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Routine first-trimester combined screening for pre-eclampsia: pregnancy-associated plasma protein-A or placental growth factor?

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KEYWORDS: blood pressure; first trimester; PAPP-A; PlGF; pre-eclampsia; screening; small-for-gestational age; trisomy 21; uterine artery Doppler

CONTRIBUTION

What are the novel findings of this work?
Using either maternal serum pregnancy-associated plasma protein-A (PAPP-A) or placental growth factor in The Fetal Medicine Foundation first-trimester combined screening algorithms for pre-eclampsia or aneuploidy results in similar performance in detecting pre-eclampsia, small-for-gestational age at birth and trisomy 21.

What are the clinical implications of this work?
Routine first-trimester combined screening for pre-eclampsia can be implemented taking advantage of PAPP-A levels available from screening for aneuploidy.

ABSTRACT

Objective *To compare the screening performance of serum pregnancy-associated plasma protein-A (PAPP-A)* vs *placental growth factor (PlGF) in routine first-trimester combined screening for pre-eclampsia (PE), small-for-gestational age (SGA) at birth and trisomy 21.*

Methods *This was a retrospective study nested in pregnancy cohorts undergoing first-trimester combined screening for PE and trisomy 21 using The Fetal Medicine Foundation (FMF) algorithm based on maternal characteristics, nuchal translucency thickness, PAPP-A, free beta-human chorionic gonadotropin, blood pressure and uterine artery Doppler. Women at high risk for preterm PE (≥ 1 in 50) received 150 mg of aspirin per day, underwent serial fetal growth scans at 28 and 36 weeks and were offered elective birth from 40 weeks of gestation. PlGF was quantified retrospectively from stored surplus first-trimester serum samples. The performance of combined first-trimester screening for PE and SGA using maternal history, blood pressure, uterine artery pulsatility index and either PAPP-A or PlGF was calculated. Similarly, the performance of combined first-trimester screening for trisomy 21 was calculated using either PAPP-A or PlGF in addition to maternal age, nuchal translucency thickness and free beta-human chorionic gonadotropin.*

Results *Maternal serum PAPP-A was assayed in 1094 women, including 82 with PE, 111 with SGA (birth weight < 10th centile), 53 with both PE and SGA and 94 with fetal trisomy 21. PlGF levels were obtained retrospectively from 1066/1094 women. Median serum PlGF multiples of the median was significantly lower in pregnancies with PE (1.0 (interquartile range (IQR), 0.8–1.4);* $P < 0.01$*), SGA (1.0 (IQR, 0.8–1.3);* $P < 0.001$*) and trisomy 21 (0.6 (IQR, 0.5–0.9);* $P < 0.0001$*) compared to in controls (1.2 (IQR, 0.9–1.5)). There was no significant difference in the performance of first-trimester screening using PAPP-A* vs *PlGF for either preterm PE (area under the receiver-operating-characteristics curve (AUC), 0.78* vs *0.79;* $P = 0.55$*) or term PE (AUC, 0.74* vs *0.74;* $P = 0.60$*). These findings persisted even after correction for the effect of targeted aspirin use on the prevalence of PE. Similarly, there were no significant differences in*

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sensitivity and specificity of combined screening for SGA or trisomy 21 when using PAPP-A vs *PlGF.*

Conclusions *Using either PlGF or PAPP-A in routine first-trimester combined screening based on maternal characteristics, blood pressure and uterine artery Doppler does not make a significant clinical difference to the detection of PE or SGA. Depending on the setting, biomarkers should be chosen to achieve a good compromise between performance and measurement requirements. This pragmatic clinical-effectiveness study suggests that combined screening for PE can be implemented successfully in a public healthcare setting without changing current protocols for the assessment of PAPP-A in the first trimester.* © *2021 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

The efficacy of a first-trimester screening algorithm for pre-eclampsia (PE) combining maternal history, mean arterial blood pressure (MAP), uterine artery pulsatility index (UtA-PI), maternal serum pregnancy-associated plasma protein-A (PAPP-A) and serum placental growth factor (PlGF) was established in the aspirin for evidence-based pre-eclampsia prevention (ASPRE) multicenter randomized controlled trial[1]. Women who were at high risk for preterm PE based on the screening algorithm and who received 150 mg of aspirin per day started before 16 weeks of gestation had a 62% reduction in the incidence of preterm (< 37 weeks) PE when compared to those receiving placebo[2].

