Ultrasound Obstet Gynecol 2017; **50**: 492–495
Published online 24 August 2017 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.18816

ASPRE trial: performance of screening for preterm pre-eclampsia

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KEYWORDS: ASPRE trial; first-trimester screening; mean arterial pressure; placental growth factor; pre-eclampsia; pregnancy-associated plasma protein-A; pyramid of pregnancy care; uterine artery Doppler

ABSTRACT

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

Methods *This was a prospective first-trimester multicenter study on 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 11–14 until 36 weeks' gestation, which showed that, in the aspirin group, the incidence of preterm PE was reduced by 62%. In the screened population, the detection rates (DRs) and false-positive rates (FPRs) for delivery with PE < 37 and ≥ 37 weeks were estimated after adjustment for the effect of aspirin in those receiving this treatment. We excluded 1144 (4.2%) pregnancies because of loss to follow-up or study withdrawal (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 with a 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% (2707/25 797) and FPR of 9.2% (2375/25 797).*

Conclusion *The performance of screening in the ASPRE study was comparable 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 a FPR of 10%. Copyright © 2017 ISUOG. Published by John Wiley & Sons Ltd.*

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 on 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 (UtA-PI), 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 a false-positive rate (FPR) of 10%[2].

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Accepted: 19 July 2017

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 11–14 weeks until 36 weeks' gestation[1]. In the aspirin group, the incidence of preterm PE was reduced by 62%.

The objective of this study was 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 was that the performance of screening would be similar to that estimated from the original model.

METHODS

Study design and participants

This was a prospective, multicenter study of singleton pregnancies at 11 + 0 to 13 + 6 weeks' gestation in women attending routine pregnancy care at one of 13 maternity hospitals in the UK, 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 difficulty and singleton pregnancy with live fetus with no major abnormality demonstrated on the 11–13-week scan. We excluded pregnancies with no follow-up and those ending in termination or miscarriage.

The Standards for Reporting Diagnostic Accuracy Studies (STARD)[3] were adhered to.

Test methods

The index test, or the test for which accuracy has been evaluated, was the previously reported algorithm for first-trimester assessment of risk for PE by maternal factors, MAP, UtA-PI, 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 UtA-PI 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, Turku, Finland). All operators undertaking the Doppler studies had received the appropriate Certificate of Competence from The Fetal Medicine Foundation. Measured values of MAP, UtA-PI, 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 to 13 + 6 weeks' gestation; gestational age was determined from 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]. PE was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least two occasions 4 h apart developing after 20 weeks of gestation in previously normotensive women. Hypertension was defined as proteinuria ≥ 300 mg in 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h collection was available. PE superimposed on chronic hypertension was defined as significant proteinuria (as defined above) developing after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or presence of hypertension at 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.

Statistical analysis

The previously described algorithm was used for the calculation of patient-specific risk of delivery with PE < 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 11–14 weeks until 36 weeks' gestation[1], which showed that, in the aspirin group, the incidence of preterm PE was reduced by 62%. In the screened population, the FPRs and detection rates (DRs) for delivery with PE < 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 pregnancy underwent screening for PE (Figure 1). For the purpose of this study, we excluded 1144 (4.2%) pregnancies because of loss to follow-up ($n = 716$), miscarriage ($n = 243$) or termination ($n = 185$). The group lost to follow-up included 152 high-risk pregnancies that participated in the trial but subsequently withdrew consent, of which 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].

The characteristics of the study population of 25 797 pregnancies are shown in Table 1. In this population, the risk for preterm PE was > 1 in 100 in 2707 (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 1116 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

