included 180 (0.7%) cases of preterm-PE, 450 (1.7%) of term-PE and 25,167 (97.6%) without PE. In combined first-trimester screening for preterm-PE and risk cut-off of 1 in 100 the DR was 76.7% (138/180) for preterm-PE and 43.1% (194/450) for term-PE, at screen positive rate of 10.5% (2,707/25,797) and FPR of 9.2% (2,375/25,797).

DISCUSSION

Main findings

This prospective multicenter study demonstrates the feasibility of incorporating first-trimester screening for PE into routine clinical practice. The performance of screening for PE at 11-13 weeks by a combination of maternal factors and biomarkers is similar to that estimated from the original model.[2] The estimated DR of screening by maternal factors, MAP, UTPI, PAPP-A and PLGF, was 77% for PE at <37 weeks and 43% for PE at ≥37 weeks, at FPR of 9.2%; the estimated rates in the dataset used for development of the model were 77%, 38% and 10%, respectively.[2]

Study limitations

There were two components to the ASPRE study; first, routine screening of all pregnancies meeting the eligibility criteria and second, participation of a high proportion of the screen positive group in a trial of aspirin vs. placebo.[1] The trial demonstrated a beneficial effect of

aspirin in reducing the rate of preterm-PE and therefore the observed number of cases with preterm-PE in the aspirin group had to be adjusted to take into account this beneficial effect. In this respect, this was not a non-intervention validation study.

Implications for practice

The ASPRE trial demonstrated that in women with singleton pregnancies who were identified by means of first trimester combined 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 until 36 weeks' gestation reduces the incidence of preterm-PE by >60%.[1]

The traditional approach of identifying women at high-risk of PE that could potentially benefit from the prophylactic use of aspirin is based on maternal characteristics and medical history. In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) recommends the identification of the high-risk group on the basis of 10 factors, including maternal characteristics and features of the medical and obstetrical histories.[13] However, the performance of such screening is poor, with DR of preterm-PE of 39% at FPR of 10%.[14] In the United States, the American College of Obstetricians and Gynecologists (ACOG) recommends the use of aspirin in women with a history of PE in more than one pregnancy or a history of PE that resulted in delivery before 34 weeks' gestation.[15] However, this subgroup constitutes only approximately 0.3% of all pregnancies and includes only 5% of women that develop preterm-PE.[14] Our approach to screening with use of Bayes' theorem to combine the *a priori* risk from maternal factors with biophysical and biochemical measurements obtained at 11-13 weeks' gestation is by far superior to those of NICE and ACOG in identifying the group that would benefit from prophylactic use of aspirin.

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Figure legend

Figure 1. Screening for preterm-PE, interventions and follow-up.