The external validity of this trial was established recently in a clinical-effectiveness study, in which an 80% decrease in the rate of preterm PE was observed over 2 years in a public healthcare setting[3]. In that study, the first-trimester combined risk for developing preterm PE was assessed in 4841 women using maternal history, blood pressure, UtA Doppler and PAPP-A without PlGF. This was a decision based on logistical and cost-effectiveness considerations as PAPP-A is measured routinely as part of combined screening for Down syndrome, according to National Screening Committee guidelines[4]. In this clinical-effectiveness study, women at high risk (≥ 1 in 50) for preterm PE received 150 mg of aspirin per day, underwent serial fetal ultrasound assessments at 28 and 36 weeks and were offered elective birth from 40 weeks of gestation[3].

The decision to use PAPP-A instead of PlGF was based partly on the findings of the first-trimester screening programme for pre-eclampsia (SPREE) study[5]. In that study, the primary comparison was between the performance of standard maternal history-based screening for PE using National Institute for Health and Care Excellence (NICE) guidelines *vs* that of an algorithm based on maternal history, blood pressure and PAPP-A in 16 747 routinely screened women, with secondary analyses including PlGF and UtA Doppler indices. *Post-hoc* analysis showed that all factors plus PlGF yielded an 82% sensitivity for predicting preterm PE, while all factors plus PAPP-A had a 76% sensitivity, at a 10% screen-positive rate[5]. The screening performance was not improved by combining PAPP-A and PlGF. Nevertheless, the SPREE study, which undertook a comparison of NICE guidelines *vs* combined testing for PE involving various combinations of maternal factors, MAP, PAPP-A and PlGF, did not compare directly the clinical value of screening combining these factors with PAPP-A *vs* PlGF in a routine healthcare setting.

The primary aim of this study was to compare the clinical effectiveness of first-trimester combined screening for PE using maternal history, blood pressure, UtA Doppler and either PAPP-A or PlGF. Secondary aims were to assess the screening performance for small-for-gestational age (SGA) at birth and fetal trisomy 21.

METHODS

This was a retrospective cohort study in which first-trimester routine screening for PE was undertaken. In order to assess the relative value of PAPP-A and PlGF, both were measured in the participating women, and the screening performance based on maternal history, MAP, UtA-PI plus PAPP-A or PlGF was assessed. In order to investigate the impact of using PAPP-A or PlGF in screening for other outcomes, the screening performance for SGA birth and trisomy 21 using the same approach was also assessed.

This retrospective study of routinely collected clinical data and surplus serum samples undertaken for ongoing clinical audit and assay validation was deemed not to require ethics approval or signed patient consent as per the NHS health research authority decision tool. Patients and the public were not involved in the design of this study.

Study cohorts

Two nested cohorts were used in this study. The first cohort included 1000 women from a population of 4841 women who underwent first-trimester combined PE screening at St George's University Hospitals NHS Foundation Trust, London, UK between March 2018 and March 2019. The risk for developing PE was assessed by The Fetal Medicine Foundation (FMF) algorithm, combining maternal risk factors, MAP, PAPP-A and UtA-PI for each woman. Women with a risk of ≥ 1 in 50 for developing preterm PE received daily 150-mg aspirin prophylaxis from 11–14 to 36 weeks' gestation[3]. A total of 246 women who subsequently developed PE ($n = 82$), had a SGA baby (< 10th centile at birth; $n = 111$) or both ($n = 53$) were compared to consecutively screened women ($n = 754$) who did not develop these pregnancy complications. The second cohort included 94 pregnancies with a fetus affected by trisomy 21, which had undergone first-trimester maternal serum biomarker assessment at the Prenatal Screening Unit, King George's Hospital,

London, UK between July 2008 and March 2016. Samples were stored at −40°C between collection and analysis and underwent a maximum of three freeze–thaw cycles.

