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Prediction and prevention of small-for-gestational-age neonates: evidence from SPREE and ASPRE

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KEYWORDS: aspirin; ASPRE; fetal growth restriction; first-trimester screening; pre-eclampsia; small-for-gestational age; SPREE

ABSTRACT

Objectives *To examine the effect of first-trimester screening for pre-eclampsia (PE) on the prediction of delivering a small-for-gestational-age (SGA) neonate and the effect of prophylactic use of aspirin on the prevention of SGA.*

Methods *The data for this study were derived from two multicenter studies. In SPREE, we investigated the performance of screening for PE by a combination of maternal characteristics and biomarkers at 11–13 weeks' gestation. In ASPRE, women with a singleton pregnancy identified by combined screening as being at high risk for preterm PE (> 1 in 100) participated in a trial of aspirin (150 mg/day from 11–14 until 36 weeks' gestation) compared to placebo. In this study, we used the data from the ASPRE trial to estimate the effect of aspirin on the incidence of SGA with birth weight < 10^{th}, < 5^{th} and < 3^{rd} percentile for gestational age. We also used the data from SPREE to estimate the proportion of SGA in the pregnancies with a risk for preterm PE of > 1 in 100.*

Results *In SPREE, screening for preterm PE by a combination of maternal factors, mean arterial pressure, uterine artery pulsatility index and serum placental growth factor identified a high-risk group that contained about 46% of SGA neonates < 10^{th} percentile born at < 37 weeks' gestation (preterm) and 56% of those born at < 32 weeks (early); the overall screen-positive rate was 12.2% (2014 of 16 451 pregnancies). In the ASPRE trial, use of aspirin reduced the overall incidence of SGA < 10^{th} percentile by about 40% in babies born at < 37 weeks' gestation and by about 70% in babies born at < 32 weeks; in babies born at ≥ 37 weeks, aspirin did not have a significant effect on incidence of SGA. The aspirin-related decrease in incidence of SGA was mainly due to its incidence decreasing in pregnancies with PE, for which the decrease was about 70% in babies born at < 37 weeks' gestation and about 90% in babies born at < 32 weeks. On the basis of these results, it was estimated that first-trimester screening for preterm PE and use of aspirin in the high-risk group would potentially reduce the incidence of preterm and early SGA by about 20% and 40%, respectively.*

Conclusion *First-trimester screening for PE by the combined test identifies a high proportion of cases of preterm SGA that can be prevented by the prophylactic use of aspirin.* © *2018 Crown copyright. Ultrasound in Obstetrics & Gynecology* © *2018 ISUOG.*

INTRODUCTION

Screening for pre-eclampsia (PE) at 11–13 weeks' gestation by a combination of maternal demographic characteristics and medical history with measurements of mean arterial pressure (MAP), uterine artery (UtA) pulsatility

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index (PI) and serum placental growth factor (PlGF) can identify about 90% of women who develop early PE with delivery at < 32 weeks' gestation, 75% of those with preterm PE at < 37 weeks and 45% with term PE, at a screen-positive rate of 10%[1–5]. A major multicenter study, the ASPRE trial, demonstrated that, in women with a singleton pregnancy identified by combined screening as being at high risk for preterm PE (> 1 in 100), prophylactic use of aspirin (150 mg/day from 11–14 until 36 weeks' gestation), compared to placebo, reduced the incidence of early PE by 89% and preterm PE by 62%, but had no significant effect on incidence of term PE[6]. A recent screening study in seven National Health Service maternity hospitals in England, SPREE (Screening ProgRamme for prE-Eclampsia), reported that the performance of screening for PE provided by a combination of maternal factors and MAP, UtA-PI and PlGF at 11–13 weeks' gestation is by far superior to that achieved by current National Institute for Health and Care Excellence (NICE) guidelines[5].

Small-for-gestational-age (SGA) neonates can be constitutionally small or growth restricted either due to impaired placentation, fetal abnormality or congenital infection. In PE, especially early and preterm PE, many fetuses are SGA[7]. Additionally, preterm SGA in the absence of PE is associated with similar maternal factors and biomarker profile as in preterm PE[8]. It could therefore be anticipated that first-trimester combined screening for preterm PE would also identify a high proportion of SGA neonates, both in the presence and absence of PE. It would also be expected that, since prophylactic use of aspirin reduces the incidence of early and preterm PE, it would also reduce the incidence of early and preterm SGA.

