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Role of routine uterine artery Doppler at 18–22 and 24–28 weeks' gestation following routine first-trimester screening for pre-eclampsia

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KEYWORDS: first trimester; pre-eclampsia; screening; uterine artery Doppler

ABSTRACT

Objectives *To assess the performance of mean uterine artery pulsatility index (UtA-PI) at 18–22 and 24–28 weeks of gestation in the prediction of pre-eclampsia (PE) and small-for-gestational age (SGA), and its role in reassessing the risk of PE and SGA in pregnancies screened for PE in the first trimester.*

Methods *This was a retrospective observational cohort study of 4464 women with singleton pregnancy screened routinely for PE in the first trimester, using the Gaussian algorithm, from March 2019 to May 2021, and who underwent UtA-PI assessment at 18–22 gestational weeks. Women were categorized as low risk or high risk based on the risk index obtained after first-trimester screening for PE. In high-risk patients, UtA-PI was also assessed at 24–28 weeks of gestation. Sensitivity, specificity, positive predictive value, negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio and area under the receiver-operating-characteristics curve were calculated to assess the performance of UtA-PI at 18–22 and 24–28 weeks in predicting PE and SGA in the high-risk group. In all participants, different UtA-PI percentiles at 18–22 or 24–28 weeks, or their combination, were analyzed to explore their role in reassessing the risk of PE and SGA following first-trimester PE screening.*

Results *The performance of UtA-PI at 18–22 and 24–28 weeks in the high-risk group was good for predicting preterm PE and preterm SGA, and excellent for predicting early-onset PE and early-onset SGA, with an NPV of > 97% for all outcomes. In the low-risk group, UtA-PI ≥ 95th percentile at 18–22 weeks' gestation identified a subgroup of pregnancies with a significantly higher risk of preterm SGA compared to the low-risk group. In the high-risk group, UtA-PI < 60th percentile at 18–22 weeks' gestation, UtA-PI < 85th percentile at 24–28 weeks' gestation, and UtA-PI < 85th percentile at 24–28 weeks' gestation in women with UtA-PI ≥ 60th percentile at 18–22 weeks, identified subgroups of pregnancies with a risk of PE and SGA comparable to that of the low-risk group.*

Conclusions *The performance of UtA-PI at 18–22 and 24–28 gestational weeks in high-risk pregnancies identified during first-trimester screening for PE is similar to that in the general population. The risk of PE and SGA in a high-risk cohort can be reassessed by measuring UtA-PI at 18–22 weeks, 24–28 weeks or both, allowing adjustment of follow-up, particularly de-escalation of care.* © *2024 The Author(s). Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

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INTRODUCTION

Pre-eclampsia (PE) is a severe multisystem disorder typically characterized by the onset of maternal high blood pressure and the presence of protein in the urine after 20 weeks of gestation[1]. It affects approximately 2–4% of pregnancies and leads to over 70 000 maternal deaths and 500 000 fetal deaths globally each year[2]. While the precise underlying causes of PE remain unclear, multiple maternal and placental factors are thought to be involved. Impaired development of the placenta is believed to be a primary contributor, particularly in early-onset and preterm cases[1,3]. In normal pregnancies, the maternal spiral arteries undergo a transformation from narrow muscular vessels to wider non-muscular channels. This process results in a decrease in resistance to blood flow in the uterine arteries (UtA) between the first and second trimesters of pregnancy[4]. An increased pulsatility index (PI) in the UtA reflects maladaptation to these physiological changes in pregnancy, which is observed most commonly in pregnant women who will later develop preterm PE[5]. Measurement of UtA-PI in the first trimester of pregnancy may be used in combination with other biomarkers to identify a group at high risk for PE[6]. This early identification allows initiation of aspirin treatment before 16 weeks, which has been shown to reduce the incidence of preterm PE and, possibly, other pregnancy complications, such as early-onset PE, preterm small-for-gestational age (SGA) and early-onset SGA at birth[7,8]. Second- and third-trimester UtA-PI values in the general pregnant population have a high negative predictive value (NPV) for ruling out the development of PE and SGA[9,10]. However, their performance in excluding PE and SGA in pregnancies previously screened for PE during the first trimester is still being studied. The aim of this study was to evaluate the performance of mean UtA-PI at 18–22 and 24–28 weeks' gestation in the prediction of PE and SGA, and its role in reassessing the risk of PE and SGA in pregnancies screened for PE routinely in the first trimester.

METHODS

This retrospective observational cohort study was conducted at three maternity units in Spain and included all singleton pregnancies undergoing routine first-trimester screening for PE from March 2019 to May 2021. During the first-trimester scan (between 11 + 0 and 13 + 6 weeks)[11], gestational age was confirmed using fetal crown–rump length measurement[12]. Additionally, demographic characteristics, obstetric and maternal history, mean arterial pressure (MAP) and mean UtA-PI were assessed and recorded for all pregnant individuals.