Laboratory analysis and assessment of pregnancy risk

In both cohorts, surplus first-trimester maternal serum samples that had been assayed for PAPP-A as part of first-trimester combined screening for PE and/or trisomy 21 were stored at −20°C. Stored aliquots were retrieved and PlGF levels determined using the Kryptor Compact Plus system analyzer (ThermoFisher Diagnostics Ltd (BRAHMS GmbH), Hennigsdorf, Germany). Samples were thawed and analyzed in batches of 50–80 samples. The BRAHMS PlGF Plus is a homogeneous sandwich immunoassay based on TRACE technology and designed to measure the free PlGF-1 isoform with a range of 3.6–7000 pg/mL with a limit of quantitation of 6.9 pg/mL.

In the PE-screened cohort, the risks for developing PE or SGA at term or preterm were calculated by using maternal characteristics, MAP, UtA Doppler and PAPP-A or PlGF in the FMF first-trimester combined PE screening algorithm, as previously described[3]. The definition for PE was based on the NICE hypertension in pregnancy guidelines[6] and SGA was defined as birth weight $< 10^{th}$ centile for gestation using the INTERGROWTH-21 birth-weight reference standard[7]. In both cohorts, the risk for trisomy 21 was calculated by either using PAPP-A or PlGF in addition to maternal age, nuchal translucency thickness and free beta-human chorionic gonadotropin using the first-trimester combined aneuploidy FMF algorithm[8].

Statistical analysis

The sensitivity and specificity of screening using PAPP-A or PlGF for the detection of term and preterm PE, as well as SGA and trisomy 21, were calculated following the STARD guidelines for diagnostic accuracy studies[9]. Receiver-operating-characteristics (ROC) curve analysis was used to compare the performance of screening by the two serum markers for PE and SGA at term and preterm. A pairwise comparison of ROC curves was performed according to the method described by DeLong *et al.*[10].

The prevalence of PE and SGA is influenced by the targeted use of aspirin, serial growth scans and elective birth from 40 weeks of gestation in the high-risk cohort. In combination, these would act to decrease the subsequent development of preterm PE by 80%[3], term PE by 20%[3] and SGA birth at term by 45%[11]. This in turn would result in a decrease in sensitivity and have a negative impact on screening performance. In order to avoid this, we undertook an additional analysis using a correction factor that was applied to calculate the adjusted sensitivity of screening using PAPP-A and PlGF, as previously described by Wright and Nicolaides[12].

A Mann–Whitney *U*-test was used to compare the median PlGF and PAPP-A values (multiples of the median; MoM) and interquartile range (IQR) between controls and women with PE, SGA or trisomy-21 fetuses. The algorithms using PAPP-A *vs* PlGF for trisomy 21 screening were compared by means of a McNemar test. MedCalc statistical software version 19.6.1 (MedCalc Ltd, Ostend, Belgium) was used to perform the statistical analyses.

RESULTS

Maternal serum PAPP-A was assayed in all pregnant women included in the study ($n = 1094$), including 82 with PE (10 at < 37 weeks), 111 with SGA (21 at < 37 weeks), 53 who had both PE and SGA (20 at < 37 weeks) and 94 with fetal trisomy 21. PlGF levels were obtained retrospectively from 1066/1094 women. Median serum PlGF MoM was significantly lower in pregnancies with PE (1.0 (IQR, 0.8–1.4); $P < 0.01$), SGA (1.0 (IQR, 0.8–1.3); $P < 0.001$) and trisomy 21 (0.6 (IQR, 0.5–0.9); $P < 0.0001$) compared to in controls (1.2 (IQR, 0.9–1.5)). Similarly, median serum PAPP-A MoM was significantly lower in pregnancies with PE (0.9 (IQR, 0.6–1.4); $P < 0.01$), SGA (0.9 (IQR, (0.6–1.3); $P < 0.0001$) and trisomy 21 (0.4 (IQR, 0.3–0.7); $P < 0.0001$) compared to controls (1.1 (IQR, 0.8–1.6)).