In this study, we use the data from SPREE and ASPRE to examine the effect of first-trimester screening for PE on the prediction of SGA neonates and the effect of prophylactic use of aspirin on the prevention of SGA.

METHODS

Study populations

In both SPREE and ASPRE, eligible women with a singleton pregnancy attending for their routine hospital visit at 11 + 0 to 13 + 6 weeks' gestation had first-trimester combined screening for preterm PE. SPREE was carried out in seven maternity hospitals in England and ASPRE was conducted in 13 maternity hospitals in England, Spain, Italy, Belgium, Greece and Israel[5,6]. Inclusion criteria for both studies were: age ≥ 18 years, singleton pregnancy and live fetus at the 11–13-week scan; exclusion criteria were: women who were unconscious or severely ill, those with learning difficulties or serious mental illness, and major fetal abnormality identified at the 11–13-week scan.

Gestational age was determined from the measurement of fetal crown–rump length[9]. Maternal characteristics and medical and obstetric history were recorded, and maternal weight and height measured. MAP and UtA-PI were measured according to standardized protocols[10,11]. Maternal serum concentrations of PAPP-A and PlGF were measured using one of two automated devices (DELFIA Xpress analyzer, PerkinElmer Life and Analytical Sciences, Waltham, MA, USA or BRAHMS KRYPTOR analyzer, Thermo Fisher Scientific, Hennigsdorf, Germany). Quality control was applied to achieve consistency of measurement of biomarkers across different hospitals throughout the duration of the studies.

In SPREE, the results of biomarker tests and risk for PE were not made available to the patients or their doctors. Approval for SPREE was obtained from the London–Surrey Borders Research Ethics Committee; the study is registered with the ISRCTN registry, number 83611527. In ASPRE, combined screening was used to calculate the risk of preterm PE, and those at high risk (> 1 in 100) were invited to participate in a double-blind trial on prophylactic use of aspirin (150 mg/day from 11–14 until 36 weeks' gestation) compared to placebo. 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 study is registered with the ISRCTN registry, number 13633058. For both SPREE and ASPRE, quality control of screening and verification of adherence to protocol were performed by the University College London Comprehensive Clinical Trials Unit.

Diagnosis of SGA

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The diagnoses of SGA < 10^{th}, 5^{th} and < 3^{rd} percentiles were based on a reference range of birth weight, according to gestational age in our population[12]. Pregnancies with a SGA fetus were subdivided according to the presence or absence of PE[13,14].

Statistical analysis

In the ASPRE trial, statistical analyses were performed on an intention-to-treat basis. In the pregnancies delivering at ≥ 24 weeks' gestation, the effect of aspirin on the incidence of SGA (< 10^{th}, < 5^{th} and < 3^{rd} percentiles), in all cases and in subgroups according to gestational age at birth (< 37 and < 32 weeks), was quantified as relative risk (RR) with 95% CI in the aspirin compared to the placebo group.

The data from SPREE were used to estimate the proportion of SGA (< 10^{th}, < 5^{th} and < 3^{rd} percentiles, born at ≥ 37, < 37 and < 32 weeks' gestation) with first-trimester combined screening risk for preterm PE of > 1 in 100.

The statistical software package R was used for data analyses[15].

RESULTS

Results from SPREE

First-trimester screening was carried out in 17 051 pregnancies, but 304 were lost to follow-up and 296 resulted in miscarriage or pregnancy termination at < 24 weeks' gestation; therefore, the study population comprised 16 451 cases[5].

Pre-eclampsia developed in 473 (2.9%) cases, including 33 of early PE, 142 of preterm PE and 331 of term PE (Table 1). In the early PE group, 84.8%, 84.8% and 81.8% of babies were SGA < 10th, < 5th and < 3rd percentile, respectively. In the preterm PE group, 70.4%, 60.6% and 54.9% of babies were SGA < 10th, < 5th and < 3rd percentile, respectively. In the term PE group, 19.3%, 13.9% and 11.5% of babies were SGA < 10th, < 5th and < 3rd percentile, respectively.

Table 1 Proportion of small-for-gestational-age (SGA) neonates in 473 pregnancies with pre-eclampsia (PE), according to birth-weight (BW) percentile in SPREE study

PE	*Total*	*BW < 10th percentile*	*BW < 5th percentile*	*BW < 3rd percentile*
< 32 weeks	33	28 (84.8)	28 (84.8)	27 (81.8)
< 37 weeks	142	100 (70.4)	86 (60.6)	78 (54.9)
≥ 37 weeks	331	64 (19.3)	46 (13.9)	38 (11.5)

Data are given as *n* or *n* (%).