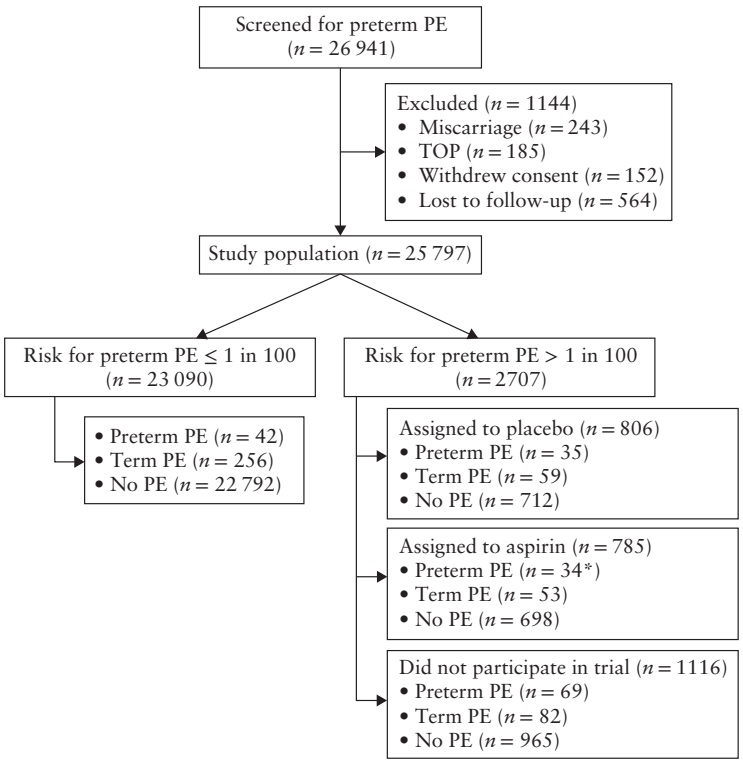

Figure 1 Flowchart summarizing screening for preterm pre-eclampsia (PE), interventions and follow-up in 26 941 singleton pregnancies. *Adjusted number, derived from 13 observed cases and assuming 62% reduction of preterm PE caused by aspirin. TOP, termination of pregnancy.

Table 1 Characteristics of study population

Characteristic	*Study population* (n = *25 797*)
Maternal age (years)	31.7 (27.7–35.2)
Maternal weight (kg)	66.0 (58.7–76.5)
Maternal height (cm)	164 (160–169)
Body mass index (kg/m^2)	24.4 (21.8–28.2)
Gestational age (weeks)	12.7 (12.3–13.1)
Racial origin	
Caucasian	20 383 (79.0)
Afro-Caribbean	3117 (12.1)
East Asian	517 (2.0)
South Asian	1194 (4.6)
Mixed	586 (2.3)
Medical history	
Chronic hypertension	319 (1.2)
Diabetes mellitus	207 (0.8)
APS/SLE	135 (0.5)
Cigarette smoker	2072 (8.0)
Family history of pre-eclampsia	851 (3.3)
Mode of conception	
Spontaneous	24 868 (96.4)
In-vitro fertilization	764 (3.0)
Ovulation drugs	165 (0.6)
Parity	
Nulliparous	12 181 (47.2)
Parous	
No previous pre-eclampsia	13 097 (50.8)
Previous pre-eclampsia	519 (2.0)
No previous SGA	12 767 (49.5)
Previous SGA	849 (3.3)
Interpregnancy interval (years)	2.8 (1.6–4.8)

Data are given as median (interquartile range) or *n* (%). APS, anti-phospholipid syndrome; SGA, small-for-gestational-age neonate; SLE, systemic lupus erythematosus.

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 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 with 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 with a 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 a screen-positive rate of 10.5% (2707/25 797) and FPR of 9.2% (2375/25 797).

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, UtA-PI, PAPP-A and PlGF was 77% for PE < 37 weeks and 43% for PE ≥ 37 weeks at a FPR of 9.2%; the 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 pregnancy 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 11–14 weeks until 36 weeks' gestation reduces the incidence of preterm PE by > 60%[1].

The traditional approach of identifying women at high risk of PE who could potentially benefit from the prophylactic use of aspirin is based on maternal characteristics and medical history. In the UK, the National Institute for Health and Care 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 obstetric histories[13]. However, the performance of such screening is poor, with a DR of preterm PE of 39% at a FPR of 10%[14]. In the USA, 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 who develop preterm PE[14]. Our approach to screening with the 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 who would benefit from prophylactic use of aspirin.

ACKNOWLEDGMENTS

The study was supported by grants from The Fetal Medicine Foundation (Charity No: 1037116) and by the European Union 7th Framework Programme – FP7-HEALTH-2013-INNOVATION-2 (ASPRE Project # 601852).

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This article has been selected for Journal Club.

A slide presentation, prepared by Dr Fiona Brownfoot, one of UOG's Editors for Trainees, is available online.

Chinese translation by Dr Yang Fang. Spanish translation by Dr Ruben Dario Fernandez.