Comparison of PAPP-A and PlGF in screening for PE

There was no significant difference in the performance of first-trimester screening using PAPP-A *vs* PlGF for either preterm PE (AUC, 0.78 *vs* 0.79; $P = 0.55$) or term PE (AUC, 0.74 *vs* 0.74; $P = 0.60$) (Table 1 and Figure 1). At a 10% screen-positive rate, the sensitivity of combined screening for preterm PE was 46.7% for PAPP-A and 51.7% for PlGF, with corresponding values of 26.7% and 27.0% for term PE (Table 2). Sensitivities were not significantly different even after adjusting for the effect of targeted aspirin use in high-risk women (Table S1).

Comparison of PAPP-A and PlGF in screening for SGA and trisomy 21

There were no significant differences in sensitivity and specificity of screening for SGA when using PAPP-A compared with when using PlGF (Table 1). For preterm SGA, the combined screening algorithm yielded a sensitivity of 34.1% and 37.5% when using PAPP-A and PlGF, respectively, with corresponding values of 16.3% and 17.8% for term SGA (Table 2). Sensitivities were not significantly different even after adjusting for the effect of targeted aspirin use in women at high risk for SGA at term (Table S1). The sensitivity of screening for trisomy 21 was assessed at a cut-off risk of 1:150 at term. Using PAPP-A this was 84.0% (95% CI, 75.1–90.8%) with a specificity of 97.0% (95% CI, 95.7–98.0%). The corresponding sensitivity for PlGF was 79.8% (95% CI, 70.3–87.4%), with a specificity of 97.3% (95% CI, 96.1–98.2%). The McNemar test showed no significant difference between the algorithms using PAPP-A *vs* PlGF for trisomy-21 screening ($P = 0.24$).

Table 1 Areas under receiver-operating-characteristics curves for the detection of pre-eclampsia (PE) and small-for-gestational age (SGA) at birth (≤ 10th centile) using The Fetal Medicine Foundation first-trimester combined screening algorithm*, according to whether pregnancy-associated plasma protein-A (PAPP-A) or placental growth factor (PlGF) was included

Parameter	*PAPP-A*	*PlGF*	P
PE < 37 weeks	0.78 (0.75–0.80)	0.79 (0.76–0.81)	0.55
PE ≥ 37 weeks	0.74 (0.71–0.77)	0.74 (0.71–0.76)	0.60
SGA < 37 weeks	0.68 (0.65–0.71)	0.68 (0.65–0.71)	0.85
SGA ≥ 37 weeks	0.59 (0.56–0.62)	0.59 (0.55–0.62)	0.69

Values in parentheses are 95% CI. *The Fetal Medicine Foundation first-trimester combined screening algorithm was based on maternal history, mean arterial blood pressure, uterine artery pulsatility index and either PAPP-A or PlGF[2].

DISCUSSION

Main findings

In this study, PAPP-A and PlGF had a similar screening performance for PE when used as part of first-trimester screening that also included maternal characteristics, blood pressure and UtA Doppler. High sensitivity of screening for preterm PE was observed when performed with either PAPP-A or PlGF. Similarly, the use of either of the two markers resulted in very similar sensitivities of screening for term PE, SGA neonate and trisomy 21.

Comparison with previous studies

The largest study to date to compare the performance of PlGF and PAPP-A in first-trimester screening for PE by a combination of maternal factors, MAP,