Table 2 Proportion of small-for-gestational-age (SGA) neonates and contribution of pre-eclampsia (PE) to its incidence in SPREE study

BW percentile/GA	*Total births*	*SGA*	
		Total	*PE**
BW < 10th percentile			
≥ 37 weeks	15 501	1761 (11.4)	64 (3.6)
< 37 weeks	950	343 (36.1)	100 (29.2)
< 32 weeks	172	71 (41.3)	28 (39.4)
BW < 5th percentile			
≥ 37 weeks	15 501	988 (6.4)	46 (4.7)
< 37 weeks	950	266 (28.0)	86 (32.3)
< 32 weeks	172	66 (38.4)	28 (42.4)
BW < 3rd percentile			
≥ 37 weeks	15 501	684 (4.4)	38 (5.6)
< 37 weeks	950	226 (23.8)	78 (34.5)
< 32 weeks	172	57 (33.1)	27 (47.4)

Data are given as *n* or *n* (%). *Percentage is of those with SGA. BW, birth weight; GA, gestational age at birth.

Birth at < 32, < 37 and ≥ 37 weeks' gestation occurred in 172 (1.0%), 950 (5.8%) and 15 501 (94.2%) pregnancies, respectively. The proportion of babies that were SGA and the contribution of PE to the incidence of SGA are shown in Table 2. Of babies born at < 32 weeks, 41.3% were SGA < 10th percentile and in 39.4% of such pregnancies there was PE. Similarly, a high proportion (36.1%) of babies born at < 37 weeks were SGA < 10th percentile and in 29.2% of these cases there was PE. In contrast, the incidence of SGA < 10th percentile in babies born at term was 11.4% and only 3.6% of these were from pregnancies with PE.

On screening by a combination of maternal factors, MAP, UtA-PI and PlGF and a risk cut-off for preterm PE of 1 in 100, the screen-positive rate was 12.2% (2014 of 16 451) and the high-risk group included 30 (90.9%) early PE, 118 (83.1%) preterm PE and 162 (48.9%) term PE. The proportions of SGA neonates from all pregnancies and those with and without PE with first-trimester combined screening risk for preterm-PE of > 1 in 100 is shown in Table 3. Of neonates born at ≥ 37 weeks' gestation, the high-risk group included 20.7%, 25.2% and 26.0% that were SGA < 10th, < 5th and < 3rd percentiles, respectively. The respective percentages for those born at < 37 weeks were 45.8%, 48.9% and 51.8% and for those born at < 32 weeks they were 56.3%, 60.0% and 63.2%. In the group of SGA neonates < 10th percentile from pregnancies with PE, the high-risk group included about 81% of those born at < 37 weeks and 89% of those born at < 32 weeks; the respective values from pregnancies without PE were about 31% and 35%. In the group of SGA neonates < 5th percentile from pregnancies with PE, the high-risk group included about 79% of those born

Table 3 Proportion of small-for-gestational-age (SGA) neonates from all pregnancies and grouped according to pre-eclampsia (PE), with first-trimester combined risk for preterm PE of > 1 in 100 from the SPREE study

BW percentile/GA	*All SGA*		*SGA with PE*		*SGA without PE*	
	Total	*PE risk > 1 in 100*	*Total*	*PE risk > 1 in 100*	*Total*	*PE risk > 1 in 100*
BW < 10th percentile						
≥ 37 weeks	1761	365 (20.7)	64	38 (59.4)	1697	327 (19.3)
< 37 weeks	343	157 (45.8)	100	81 (81.0)	243	76 (31.3)
< 32 weeks	71	40 (56.3)	28	25 (89.3)	43	15 (34.9)
BW < 5th percentile						
≥ 37 weeks	988	249 (25.2)	46	31 (67.4)	942	218 (23.1)
< 37 weeks	266	130 (48.9)	86	68 (79.1)	180	62 (34.4)
< 32 weeks	65	39 (60.0)	28	25 (89.3)	37	14 (37.8)
BW < 3rd percentile						
≥ 37 weeks	684	178 (26.0)	38	27 (71.1)	646	151 (23.4)
< 37 weeks	226	117 (51.8)	78	61 (78.2)	148	56 (37.8)
< 32 weeks	57	36 (63.2)	27	24 (88.9)	30	12 (40.0)

Data are given as *n* or *n* (%). BW, birth weight; GA, gestational age at birth.

at < 37 weeks and 89% of those born at < 32 weeks; the respective values for pregnancies without PE were about 34% and 38%. In the group of SGA neonates < 3rd percentile from pregnancies with PE, the high-risk group included about 78% of those born at < 37 weeks and 89% of those born at < 32 weeks; the respective values from pregnancies without PE were about 38% and 40%.