Serum levels of pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) were measured in maternal blood samples using the fully automated Elecsys assay on an electrochemiluminescence immunoassay platform (cobas analyzer; Roche Diagnostics, Rotkreuz, Switzerland). All data used for PE risk assessment were entered into prenatal screening software, SsdwLab6 (SBP SOFT 2007 S.L; Girona, Spain), to calculate PE risk using the Gaussian algorithm[13]. Women with a risk of early-onset PE $\geq$ 1/170 were categorized as high risk and prescribed aspirin at a dose of 150 mg nightly was from the point of risk assessment until 36 gestational weeks[14]. Additionally, UtA Doppler velocimetry was conducted routinely at 18–22 weeks' gestation in all patients and at 24–28 weeks' gestation in the high-risk patients, using transabdominal ultrasound and following standard methodology[15]. UtA-PI alone did not influence the management of pregnancy, and induction of labor was not recommended unless poor fetal growth or PE was diagnosed.

PE was defined according to the criteria of the American College of Obstetricians and Gynecologists[16]. Patients diagnosed with PE with severe features[16] were delivered at 34 weeks, while delivery was delayed until 37 weeks in cases of PE without severe features. If any of the following was present, delivery was indicated at any time during pregnancy: pulmonary edema, serum creatinine $>$ 1.1 mg/dL, oliguria ($\leq$ 500 mL in 24 h or $\leq$ 20 mL/h), persistent hypertension despite appropriate antihypertensive therapy with two or more different antihypertensive drugs, persistent cerebral or visual symptoms, placental abruption or eclampsia. PE was classified as early-onset or preterm when delivery was required due to PE at $<$ 34 weeks or $<$ 37 weeks, respectively[16]. All cases diagnosed with early-onset or preterm PE were cross-checked to confirm the diagnosis and that elective delivery followed the criteria specified above. SGA was defined as birth weight $<$ 10th percentile according to local charts[17]. SGA was considered early-onset if delivery occurred before 32 weeks and preterm if delivery occurred before 37 weeks.

Pregnancy outcome data, including occurrence of PE or SGA, were extracted from patient medical records. In the high-risk cohort, the predictive performance for PE and SGA of mean UtA-PI at 18–22 and 24–28 weeks was evaluated by calculating the sensitivity, specificity, positive predictive value (PPV), NPV, positive likelihood ratio (LR+) and negative likelihood ratio (LR−) for various mean UtA-PI percentile cut-offs. Additionally, the performance of mean UtA-PI at 18–22 and 24–28 weeks for the prediction of PE and SGA was assessed by calculation of the area under the receiver-operating-characteristics curve (AUC) using UtA-PI as a quantitative variable. To reassess the risk of complications in the second and third trimesters, within both the low-risk group and the high-risk group we analyzed the rates of PE and SGA based on various UtA-PI percentile cut-offs and compared them to those of the entire low-risk group. In the high-risk group, we sought to identify the mean UtA-PI percentile cut-off that distinguished a subgroup of women with a risk of complications similar to that of the low-risk group. Conversely, in the low-risk group, our aim was to determine the mean UtA-PI percentile cut-off that distinguished a subgroup of women at heightened risk of complications compared to the entire low-risk group.

Descriptive data were presented as medians and interquartile ranges for continuous variables, while numbers and percentages were used for categorical variables. Group comparisons were conducted using the Mann–Whitney *U*-test for quantitative variables, while the chi-square test or Fisher's exact test was used for categorical variables, as appropriate. The statistical software R Commander, R package version 2.3–1 (https://www.R-project.org/), was used for data analysis. The level of statistical significance was set at $P < 0.05$.

The study protocol was approved by the Institutional Review Board at each participating site (PR-AMI-147/2021) on 3 March 2021. Written informed consent was waived.

RESULTS

During the study period, mean UtA-PI was assessed at 18–22 weeks' gestation in 4686 women with singleton pregnancy, following routine first-trimester screening for PE. Among these women, 222 (4.7%) were excluded from all analyses for various reasons (missing outcome data, termination of pregnancy, stillbirth, spontaneous live birth before 24 weeks) (Figure 1).

Thus, 4464 participants were included in the analysis, of whom 728 (16.3%) were classified as being high risk and 3736 as being low risk, based on first-trimester screening for PE. The maternal characteristics of both risk groups are described in Table 1. Preterm PE occurred in nine cases (0.24%) among the low-risk group and 16 cases (2.20%) among the high-risk group ($P < 0.001$). Notably, no cases of early-onset PE were diagnosed in the low-risk group, while three cases (0.41%) were diagnosed in the high-risk group ($P = 0.004$). Preterm SGA was observed in 17 participants (0.46%) from the low-risk group and in 22 participants (3.02%) from the high-risk group ($P < 0.001$). Early-onset SGA was reported in four (0.11%) cases within the low-risk group and six (0.82%) cases within the high-risk group ($P = 0.002$).