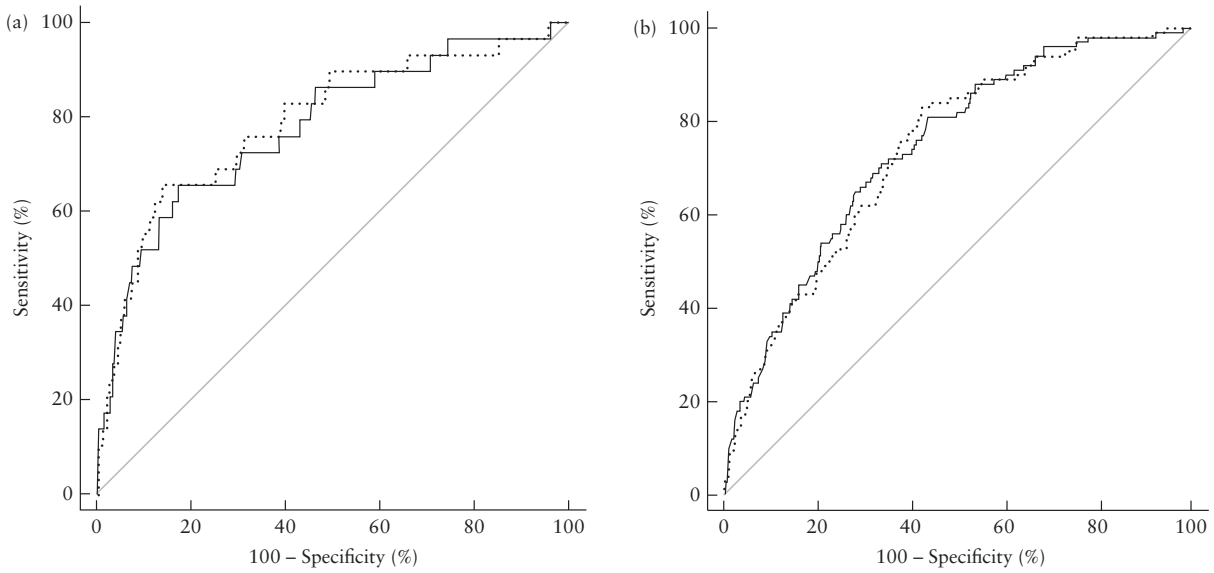

Figure 1 Receiver-operating-characteristics curves for performance of first-trimester screening for preterm (< 37 weeks) (a) and term (≥ 37 weeks) (b) pre-eclampsia by an algorithm[2] combining maternal risk factors, mean arterial blood pressure, uterine artery pulsatility index and either pregnancy-associated plasma protein-A (——) or placental growth factor (·····) to assess the patient's individual risk.

Table 2 Performance of screening for pre-eclampsia (PE) and small-for-gestational age (SGA) at birth (≤ 10th centile) using The Fetal Medicine Foundation first-trimester combined screening algorithm* at a fixed 10% screen-positive rate, according to whether pregnancy-associated plasma protein-A (PAPP-A) or placental growth factor (PlGF) was included

	PE < 37 weeks		*PE ≥ 37 weeks*	
	Sensitivity (95% CI)	*Specificity (95% CI)*	*Sensitivity (95% CI)*	*Specificity (95% CI)*
PAPP-A	46.7 (14/30) (28.3–65.7)	91.2 (885/970) (89.3–92.9)	26.7 (28/105) (18.5–36.2)	92.1 (824/895) (90.1–93.8)
PlGF	51.7 (15/29) (32.5–70.6)	91.3 (861/943) (89.3–93.0)	27.0 (27/100) (18.6–36.8)	92.0 (802/872) (90.0–93.7)
Difference	5.0 (−20.5 to 30.6)	—	0.3 (−11.8 to 12.5)	—
	SGA < 37 weeks		*SGA ≥ 37 weeks*	
	Sensitivity (95% CI)	*Specificity (95% CI)*	*Sensitivity (95% CI)*	*Specificity (95% CI)*
PAPP-A	34.1 (14/41) (20.1–50.6)	91.1 (874/959) (89.2–92.9)	16.3 (20/123) (10.2–24.0)	91.0 (798/877) (88.9–92.8)
PlGF	37.5 (15/40) (22.7–54.2)	91.2 (850/932) (89.2–92.9)	17.8 (21/118) (11.4–25.9)	91.1 (778/854) (89.0–92.9)
Difference	3.4 (−17.5 to 24.2)	—	1.5 (−8.0 to 11.0)	—

Data are given as % (*n*/*N*) (95% CI) or %. *The Fetal Medicine Foundation first-trimester combined screening algorithm was based on maternal history, mean arterial blood pressure, uterine artery pulsatility index and either PAPP-A or PlGF[2].