Results from ASPRE trial

In the ASPRE trial, there were 822 participants in the placebo group and 798 in the aspirin group[6]. There were no significant differences in baseline characteristics between the aspirin and placebo groups[6]. In this study, we excluded miscarriages or pregnancy terminations at < 24 weeks' gestation and therefore the study population comprised 807 cases in the placebo group and 785 in the aspirin group.

The cumulative number of SGA neonates (< 10th and < 3rd percentiles) according to gestational age at birth for all pregnancies as well as those with and without PE in the aspirin and placebo groups is shown in Figure 1. The incidence of SGA neonates in the aspirin and placebo groups is compared in Table 4. Use of aspirin reduced the overall incidence of SGA < 10th, < 5th and < 3rd percentiles by 30–40% in babies born at < 37 weeks' gestation and by about 70% in babies born at < 32 weeks; in babies born at ≥ 37 weeks, aspirin did not have a significant effect on incidence of SGA. The aspirin-related decrease in incidence of SGA was mainly due to its incidence decreasing in pregnancies with PE, for which the decrease was about 70% in babies born at < 37 weeks' gestation and about 90% in babies born at < 32 weeks. In pregnancies without PE, use of aspirin was associated with a non-significant reduction in incidence of SGA < 10th percentile born at < 32 weeks (RR, 0.367 (95% CI, 0.138–0.974)).

Potential impact of screening for PE and treatment with aspirin on birth of SGA neonate

Prediction and prevention of SGA born at ≥ 37 weeks' gestation

Data from SPREE have shown that very few of the SGA neonates born at ≥ 37 weeks' gestation could be identified by first-trimester screening for preterm PE; only 20.7%, 25.2% and 26.0% of SGA neonates with respective birth weights < 10th, < 5th and < 3rd percentiles were in the high-risk group for preterm PE (Table 3). Data from ASPRE have demonstrated that prophylactic use of aspirin does not significantly reduce the incidence of such neonates (Table 4). Consequently, first-trimester screening for preterm PE and use of aspirin in the high-risk group does not reduce the incidence of term SGA.

Prediction and prevention of SGA born at < 37 weeks' gestation

Data from SPREE have shown that nearly half of the SGA neonates born at < 37 weeks' gestation could be identified by first-trimester screening for preterm PE; 45.8%, 48.9% and 51.8% of SGA neonates with respective birth weights < 10th, < 5th and < 3rd percentiles were in the high-risk group for preterm PE (Table 3). Data from ASPRE have demonstrated that prophylactic use of aspirin in the high-risk group reduces the birth incidence of SGA < 10th percentile by 40% (RR, 0.607 (95% CI, 0.415–0.889)); there was also a non-significant reduction in SGA < 5th percentile by 31% (RR, 0.685 (95% CI, 0.456–1.029) and SGA < 3rd percentile by 35% (RR, 0.650 (95% CI, 0.421–1.005)) (Table 4).

In a population of 1000 pregnant women who would deliver a SGA neonate < 10th percentile at < 37 weeks' gestation, about 46% ($n = 460$) would be classified by first-trimester screening as being at high-risk for preterm PE (Figure 2). If these high-risk women take aspirin, their risk for preterm SGA would be reduced by 40% (184 of 460) and the total number of preterm-SGA neonates < 10th percentile would be 816 rather than 1000. Consequently, first-trimester screening for preterm PE and use of aspirin in the high-risk group would potentially reduce the incidence of preterm SGA by about 20%.

Prediction and prevention of SGA born at < 32 weeks' gestation

Data from SPREE have shown that more than half of the SGA neonates born at < 32 weeks' gestation could be identified by first-trimester screening for preterm PE; 56.3%, 60.0% and 63.2% of SGA neonates with respective birth weights < 10th, < 5th and < 3rd percentiles were in the high-risk group for preterm PE (Table 3). Data from ASPRE have demonstrated that prophylactic use of aspirin in the high-risk group reduces the incidence of SGA neonate with birth weight < 10th, < 5th and < 3rd percentiles by the respective values of 73% (RR, 0.268 (95% CI, 0.113–0.636)), 72% (RR, 0.280 (95% CI, 0.117–0.668)) and 71% (RR, 0.294 (95% CI, 0.122–0.703)) (Table 4).