Performance of mean UtA-PI for prediction of PE and SGA in high-risk group on first-trimester PE screening

For the prediction of preterm PE in the group defined as high risk on first-trimester PE screening, mean UtA-PI at 18–22 weeks yielded an AUC of 0.761 (95% CI, 0.630–0.892) and at 24–28 weeks it yielded an AUC of 0.886 (95% CI, 0.834–0.939). For the prediction of early-onset PE, the AUCs were 0.945 (95% CI, 0.869–1.000) for mean UtA-PI at 18–22 weeks and 0.944 (95% CI, 0.877–1.000) for mean UtA-PI at 24–28 weeks. For the prediction of preterm SGA, the AUCs were 0.727 (95% CI, 0.625–0.829) for mean UtA-PI at 18–22 weeks and 0.885 (95% CI, 0.807–0.963) for mean UtA-PI at 24–28 weeks. For prediction of early-onset SGA, the AUC values were 0.723 (95% CI, 0.542–0.905) for mean UtA-PI at 18–22 weeks and 0.959 (95% CI, 0.936–0.983) for mean UtA-PI at 24–28 weeks (Figure S1). The sensitivity, specificity, PPV, NPV, LR+ and LR− varied

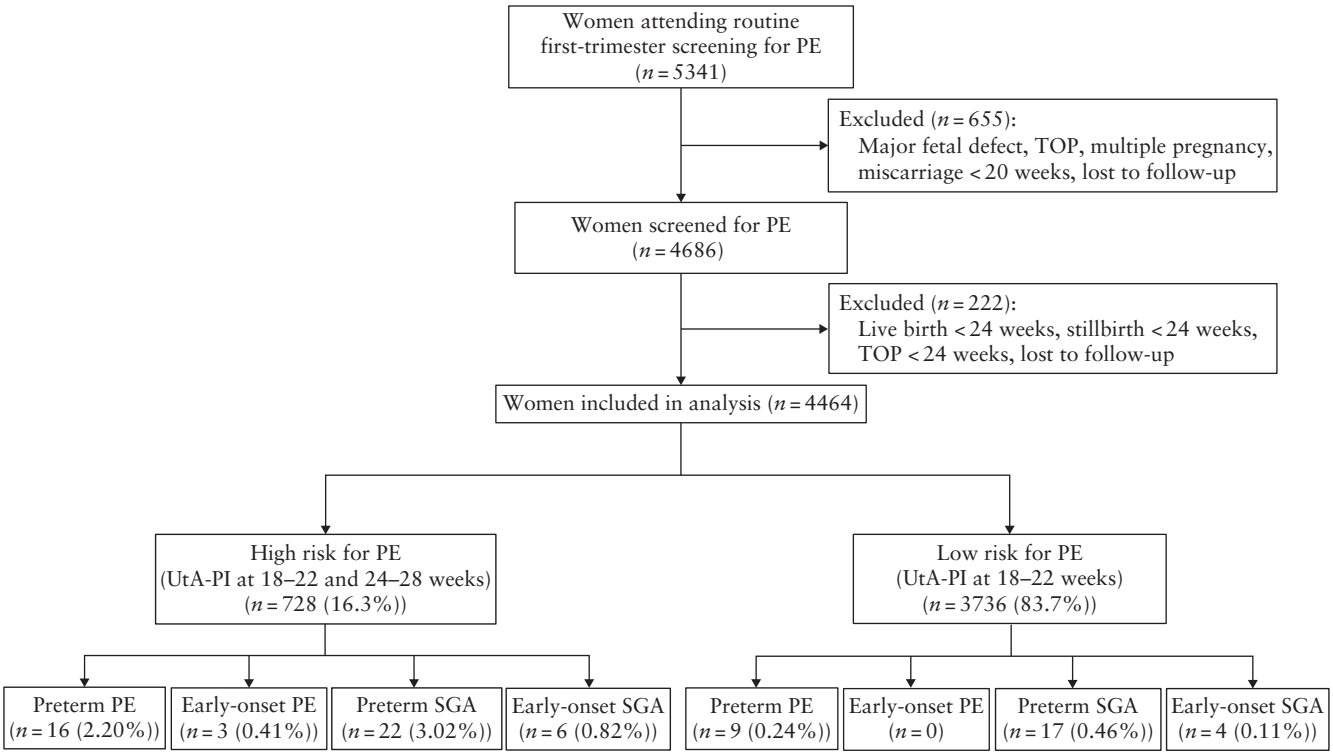

Figure 1 Flowchart summarizing study population. PE, pre-eclampsia; SGA, small-for-gestational age; TOP, termination of pregnancy; UtA-PI, uterine artery pulsatility index.

according to gestational age and the mean UtA-PI percentile used (Tables S1–S4). Consistent with the general population, the NPV was exceptionally high, exceeding 97% for all mean UtA-PI percentiles and outcomes analyzed.