UtA-PI and one of the two serum markers, which was conducted retrospectively on 57 131 pregnancies in a research setting, concluded that the preferred biomarker is PlGF[13]. At a 10% screen-positive rate, the authors reported a sensitivity of 74.1% for preterm PE when using PlGF, which was significantly higher than when using PAPP-A (difference in detection rate (DR), 7.1% (95% CI, 3.8–10.6%)). However, the difference was non-significant for the prediction of term PE, which constituted the majority of cases (difference in DR, 1.8% (95% CI, 0.0–3.6%)). It should be noted that the studies by this research group[13,14] were conducted only in women who had consented to first-trimester trisomy 21 screening; this limits the generalizability of the findings of the studies as in the UK, for example, a third of women decline such assessment[15]. These studies were also labeled as non-interventional because the researchers did not prescribe aspirin prophylaxis. However, PAPP-A levels were revealed routinely to clinicians when national guidelines recommended the use of aspirin prophylaxis in pregnancies with low PAPP-A levels[16]. Therefore, it is difficult to ascertain whether aspirin was prescribed by clinicians managing the pregnancy, leading to selective suppression of PAPP-A screening efficiency.

In a prospective multicenter observational study, the same researchers compared conventional risk-factor-based assessment by NICE guidelines with first-trimester combined screening for PE in 16 747 pregnancies[17]. They demonstrated that, for the same screen-positive rate, the sensitivity of first-trimester screening for preterm PE by a combination of maternal characteristics, blood pressure and PAPP-A was significantly higher than by using current NICE guidelines. Unfortunately, in that study, no direct comparison between screening with PAPP-A *vs* PlGF was undertaken as it was not part of the prespecified commissioned analysis[17]. A *post-hoc* analysis of the data of the study, carried out by authors of the SPREE report, using the McNemar test for comparison of the screening using maternal characteristics, blood pressure, UtA Doppler and either PlGF or PAPP-A for detection of preterm PE at a 10% screen-positive rate showed no significant difference ($P = 0.10$) (unpubl. data). The corresponding 95% CI for the difference in sensitivity for the use of PlGF *vs* PAPP-A ranged from −0.2% to 12.1%. A more recent study on first-trimester combined screening for PE from China was conducted in 10 899 pregnancies, including 312 cases of PE (117 cases of preterm PE), in a clinical setting in which aspirin prophylaxis is not prescribed routinely[18]. The authors concluded that the first-trimester combined test for PE using maternal characteristics, blood pressure, UtA Doppler and PAPP-A achieved a detection rate of 65.0% for preterm PE at a 10% fixed false-positive rate, without any improvement in detection when replacing PAPP-A with PlGF, or when adding PlGF to the screening test. These findings do not demonstrate equivalence of PAPP-A and PlGF in first-trimester combined screening for preterm PE, but neither do they indicate inferiority of PAPP-A compared with PlGF in this context.

Implications of study findings

First-trimester combined screening for PE is useful because treatment of the high-risk group with aspirin reduces the rate of preterm PE by 60% to 80% in both efficacy trials and clinical effectiveness studies[2,3]. Previous work suggested that the best way of identifying the high-risk group is by a combination of maternal factors, blood pressure, uterine artery Doppler and PlGF[13]. It was concluded that, with the use of PAPP-A in place of PlGF, the same sensitivity may be achieved, but at a much higher screen-positive rate[13]. If public healthcare budgets allow measurement of one of these markers, which one is preferable? The current study has demonstrated that PAPP-A, which is already offered routinely as part of first-trimester trisomy screening in most countries, appears to have acceptable clinical effectiveness for detection of PE and SGA. A possible advantage using first-trimester PlGF is that this would confer significant cost advantage for PlGF testing in later pregnancy[19,20]. However, substituting PAPP-A with PlGF as a marker for the national screening program for trisomy would require extensive prior evaluation. Depending on the setting, biomarkers should be chosen to achieve a good compromise between performance and measurement requirements. If first-trimester combined screening for PE is to be undertaken without the use of UtA Doppler, current evidence would support the superiority of using PlGF over PAPP-A[17].

There is now robust evidence that demonstrates intervention bias with aspirin prophylaxis (lowers preterm PE by 60%) and elective birth from 40 weeks' gestation (lowers term PE by 36%)[2,21]. Future evaluation of screening performance should account for these factors by statistical adjustment for aspirin prophylaxis and competing-risk analysis to account for the effect of scheduled birth[22,23]. Furthermore, it has been established that population characteristics influence detection and false-positive rates when screening for PE[17]. Therefore, screen-positive rates will vary according to local population characteristics even when using the same screening threshold, which is not conventionally expected or observed in other national screening programs, such as aneuploidy screening.