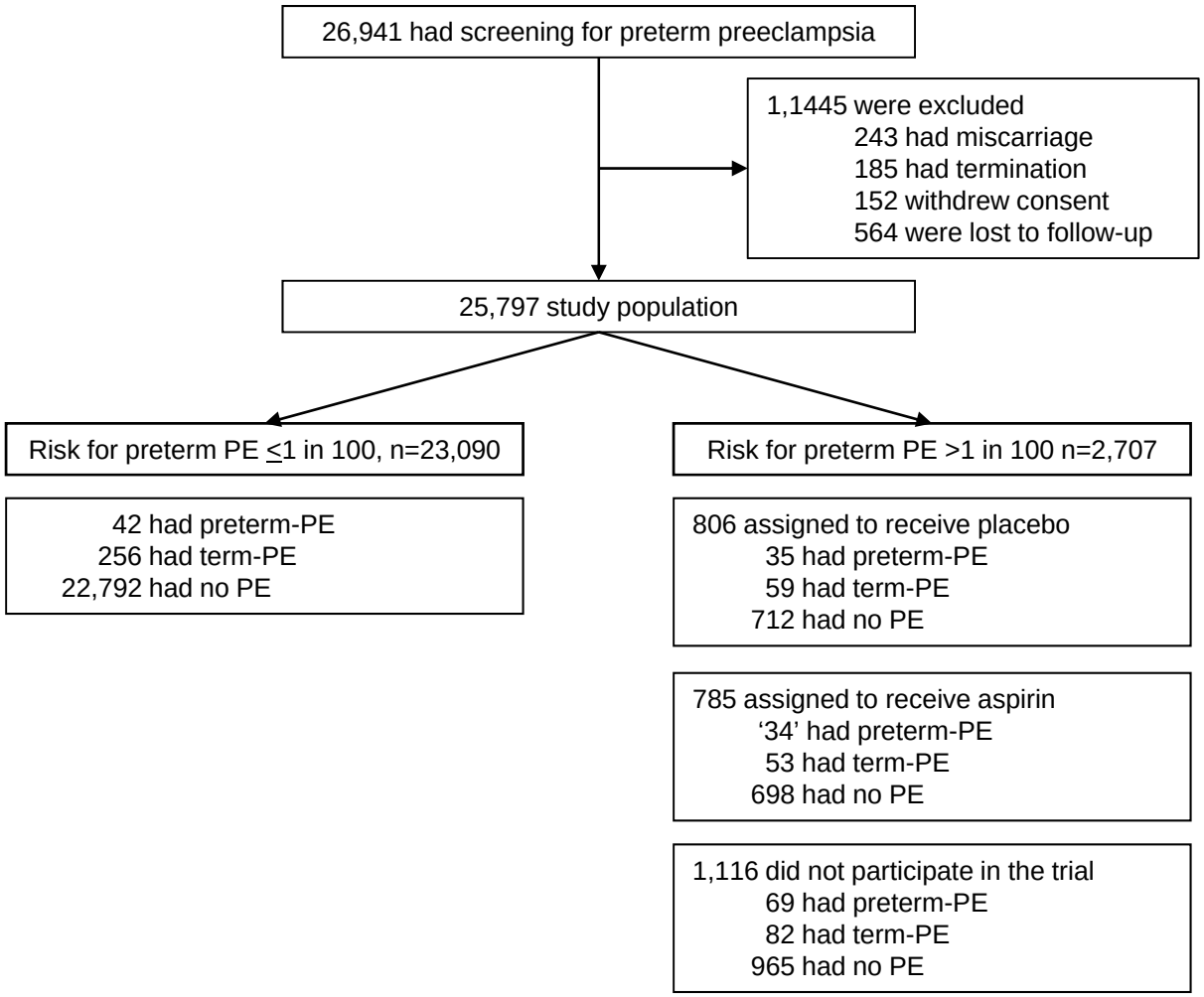

Fig. 1

Table 1. Characteristics of the study population.

Maternal characteristics	**Study population (n=25,797)**
Maternal age in years, median (IQR)	31.7 (27.7-35.2)
Maternal weight in Kg, median (IQR)	66.0 (58.7-76.5)
Maternal height in cm, median (IQR)	164 (160-169)
Body mass index, median (IQR)	24.4 (21.8-28.2)
Gestational age in weeks, median (IQR)	12.7 (12.3-13.1)
Racial origin, n (%)	
Caucasian	20,383 (79.0)
Afro-Caribbean	3,117 (12.1)
East Asian	517 (2.0)
South Asian	1,194 (4.6)
Mixed	586 (2.3)
Medical history, n (%)	
Chronic hypertension	319 (1.2)
Diabetes mellitus	207 (0.8)
SLE or APS	135 (0.5)
Cigarette smoking, n (%)	2,072 (8.0)
Family history of preeclampsia, n (%)	851 (3.3)
Conception, n (%)	
Spontaneous	24,868 (96.4)
In vitro fertilization	764 (3.0)
Ovulation drugs	165 (0.6)
Parity, n (%)	
Nulliparous	12,181 (47.2)
Parous: no previous preeclampsia	13,097 (50.8)
Parous: previous preeclampsia	519 (2.0)
Parous: no previous SGA	12,767 (49.5)
Parous: previous SGA	849 (3.3)
Pregnancy interval in years, median (IQR)	2.8 (1.6-4.8)

IQR = interquartile range; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome; SGA = small for gestational age.