In a population of 1000 pregnant women who would deliver a SGA neonate < 10th percentile at < 32 weeks' gestation, about 56% ($n = 560$) would be classified by first-trimester screening as being at high-risk for preterm PE (Figure 2). If these high-risk women take aspirin, their risk for early SGA would be reduced by 73% (409 of 560) and the total number of early SGA neonates < 10th percentile would be 591 rather than 1000. The respective number for SGA < 5th percentile is 568 and for SGA < 3rd percentile it is 553, rather than 1000. Consequently, first-trimester screening for preterm PE and use of aspirin in the high-risk group would potentially reduce the incidence of early SGA < 10th percentile by about 40% and early SGA < 3rd percentile by about 45%.

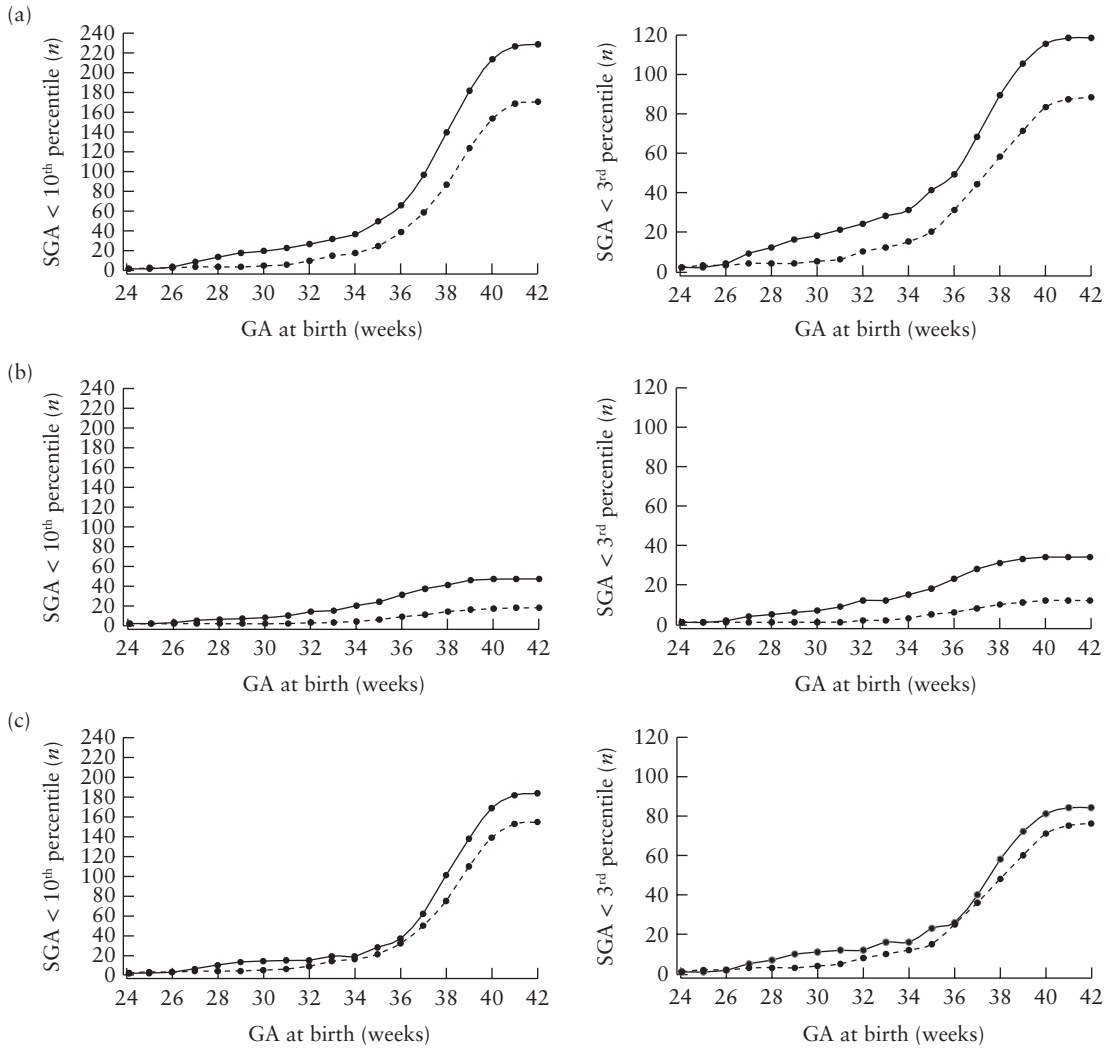

Figure 1 Cumulative number of small-for-gestational-age (SGA) babies according to gestational age (GA) at birth for placebo (——) and aspirin (- - - -) groups in all pregnancies (a) and those with (b) and those without (c) pre-eclampsia.