Strengths and limitations

This study evaluated concomitantly the performance of screening for PE, SGA and trisomy 21 and assessed the relative merits of using either PAPP-A or PlGF as a maternal serum biomarker. The strength of this study is that it evaluated the real-world performance of routine first-trimester screening for PE in a public healthcare setting, in which aspirin prophylaxis was guided by the results of risk assessment. This is also a limitation of the study as it was, by design, a retrospective nested cohort analysis. Using this design meant that the prevalence of PE, SGA and trisomy 21 was higher than would be expected in a routine population, thereby influencing estimates of positive and negative predictive values. Mitigation of these biases was undertaken by reporting

sensitivity and specificity values, which are not affected by disease prevalence. Furthermore, ROC curve analysis was used only to compare the relative performance of PAPP-A *vs* PlGF rather than to demonstrate their screening performance. The main limitation of this study is that there were only 30 cases of preterm PE among a total of 135 PE cases, making this study potentially underpowered. This was due to an unexpected effect of the efficacy of targeted aspirin use in reducing the number of preterm PE cases in our population. We mitigated this issue by reporting and discussing a *post-hoc* analysis of a much larger study containing 142 cases of preterm PE, which showed similar results to the current study[17].

Conclusions

Early-pregnancy combined screening for PE is superior to conventional risk-factor-based screening that is undertaken typically in most clinical settings. Although there is evidence of superiority of PlGF over PAPP-A when used as a single marker or in combination with blood pressure, this study shows that PAPP-A is as clinically effective as PlGF in first-trimester combined PE screening when used in combination with maternal characteristics, blood pressure and UtA Doppler. Consideration should be given to routine implementation of first-trimester combined screening for preterm PE without changing current protocols for the assessment of PAPP-A.