Ultrasound Obstet Gynecol 2017; **50**: 492–495
Published online 24 August 2017 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.18816

Ensayo ASPRE: el comportamiento del cribado de preeclampsia pretérmino

RESUMEN

Objetivo Estudiar el comportamiento del cribado de pre-eclampsia pretérmino y a término (PE) en la población de estudio que participa en el ensayo ASPRE (Cribado combinado basado en evidencia mediante múltiples marcadores y tratamiento aleatorizado de la paciente con aspirina para la prevención de preeclampsia).

Métodos Se trata de un estudio multicéntrico prospectivo de primer trimestre sobre el cribado de PE pretérmino en 26 941 embarazos con feto único, mediante un algoritmo que combina factores maternos como la presión arterial promedio, el índice de pulsatilidad de la arteria uterina y la proteína plasmática A del suero materno asociada al embarazo y el factor de crecimiento de la placenta a las 11-13 semanas de gestación. Se invitó a las mujeres con posibilidades de ser elegidas por tener un riesgo estimado de PE pretérmino >1 entre 100 a participar en un ensayo doble ciego de aspirina (150 mg por día) versus un placebo, desde las semanas 11-14 a las 36 semanas de gestación, que resultó en una reducción de la incidencia de PE prematura de un 62% en el grupo que tomó aspirina. En la población en la que se hizo el cribado, después del ajuste del efecto de la aspirina en las mujeres que recibieron este tratamiento, se estimaron las tasas de detección (TD) y las tasas de falsos positivos (TFP) para el parto con PE <37 y >37 semanas. Se excluyeron 1144 (4,2%) embarazos debido a falta de seguimiento o abandono del estudio ($n = 716$), aborto ($n = 243$) o terminación ($n = 185$).

Resultados La población estudiada de 25 797 embarazos incluyó 180 (0,7%) casos de PE pretérmino, 450 (1,7%) de PE a término y 25 167 (97,6%) sin PE. En el cribado combinado del primer trimestre para PE pretérmino con un límite de riesgo de 1 entre 100, la TD fue del 76,7% (138/180) para PE pretérmino y 43,1% (194/450) para PE a término, con una tasa positiva del cribado del 10,5% (2707/25797) y una TFP del 9,2% (2375/25797).

Conclusión El comportamiento del cribado en el estudio ASPRE fue comparable con el de un estudio de aproximadamente 60 000 embarazos con feto único utilizados para el desarrollo del algoritmo; en ese estudio, el cribado combinado detectó el 76,6% de los casos de PE pretérmino y el 38,3% de los de PE a término con una TFP del 10%.

ASPRE 试验：对早产子痫前期的筛查能力

目的：检测在 ASPRE（多种标志物联合筛查和随机患者阿斯匹林治疗，进行循证子痫前期预防）试验的研究人群中对早产和足月子痫前期（pre-eclampsia，PE）的筛查能力。

方法：本研究为一项前瞻性孕早期多中心研究，通过一种在孕 11~13 周时联合母体因素、平均动脉压、子宫动脉搏动指数以及母体血清妊娠相关血浆蛋白 A 和胎盘生长因子的方法对 26 941 例单胎妊娠进行早产 PE 筛查。符合纳入标准的估计早产 PE 风险>1%的孕妇从孕 11~14 周起参加阿斯匹林（150 mg/day）和安慰剂双盲试验，直至孕 36 周，结果显示，阿斯匹林组早产 PE 发生率降低 62%。筛查人群中，校正接受治疗的孕妇中阿斯匹林的作用后，估计 PE<37 周和≥37 周分娩的检出率（detection rates，DRs）和假阳性率（false-positive rates，FPRs）。由于失访或者退出研究（*n*=716）、流产（*n*=243）或终止妊娠（*n*=185），排除 1144 例（4.2%）孕妇。

结果：研究人群为 25 797 例孕妇，包括 180 例（0.7%）早产 PE，450 例（1.7%）足月 PE，25 167 例（97.6%）无 PE 孕妇。孕早期联合筛查早产 PE 在风险截断值为 1%时，早产 PE 的 DR 为 76.7%（138/180），足月 PE 的 DR 为 43.1%（194/450），筛查阳性率为 10.5%（2707/25 797），FPR 为 9.2%（2375/25 797）。

结论：ASPRE 研究中筛查能力与用于开发这种方法的基于约 60 000 例单胎妊娠的研究相似；后者在 FPR 为 10%时联合筛查检出 76.6%的早产 PE 和 38.3%的足月 PE。