DISCUSSION

Principal findings of the study

Data from SPREE have demonstrated that: first, neonates are SGA < 10th percentile in 70% of pregnancies with preterm PE and in 85% of those with early PE (Table 1); second, in pregnancies that deliver preterm and early SGA neonates, there is PE in 29% and 39% of cases, respectively (Table 2); and third, screening for preterm PE by a combination of maternal factors, MAP, UtA-PI and PlGF at 11–13 weeks' gestation, identifies a high-risk group that contains about 46% of cases of preterm SGA and 56% of cases of early SGA (Table 3).

Data from ASPRE have demonstrated that, in pregnancies identified by first-trimester combined screening as being at high-risk for preterm PE, use of aspirin reduces the incidence of preterm SGA by about 40% and that of early SGA by 73%. The aspirin-related decrease in incidence of SGA was mainly due to its incidence decreasing in pregnancies with PE, for which the decrease was about 70% in babies born at < 37 weeks' gestation and about 90% in babies born at < 32 weeks. In pregnancies without PE, use of aspirin was not associated with significant reduction in incidence of SGA.

On the basis of these results, it was estimated that first-trimester screening for preterm PE and use of aspirin in the high-risk group would potentially reduce the incidence of preterm and early SGA by about 20% and 40%, respectively.

Strengths and limitations of the study

The main strength of this study is that the data were derived from two major multicenter studies[5,6]. In both SPREE and ASPRE, there was prospective examination of a large number of pregnant women in several maternity units covering a wide spectrum of demographic and racial characteristics; the results are therefore likely to be generalizable across the UK and other countries. Consistency in data collection was maintained throughout the study period by ensuring adequate training for all investigators based on standardized protocols,

Table 4 Incidence of small-for-gestational-age neonates in aspirin and placebo groups from ASPRE trial