Mean UtA-PI percentiles at 18–22 weeks in low-risk group on first-trimester PE screening

In the group defined as low risk on first-trimester PE screening, mean UtA-PI $\geq 95^{th}$ percentile at 18–22 weeks' gestation identified a group of 78 pregnancies (2.09%) with a risk of preterm SGA significantly higher than that of the low-risk group (3.85% *vs* 0.46%, $P = 0.008$). However, the mean UtA-PI in this low-risk group was not able to identify a subgroup of patients at higher risk of preterm PE, early-onset PE or early-onset SGA (Table 2).

Mean UtA-PI percentiles at 18–22 weeks in high-risk group on first-trimester PE screening

In the group defined as high risk on first-trimester PE screening, mean UtA-PI $< 60^{th}$ percentile at 18–22 weeks' gestation identified a cohort of 377 pregnancies (51.8%) with a risk of PE and SGA that was not significantly different from that in the cohort of 3736 pregnancies classified as low risk at first-trimester screening (Table 3 and Figure 2).

Mean UtA-PI percentiles at 24–28 weeks in high-risk group on first-trimester PE screening

In the group defined as high risk on first-trimester PE screening, mean UtA-PI $< 85^{th}$ percentile identified a group of 472 pregnancies (64.8%) with a rate of PE and SGA comparable to that of the cohort classified as low risk at first-trimester screening (Table 4 and Figure 2).

Table 1 Characteristics of women with singleton pregnancy according to risk at routine first-trimester screening for pre-eclampsia (PE)

Characteristic	*High-risk group (n = 728)*	*Low-risk group (n = 3736)*	P
Maternal age (years)	32.6 (27.9–36.4)	32.6 (28.1–36.5)	0.719
Body mass index (kg/m^2)	27.9 (24.0–32.2)	23.9 (21.4–27.3)	< 0.001
Race or ethnic group			< 0.001
White	605 (83.1)	3355 (89.8)	
Black	47 (6.4)	81 (2.2)	
South Asian	21 (2.9)	101 (2.7)	
East Asian	6 (0.8)	23 (0.6)	
Mixed race	49 (6.7)	177 (4.7)	
Method of conception			0.09
Natural	707 (97.1)	3674 (98.3)	
In-vitro fertilization	21 (2.9)	62 (1.7)	
Cigarette smoker	67 (9.2)	354 (9.5)	
Medical history			
Chronic hypertension	40 (5.5)	12 (0.32)	< 0.001
Diabetes mellitus Type 1 or 2	7 (1.0)	32 (0.9)	0.827
Obstetric history			< 0.001
Nulliparous	321 (44.1)	1465 (39.2)	
Parous without previous PE	349 (47.9)	2221 (59.5)	
Parous with previous PE	58 (8.0)	50 (1.3)	
Risk of preterm PE as assessed at screening at 11–13 weeks	2.27 (1.04–7.14)	0.01 (0.00–0.07)	< 0.001
Aspirin treatment initiated at < 16 weeks	661 (90.8)	7 (0.2)	< 0.001

Data are shown as median (interquartile range) or *n* (%).

Table 2 Adverse outcomes in singleton pregnancies with low risk for pre-eclampsia (PE) at first-trimester screening, according to mean uterine artery pulsatility index (UtA-PI) percentile at 18–22 weeks of gestation

		Preterm PE		*Early-onset PE*		*Preterm SGA*		*Early-onset SGA*	
	N	n *(%)*	P*	n *(%)*	P*	n *(%)*	P*	n *(%)*	P*
Low risk for PE at T1 screening (all)	3736	9 (0.24)	NA	0	NA	17 (0.46)	NA	4 (0.11)	NA
Low-risk subgroup with UtA-PI at 18–22 weeks:									
$\geq 95^{th}$ percentile	78	1 (1.28)	0.189	0	1.000	3 (3.85)	0.008	1 (1.28)	0.099
$\geq 90^{th}$ percentile	150	1 (0.67)	0.327	0	1.000	3 (2.00)	0.041	1 (0.67)	0.180
$\geq 85^{th}$ percentile	222	1 (0.45)	0.440	0	1.000	3 (1.35)	0.100	1 (0.45)	0.252
$\geq 80^{th}$ percentile	325	1 (0.31)	0.566	0	1.000	3 (0.92)	0.214	1 (0.31)	0.342
$\geq 75^{th}$ percentile	409	2 (0.49)	0.298	0	1.000	3 (0.73)	0.441	1 (0.24)	0.406
$\geq 70^{th}$ percentile	500	3 (0.60)	0.162	0	1.000	4 (0.80)	0.302	1 (0.20)	0.467
$\geq 65^{th}$ percentile	600	3 (0.50)	0.226	0	1.000	5 (0.83)	0.218	1 (0.17)	0.525
$\geq 60^{th}$ percentile	715	3 (0.42)	0.424	0	1.000	5 (0.70)	0.383	1 (0.14)	0.584

*Low-risk group with specified UtA-PI percentile *vs* entire low-risk group. NA, not applicable; SGA, small-for-gestational age; T1, first-trimester.