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REFERENCES

1. Rolnik DL, Wright D, Poon LCY, Syngelaki A, O'Gorman N, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Nicolaides KH. ASPRE trial: performance of screening for preterm pre-eclampsia. *Ultrasound Obstet Gynecol* 2017; **50**: 492–495.
2. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Meiri H, Gizurarson S, Maclagan K, Nicolaides KH. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. *N Engl J Med* 2017; **377**: 613–622.
3. Guy GP, Leslie K, Diaz Gomez D, Forenc K, Buck E, Khalil A, Thilaganathan B. Implementation of routine first trimester combined screening for pre-eclampsia: a clinical effectiveness study. *BJOG* 2021; **128**: 149–156.
4. National Institute for Health and Care Excellence (2019). *Antenatal care for uncomplicated pregnancies*. [Clinical Guideline CG62]. https://www.nice.org.uk/guidance/cg62
5. Tan MY, Wright D, Syngelaki A, Akolekar R, Cicero S, Janga D, Singh M, Greco E, Wright A, Maclagan K, Poon LC, Nicolaides KH. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. *Ultrasound Obstet Gynecol* 2018; **51**: 743–750.
6. National Institute for Health and Care Excellence (2019). *Hypertension in pregnancy: diagnosis and management*. [NICE Guideline NG133]. https://www.nice.org.uk/guidance/ng133
7. Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, Lambert A, Papageorghiou AT, Carvalho M, Jaffer YA, Gravett MG, Purwar M, Frederick IO, Noble AJ, Pang R, Barros FC, Chumlea C, Bhutta ZA, Kennedy SH. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet* 2014; **384**: 857–868.
8. Mazer Zumaeta A, Wright A, Syngelaki A, Maritsa VA, Bardani E, Nicolaides KH. Screening for trisomy at 11–13 weeks' gestation: use of pregnancy-associated plasma protein-A, placental growth factor or both. *Ultrasound Obstet Gynecol* 2020; **56**: 408–415.
9. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, Irwig L, Levine D, Reitsma JB, de Vet HC, Bossuyt PM. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open* 2016; **6**: e012799.
10. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; **44**: 837–845.
11. Guy GP, Leslie K, Diaz Gomez D, Forenc K, Buck E, Bhide A, Thilaganathan B. Effect of routine first trimester combined screening for pre-eclampsia on small for gestational age birth: a secondary interrupted time series analysis. *Ultrasound Obstet Gynecol* 2021. DOI: 10.1002/uog.23741.
12. Wright D, Nicolaides K. Re: Implementation of routine first trimester combined screening for pre-eclampsia: a clinical effectiveness study. *BJOG* 2021; **128**: 141–142.
13. Mazer Zumaeta A, Wright A, Syngelaki A, Maritsa VA, Da Silva AB, Nicolaides KH. Screening for pre-eclampsia at 11–13 weeks' gestation: use of pregnancy-associated plasma protein-A, placental growth factor or both. *Ultrasound Obstet Gynecol* 2020; **56**: 400–407.
14. O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, de Alvarado M, Carbone IF, Dutemeyer V, Fiolna M, Frick A, Karagiotis N, Mastrodima S, de Paco Matallana C, Papaioannou G, Pazos A, Plasencia W, Nicolaides KH. Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation: comparison with NICE guidelines and ACOG recommendations. *Ultrasound Obstet Gynecol* 2017; **49**: 756–760.
15. Crombag NM, Vellinga YE, Kluijfhout SA, Bryant LD, Ward PA, Iedema-Kuiper R, Schielen PC, Bensing JM, Visser GH, Tabor A, Hirst J. Explaining variation in Down's syndrome screening uptake: comparing the Netherlands with England and Denmark using documentary analysis and expert stakeholder interviews. *BMC Health Serv Res* 2014; **14**: 437.
16. RCOG. Small-for-Gestational-Age Fetus, Investigation and Management (Green-top Guideline No. 31). 2013. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg31/.
17. Poon LC, Wright D, Thornton S, Akolekar R, Brocklehurst P, Nicolaides KH. Mini-combined test compared with NICE guidelines for early risk-assessment for pre-eclampsia: the SPREE diagnostic accuracy study. *Efficacy Mech Eval* 2020; **7**.
18. Hu J, Gao J, Liu J, Meng H, Hao N, Song Y, Ma L, Luo W, Sun J, Gao W, Meng W, Sun Y. Prospective evaluation of first-trimester screening strategy for preterm pre-eclampsia and its clinical applicability in China. *Ultrasound Obstet Gynecol* 2021; **58**: 529–539.
19. Duhig KE, Myers J, Seed PT, Sparkes J, Lowe J, Hunter RM, Shennan AH, Chappell LC. Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial. *Lancet* 2019; **393**: 1807–1818.
20. Panaitescu A, Ciobanu A, Syngelaki A, Wright A, Wright D, Nicolaides KH. Screening for pre-eclampsia at 35–37 weeks' gestation. *Ultrasound Obstet Gynecol* 2018; **52**: 501–506.
21. Grobman WA, Rice MM, Reddy UM, Tita ATN, Silver RM, Mallett G, Hill K, Thom EA, El-Sayed YY, Perez-Delboy A, Rouse DJ, Saade GR, Boggess KA, Chauhan SP, Iams JD, Chien EK, Casey BM, Gibbs RS, Srinivas SK, Swamy GK, Simhan HN, Macones GA. Labor Induction versus Expectant Management in Low-Risk Nulliparous Women. *N Engl J Med* 2018; **379**: 513–523.
22. Wright D, Nicolaides KH. Aspirin delays the development of preeclampsia. *Am J Obstet Gynecol* 2019; **220**: 580.e1–6.
23. Wright D, Wright A, Nicolaides KH. The competing risk approach for prediction of preeclampsia. *Am J Obstet Gynecol* 2020; **223**: 12–23.e7.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Sensitivity (95% CI) of screening for pre-eclampsia (PE) and small-for-gestational age (SGA) at birth ($\leq 10^{th}$ centile) using The Fetal Medicine Foundation algorithm combining maternal risk factors, mean arterial blood pressure, uterine artery pulsatility index and pregnancy-associated plasma protein-A (PAPP-A) or placental growth factor (PlGF)[2] after correction for the effect of targeted aspirin use in high-risk women at a 10% screen-positive rate