BW percentile/GA	*Placebo* (n = *807*) (n *(%)*)	*Aspirin* (n = *785*) (n *(%)*)	*Relative risk (95% CI)*	P
All pregnancies				
BW < 10th percentile				
Any gestation	229 (28.4)	171 (21.8)	0.768 (0.646–0.911)	0.0029
≥ 37 weeks	163 (20.2)	132 (16.8)	0.833 (0.677–1.024)	0.0945
< 37 weeks	66 (8.2)	39 (5.0)	0.607 (0.415–0.889)	0.0132
< 32 weeks	23 (2.9)	6 (0.8)	0.268 (0.113–0.636)	0.0035
BW < 5th percentile				
Any gestation	160 (19.8)	114 (14.5)	0.732 (0.588–0.911)	0.0062
≥ 37 weeks	106 (13.1)	78 (9.9)	0.756 (0.575–0.995)	0.0552
< 37 weeks	54 (6.7)	36 (4.6)	0.685 (0.456–1.029)	0.0873
< 32 weeks	22 (2.7)	6 (0.8)	0.280 (0.117–0.668)	0.0053
BW < 3rd percentile				
Any gestation	118 (14.6)	88 (11.2)	0.767 (0.592–0.991)	0.0508
≥ 37 weeks	69 (8.6)	57 (7.3)	0.849 (0.607–1.187)	0.3900
< 37 weeks	49 (6.1)	31 (3.9)	0.650 (0.421–1.005)	0.0682
< 32 weeks	21 (2.6)	6 (0.8)	0.294 (0.122–0.703)	0.0082
Pre-eclampsia				
BW < 10th percentile				
Any gestation	46 (5.7)	17 (2.2)	0.380 (0.221–0.652)	0.0005
≥ 37 weeks	16 (2.0)	9 (1.1)	0.578 (0.262–1.273)	0.2543
< 37 weeks	30 (3.7)	8 (1.0)	0.274 (0.129–0.583)	0.0008
< 32 weeks	9 (1.1)	1 (0.1)	0.114 (0.019–0.695)	0.0295
BW < 5th percentile				
Any gestation	41 (5.1)	14 (1.8)	0.351 (0.194–0.632)	0.0005
≥ 37 weeks	14 (1.7)	7 (0.9)	0.514 (0.214–1.231)	0.2097
< 37 weeks	27 (3.3)	7 (0.9)	0.267 (0.119–0.594)	0.0013
< 32 weeks	9 (1.1)	1 (0.1)	0.114 (0.019–0.695)	0.0295
BW < 3rd percentile				
Any gestation	34 (4.2)	12 (1.5)	0.363 (0.191–0.687)	0.0023
≥ 37 weeks	11 (1.4)	6 (0.8)	0.561 (0.216–1.454)	0.3585
< 37 weeks	23 (2.9)	6 (0.8)	0.268 (0.113–0.636)	0.0035
< 32 weeks	9 (1.1)	1 (0.1)	0.114 (0.019–0.695)	0.0295
No pre-eclampsia				
BW < 10th percentile				
Any gestation	183 (22.7)	154 (19.6)	0.865 (0.715–1.046)	0.1521
≥ 37 weeks	147 (18.2)	123 (15.7)	0.860 (0.691–1.069)	0.1981
< 37 weeks	36 (4.5)	31 (3.9)	0.885 (0.555–1.410)	0.7012
< 32 weeks	14 (1.7)	5 (0.6)	0.367 (0.138–0.974)	0.0741
BW < 5th percentile				
Any gestation	119 (14.7)	100 (12.7)	0.864 (0.675–1.105)	0.2759
≥ 37 weeks	92 (11.4)	71 (9.0)	0.793 (0.592–1.063)	0.1423
< 37 weeks	27 (3.3)	29 (3.7)	1.104 (0.664–1.838)	0.8093
< 32 weeks	13 (1.6)	5 (0.6)	0.395 (0.147–1.059)	0.1095
BW < 3rd percentile				
Any gestation	84 (10.4)	76 (9.7)	0.930 (0.694–1.247)	0.6897
≥ 37 weeks	58 (7.2)	51 (6.5)	0.904 (0.630–1.297)	0.6556
< 37 weeks	26 (3.2)	25 (3.2)	0.988 (0.580–1.686)	1.0000
< 32 weeks	12 (1.5)	5 (0.6)	0.428 (0.158–1.160)	0.1598

BW, birth weight; GA, gestational age at birth.

external validation and quality assurance of biomarker measurements, and regular monitoring by an independent clinical trials unit.

The ASPRE trial was powered for a global test of the aspirin effect on preterm PE in a high-risk population. The statistical power for detecting effects in smaller subgroups of data is inevitably poor, resulting in wide CIs for RRs. Consequently, there is some uncertainty on the estimation of the effect of aspirin on the reduction of risk of preterm and early SGA. Nevertheless, there was a very clear trend in ASPRE for the effect of aspirin to be considerably greater for prevention of earlier than later PE, and in SPREE for a considerably greater proportion of SGA in earlier than later PE; therefore, the finding that aspirin has a considerable impact in reducing earlier rather than later SGA was as expected.

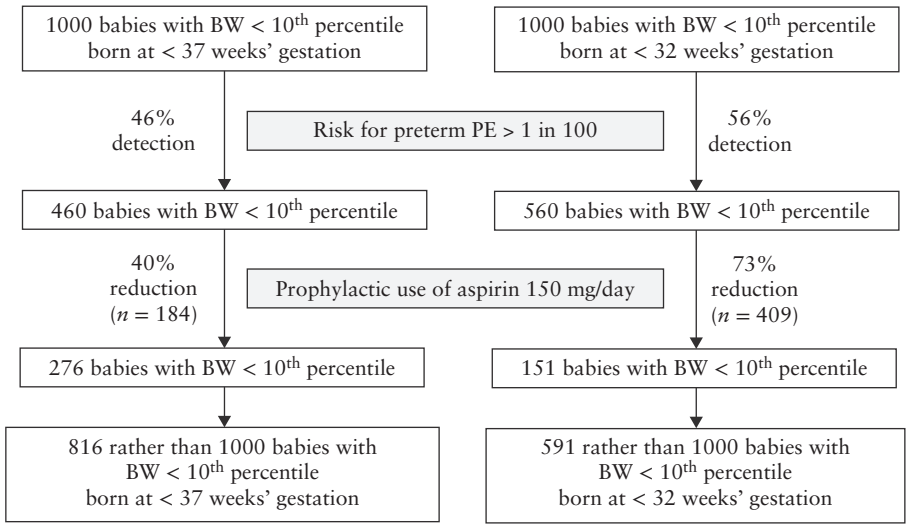

Figure 2 Prediction and prevention of small-for-gestational age by first-trimester screening for preterm pre-eclampsia (PE) and treatment of high-risk group with aspirin. BW, birth weight.