Table 3 Adverse outcomes in singleton pregnancies with high risk for pre-eclampsia (PE) at first-trimester screening, according to mean uterine artery pulsatility index (UtA-PI) percentile at 18–22 weeks of gestation

		Preterm PE		*Early-onset PE*		*Preterm SGA*		*Early-onset SGA*	
	N	n *(%)*	P*	n *(%)*	P*	n *(%)*	P*	n *(%)*	P*
Low risk for PE at T1 screening (all)	3736	9 (0.24)	NA	0	NA	17 (0.46)	NA	4 (0.11)	NA
High risk for PE at T1 screening (all)	728	16 (2.20)	< 0.001	3 (0.41)	0.004	22 (3.02)	< 0.001	6 (0.82)	0.002
High-risk subgroup with UtA-PI at 18–22 weeks:									
< 95th percentile	637	9 (1.41)	< 0.001	1 (0.16)	0.146	14 (2.20)	< 0.001	4 (0.63)	0.019
< 90th percentile	582	6 (1.03)	0.01	0	1.0	12 (2.06)	< 0.001	3 (0.52)	0.056
< 85th percentile	545	5 (0.92)	0.025	0	1.0	11 (2.02)	< 0.001	3 (0.55)	0.048
< 80th percentile	508	5 (0.98)	0.019	0	1.0	11 (2.17)	< 0.001	3 (0.59)	0.041
< 75th percentile	476	5 (1.05)	0.015	0	1.0	10 (2.10)	< 0.001	3 (0.63)	0.035
< 70th percentile	447	4 (0.89)	0.042	0	1.0	9 (2.01)	< 0.001	3 (0.67)	0.031
< 65th percentile	416	4 (0.96)	0.034	0	1.0	7 (1.68)	0.004	3 (0.72)	0.026
< 60th percentile	377	2 (0.53)	0.269	0	1.0	4 (1.06)	0.120	2 (0.53)	0.098

*High-risk group with specified UtA-PI percentile *vs* entire low-risk group. NA, not applicable; SGA, small-for-gestational age; T1, first-trimester.

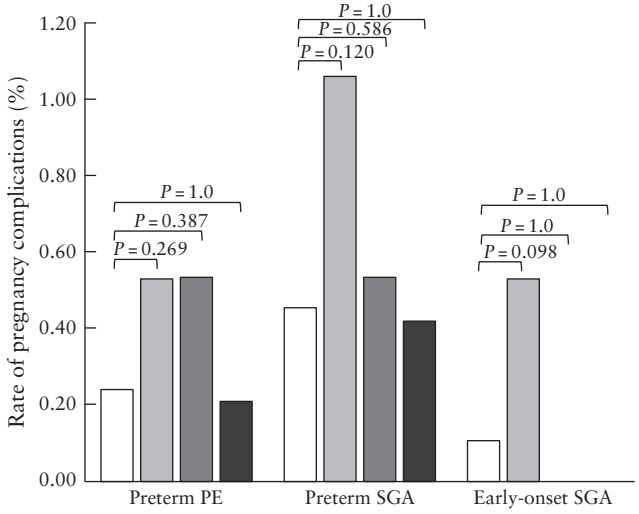

Figure 2 Outcomes of singleton pregnancies with high risk for pre-eclampsia (PE) on first-trimester screening, according to mean uterine artery pulsatility index (UtA-PI) in the second and/or third trimester (UtA-PI < 60th percentile (p60) at 18–22 weeks (▣); UtA-PI ≥ p60 at 18–22 weeks and < 85th percentile (p85) at 24–28 weeks (■); UtA-PI < p85 at 24–28 weeks (■); and comparison with low-risk control group (□). SGA, small-for-gestational age.

Mean UtA-PI percentiles at 24–28 weeks in cases with mean UtA-PI > 60th percentile at 18–22 weeks in high-risk group on first-trimester PE screening

If the mean UtA-PI at 24–28 weeks' gestation was assessed only in the 351 women with mean UtA-PI ≥ 60th percentile at 18–22 weeks' gestation, the mean UtA-PI < 85th percentile would identify a subgroup of 187 women (53.3%) with a risk of PE and SGA comparable to that of the pregnancies classified as low risk at first-trimester screening (Table 5 and Figure 2).

DISCUSSION

In a cohort of singleton pregnancies with high risk for PE at first-trimester screening, the performance of mean UtA-PI at 18–22 and 24–28 weeks was good for predicting preterm PE and preterm SGA, and excellent for predicting early-onset PE and early-onset SGA, notably showing an NPV of > 97% for all outcomes. In the group identified at first-trimester screening as low risk, the mean UtA-PI ≥ 95th percentile at 18–22 weeks' gestation identified a group of pregnancies with a significantly higher risk of preterm SGA compared to the low-risk group. In the high-risk group, mean UtA-PI < 60th percentile at 18–22 weeks' gestation, mean UtA-PI < 85th percentile at 24–28 weeks' gestation, and mean UtA-PI < 85th percentile at 24–28 weeks in women with mean UtA-PI ≥ 60th percentile at 18–22 weeks, identified subgroups of pregnancies with a risk of PE and SGA comparable to that of the low-risk group.

Several studies have demonstrated that a normal UtA-PI in the second and third trimesters has a NPV > 90% for excluding PE and SGA[18,19]. However, no previous study has assessed the performance of UtA-PI for predicting PE and SGA in a cohort previously classified as high risk after first-trimester screening for PE. Furthermore, only one previous study[20] has evaluated the clinical usefulness of UtA-PI in the second trimester for reassessing the risk of complications after first-trimester screening for PE. In that study, Meroni *et al.*[20] assessed the risk for PE in the first trimester according to the Fetal Medicine Foundation algorithm, without considering PlGF, and using maternal characteristics, MAP, mean UtA-PI and PAPP-A. Women with a risk of > 1/50, which corresponded to 7.7% of the population, were prescribed daily prophylactic aspirin (150 mg) and mid-gestation UtA-PI was assessed during the routine anomaly scan (at 20–22 weeks' gestation). At that time, women with a mean UtA-PI > 1.25, corresponding to the 90th percentile,

Table 4 Adverse outcomes in singleton pregnancies with high risk for pre-eclampsia (PE) at first-trimester screening, according to mean uterine artery pulsatility index (UtA-PI) percentile at 24–28 weeks of gestation

		Preterm PE		*Early-onset PE*		*Preterm SGA*		*Early-onset SGA*	
	N	n *(%)*	P*	n *(%)*	P*	n *(%)*	P*	n *(%)*	P*
Low risk for PE at T1 screening (all)	3736	9 (0.24)	NA	0	NA	17 (0.46)	NA	4 (0.11)	NA
High risk for PE at T1 screening (all)	728	16 (2.20)	< 0.001	3 (0.41)	0.004	22 (3.02)	< 0.001	6 (0.82)	0.002
High-risk subgroup with UtA-PI at 24–28 weeks:									
< 95th percentile	541	8 (1.48)	< 0.001	1 (0.18)	0.127	6 (1.11)	0.063	0	1.0
< 90th percentile	507	5 (1.00)	0.02	0	1.0	6 (1.18)	0.050	0	1.0
< 85th percentile	472	1 (0.21)	1.0	0	1.0	2 (0.42)	1.0	0	1.0
< 80th percentile	444	1 (0.23)	1.0	0	1.0	2 (0.45)	1.0	0	1.0
< 75th percentile	420	1 (0.24)	1.0	0	1.0	2 (0.48)	1.0	0	1.0
< 70th percentile	400	1 (0.25)	1.0	0	1.0	2 (0.50)	1.0	0	1.0
< 65th percentile	377	1 (0.27)	1.0	0	1.0	1 (0.27)	1.0	0	1.0
< 60th percentile	354	0	1.0	0	1.0	1 (0.28)	1.0	0	1.0

*High-risk group with specified UtA-PI percentile *vs* entire low-risk group. NA, not applicable; SGA, small-for-gestational age; T1, first-trimester.

Table 5 Adverse outcomes in singleton pregnancies with high risk for pre-eclampsia (PE) at first-trimester screening and with mean uterine artery pulsatility index (UtA-PI) ≥ 60th percentile at 18–22 weeks of gestation, according to mean UtA-PI percentile at 24–28 weeks

		Preterm PE		*Early-onset PE*		*Preterm SGA*		*Early-onset SGA*	
	N	n *(%)*	P*	n *(%)*	P*	n *(%)*	P*	n *(%)*	P*
Low risk for PE at T1 screening (all)	3736	9 (0.24)	NA	0	NA	17 (0.46)	*NA*	4 (0.11)	NA
High-risk subgroup with UtA-PI ≥ 60th percentile at 18–22 weeks and UtA-PI at 24–28 weeks:	351	14 (4.00)	< 0.001	3 (0.85)	< 0.001	18 (5.13)	< 0.001	4 (1.14)	0.003
< 95th percentile	244	6 (2.46)	< 0.001	1 (0.41)	0.061	4 (1.64)	0.036	0	1.0
< 90th percentile	218	4 (1.83)	0.004	0	1.0	4 (1.83)	0.026	0	1.0
< 85th percentile	187	1 (0.53)	0.387	0	1.0	1 (0.53)	0.586	0	1.0
< 80th percentile	168	1 (0.60)	0.356	0	1.0	1 (0.60)	0.548	0	1.0
< 75th percentile	153	1 (0.65)	0.331	0	1.0	1 (0.65)	0.515	0	1.0
< 70th percentile	137	1 (0.73)	0.303	0	1.0	0	1.0	0	1.0
< 65th percentile	125	1 (0.80)	0.281	0	1.0	0	1.0	0	1.0
< 60th percentile	104	0	1.0	0	1.0	0	1.0	0	1.0

*High-risk group with specified UtA-PI percentile *vs* entire low-risk group. NA, not applicable; SGA, small-for-gestational age; T1, first-trimester.