Comparison with results of previous studies

In SPREE, we found that the incidence of SGA < 10th percentile was 70% in the preterm PE group and 19% in those with term PE (Table 1). Such inverse association of gestational age at delivery with PE and incidence of SGA is compatible with results from previous studies. Yu *et al.* reported that the incidence of SGA < 10th percentile was 60% in cases of PE < 38 weeks' gestation and 24% in PE ≥ 38 weeks[7]. Hung *et al.* reported that the incidence of SGA < 10th percentile was 51% in cases of PE < 34 weeks' gestation and 25% in PE ≥ 34 weeks[16].

In SPREE, we found that the incidence of PE in pregnancies with SGA < 10th percentile was 39% for those born < 32 weeks' gestation, 29% for births < 37 weeks and only 4% for births ≥ 37 weeks (Table 2). Rasmussen and Irgens reported that the incidence of PE in pregnancies delivering SGA < 10th percentile was 28% in births at < 37 weeks and 7% in births at ≥ 37 weeks[17]. Yu *et al.* reported that the incidence of PE in pregnancies delivering SGA < 10th percentile was 51% in births at < 32 weeks, 25% in births at < 38 weeks and 2% in births at ≥ 38 weeks[7]. Hung *et al.* reported that the incidence of PE in pregnancies delivering SGA < 10th percentile was 63% in cases born at < 34 weeks, and 6% in those born at ≥ 34 weeks[16]. Crovetto *et al.* reported that the incidence of PE in pregnancies with fetal growth restriction (defined as SGA < 10th percentile with abnormal UtA, umbilical artery or middle cerebral artery Doppler, or SGA < 3rd percentile irrespective of Doppler findings) was 63% in cases born at < 34 weeks and 6% in those born at > 34 weeks[18].

In this study, the incidence of SGA was higher than we reported previously in the ASPRE trial[6]. The reason for this discrepancy is use of different birth weight charts[12,19]. In the ASPRE trial, the birth weight chart was derived from live births[19] but, since many pregnancies resulting in preterm birth are pathological, use of such charts underestimates the incidence of preterm SGA. In this study, we used a new birth-weight chart, derived from the distribution of all babies at a given gestational age including those still *in utero,* which overcomes the problem of underestimation of preterm SGA[12].

Implications for clinical practice

Preterm PE is, to a great extent, predictable by first-trimester combined screening and preventable by use of aspirin (150 mg/day from the first to the third trimester)[1–6]. A beneficial consequence of such a strategy is the prevention of a high proportion of cases of preterm SGA because, first, preterm PE is commonly associated with SGA and, second, a high proportion of preterm SGA is associated with PE.

The ASPRE trial demonstrated that, in women identified by means of first-trimester screening as being at high-risk for PE, use of aspirin reduces the incidence of preterm and early PE by approximately 60% and 90%, respectively[6]. A secondary analysis of the trial demonstrated that use of aspirin reduces the length of stay in the neonatal intensive care unit (NICU) by approximately 70%[20]. More than 80% of length of stay was attributable to babies born at < 32 weeks' gestation, and the aspirin-related reduction in length of stay could essentially be attributed to prevention of early PE. The consequence of reduction in length of stay in NICU is a substantial saving in healthcare cost which is well in excess of the cost of population screening and treatment of the high-risk group with aspirin. Reduction in the risk of birth at < 32 weeks is also likely to be associated with reduction in risk of infant death, cerebral palsy and long-term use of specialized healthcare resources[21–23].

Most cases of SGA, particularly those delivering at term, are neither predictable in the first-trimester nor are they preventable by prophylactic use of aspirin. More effective prediction of SGA is achieved by combined screening in the second and third trimesters of pregnancy[24–32]. However, unlike screening in the first trimester, for which the objective is prevention of SGA, screening later in pregnancy aims to reduce the perinatal mortality and morbidity associated with SGA through close monitoring, appropriate timing of delivery and prompt neonatal care[33].

Conclusion

First-trimester screening for PE by the combined test identifies a high proportion of cases of preterm SGA that can be prevented by the prophylactic use of aspirin.

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