were classified as being at high risk. The authors concluded that a normal mid-gestation mean UtA-PI in the high-risk group would not be useful to de-escalate care, as the prevalence of preterm PE was significantly higher than that in the low-risk group identified in the first trimester (4.5% *vs* 0.4%, $P < 0.001$), and that women with increased mid-gestation mean UtA-PI in the low-risk group would be at greater risk of complications, which would possibly support escalation of care under these circumstances. In contrast, we observed in our study that second- and third-trimester mean UtA-PI in the high-risk group effectively identified a group of women with a low risk of complications, comparable to that of the entire low-risk group, which could be used to recommend de-escalation of care in women deemed to be at high risk in the first trimester. We also found that mean UtA-PI ≥ 95th percentile in the low-risk group identified a group of women at higher risk of preterm SGA compared with the low-risk group identified at first-trimester PE screening, therefore, mean UtA-PI may be used to recommend escalation of care in the low-risk group. The expected benefit would be low, however, since UtA-PI assessment would have been required in all low-risk women in our cohort in order to detect only three cases of preterm SGA, which would otherwise have been detected anyway because they occurred in women with other risk factors for SGA (two current smokers and one with maternal age > 40 years). These discordant results may be explained by the different screen-positive rates (7.7%[20] *vs* 16.3%) and the use of PlGF in our study, both resulting in greater detection of PE and SGA. Furthermore, different UtA-PI percentiles were explored in our study, while a single cut-off (90th percentile) was analyzed in the previous study[20]. The fact that Meroni *et al.*[20] used a different algorithm from ours may not explain the discordant findings because the two

algorithms have shown comparable detection rates for PE and SGA[21].

This study has important clinical implications because our findings suggest that UtA-PI assessment after routine first-trimester screening for PE with PlGF may have a role in further stratifying the risk of PE and SGA, especially in cases classified as high risk during first-trimester screening. This is due mainly to the exceptionally high NPV of mean UtA-PI for PE and SGA in high-risk pregnancies, which allows safe exclusion of the subsequent development of these complications. According to our results, we propose three different options for implementing measurement of second- and third-trimester mean UtA-PI for reassessing the risk of PE and SGA in women with high risk on first-trimester screening for PE (Figure 3). In Option 1, 51.8% of women, with mean UtA-PI $< 60^{th}$ percentile at 18–22 weeks' gestation, would have a risk of complications similar to that of the low-risk group, which would justify de-escalation of care. While this option involves the cost of assessing UtA-PI in all high-risk women at 18–22 weeks, this could be done during the anomaly scan, which is performed routinely in many countries; this would result in a moderate (approximately 50%) reduction in the number of women classified as high risk. Option 2 would involve de-escalating care in women with mean UtA-PI $< 85^{th}$ percentile at 24–28 weeks' gestation. This protocol would result in a 64.8% reduction in the number of women classified as high risk at the cost of having to perform an additional scan at 24–28 weeks for all women in the high-risk group. Option 3 would combine the two previous approaches by assessing UtA-PI at 24–28 weeks' gestation only in cases with mean UtA-PI $\geq 60^{th}$ percentile at 18–22 weeks. This protocol would allow de-escalation of care in 77.5% of women in the high-risk group at the cost of assessing UtA-PI in all high-risk women during the anomaly scan and in approximately 50% of them (the cases with mean UtA-PI $\geq 60^{th}$ percentile) at 24–28 weeks' gestation.

This was a large study performed in a routinely screened population, investigating how different second- and third-trimester UtA-PI percentiles may be used to reassess the risk of PE and SGA in a population screened in the first trimester using a combined algorithm for PE. While it was a retrospective study, the data were recorded prospectively in medical records as part of routine clinical practice. Our study has several limitations. First, a 16.3% screen-positive rate may be considered high, as most screening programs use risk cut-offs that correspond to a 10% false-positive rate. In our study, at the time of screening, the rate of screen-positive cases was 14.9%, only 1–2% over the 13% anticipated according to the recommended cut-off for our population (1/170)[14]. The rise from 14.9% to 16.3% in the analyzed cohort could be attributed to a higher proportion of low-risk patients being lost to follow-up. The screen-positive rate depends on several factors, such as the accuracy of the algorithm used, the *a-priori* risk of the population, the number of markers included in the algorithm and the desired detection rate. A 1/170 risk cut-off was selected specifically for our population in order to achieve a 90% detection rate, to enhance the preventive effect of aspirin, since > 80% of women in our population are of white race, in whom the accuracy of first-trimester screening for predicting PE is markedly lower than in other ethnic groups[22]. This could reduce the external validity of our results because they may be applicable only when using

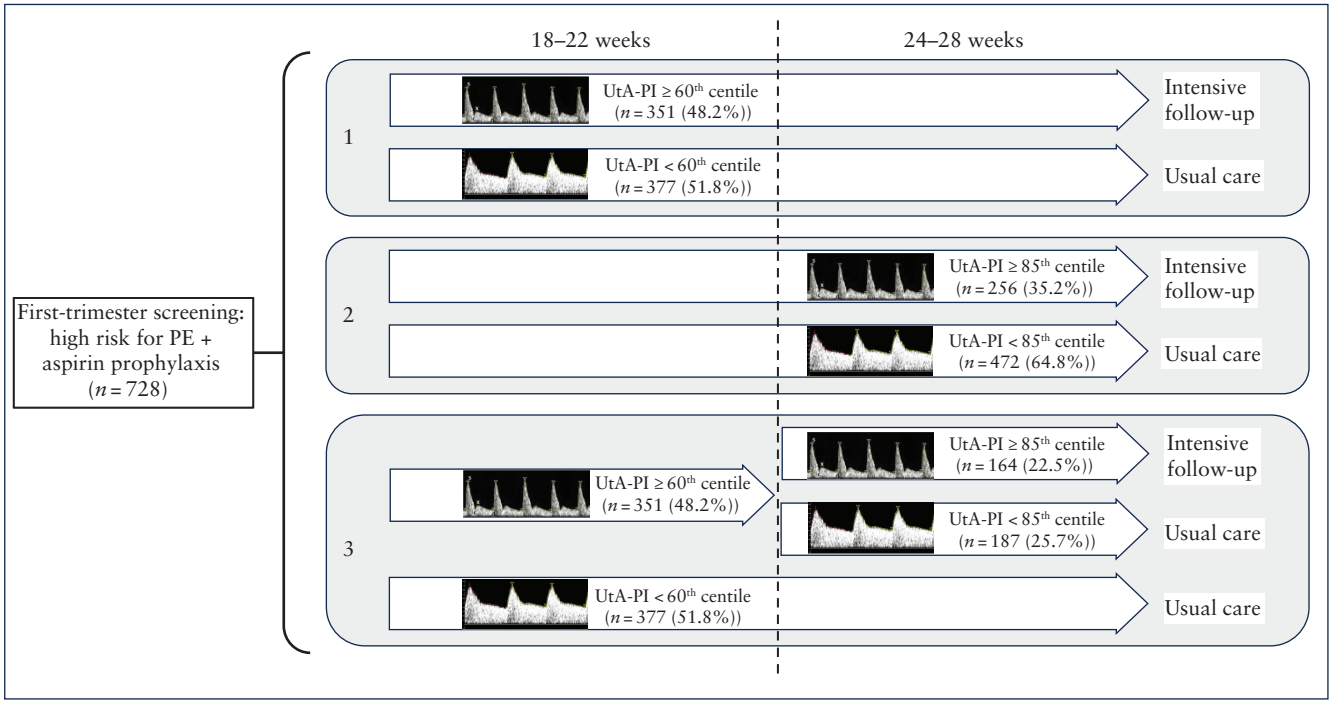

Figure 3 Options for de-escalating care in singleton pregnancies with high risk for pre-eclampsia (PE) on first-trimester screening, using mean uterine artery pulsatility index (UtA-PI) in the second and/or third trimester of pregnancy.

cut-offs that correspond to a detection rate similar to that of our study. Second, to simplify its implementation in clinical practice, UtA-PI was considered alone in a dichotomous way instead of as a continuous variable or in combination with other markers, which could have resulted in a less accurate individual risk assessment. Finally, aspirin compliance was not verified; therefore, the impact of treatment adherence could not be assessed.

In conclusion, the performance of mean UtA-PI at 18–22 and 24–28 gestational weeks in high-risk pregnancies identified during first-trimester screening for PE was good for predicting preterm PE and preterm SGA, and excellent for predicting early-onset PE and early-onset SGA, notably showing an NPV of > 97% for all outcomes. The risk of PE and SGA in these pregnancies could be reassessed by measuring mean UtA-PI at 18–22 weeks, at 24–28 weeks or both, and this may allow adjustment of follow-up, especially de-escalation of care in a proportion of these women.

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Disclosure

M. Mendoza received lecture fees from Roche Diagnostics. Roche Diagnostics had no influence on the study design, data collection and analysis or interpretation of results. The other authors report no conflicts of interest.

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SUPPORTING INFORMATION ON THE INTERNET

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

Figure S1 Receiver-operating-characteristics curves for performance of mean uterine artery pulsatility index (as a continuous variable) in the prediction of pre-eclampsia (PE) and small-for-gestational age (SGA).

Table S1 Performance of mean uterine artery pulsatility index (UtA-PI) for predicting preterm pre-eclampsia in pregnancies with high risk for pre-eclampsia at first-trimester screening

Table S2 Performance of mean uterine artery pulsatility index (UtA-PI) for predicting preterm small-for-gestational age in pregnancies with high risk for pre-eclampsia at first-trimester screening

Table S3 Performance of mean uterine artery pulsatility index (UtA-PI) for predicting early-onset pre-eclampsia in pregnancies with high risk for pre-eclampsia at first-trimester screening

Table S4 Performance of mean uterine artery pulsatility index (UtA-PI) for predicting early-onset small-for-gestational age in pregnancies with high risk for pre-eclampsia at first-trimester screening