Received: 2 July 2023 | Revised: 10 September 2023 | Accepted: 12 September 2023

DOI: 10.1111/aogs.14687

AOGS Acta Obstetricia et Gynecologica Scandinavica

ORIGINAL RESEARCH ARTICLE

Clinical effectiveness of routine first-trimester combined screening for pre-eclampsia in Spain with the addition of placental growth factor

Pablo Garcia-Manau[1,2] | Erika Bonacina[1,2] | Berta Serrano[1,2] | Sara Caamiña[3] | Marta Ricart[4] | Eva Lopez-Quesada[5] | Àngels Vives[6] | Monica Lopez[7] | Elena Pintado[8] | Anna Maroto[9] | Sara Catalan[1] | Marta Dalmau[1] | Ester Del Barco[1] | Alina Hernandez[1] | Marta Miserachs[1] | Marta San Jose[1] | Mireia Armengol-Alsina[1] | Elena Carreras[1] | Manel Mendoza[1,2]

[1]Universitat Autònoma de Barcelona, Barcelona, Spain

[2]Department of Obstetrics, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain

[3]Department of Obstetrics, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain

[4]Department of Obstetrics, Hospital Universitari Germans Trias i Pujol, Badalona, Spain

[5]Department of Obstetrics, Hospital Universitari Mútua Terrassa, Terrassa, Spain

[6]Department of Obstetrics, Consorci Sanitari de Terrassa, Terrassa, Spain

[7]Department of Obstetrics, Hospital Universitari de Tarragona Joan XXIII, Tarragona, Spain

[8]Department of Obstetrics, Hospital Universitario de Getafe, Getafe, Spain

[9]Department of Obstetrics, Hospital Universitari de Girona Dr. Josep Trueta, Girona, Spain

Correspondence
Manel Mendoza, Universitat Autònoma de Barcelona, 119-129, 08035 Barcelona, Spain.
Email: manel.mendoza@vallhebron.cat

Abstract

Introduction: Pre-eclampsia affects 2%–8% of pregnancies and is one of the leading causes of maternal and perinatal morbidity and mortality. First-trimester screening using an algorithm that combines maternal characteristics, mean arterial blood pressure, uterine artery pulsatility index and biomarkers (pregnancy-associated plasma protein-A and placental growth factor) is the method that achieves a greater diagnostic accuracy. It has been shown that daily salicylic acid administration before 16 weeks in women at a high risk for pre-eclampsia can reduce the incidence of preterm pre-eclampsia. However, no previous studies have evaluated the impact of routine first-trimester combined screening for pre-eclampsia with placental growth factor after being implemented in the clinical practice.

Material and methods: This was a multicenter cohort study conducted in eight different maternities across Spain. Participants in the reference group were prospectively recruited between October 2015 and September 2017. Participants in the study group were retrospectively recruited between March 2019 and May 2021. Pre-eclampsia risk was calculated between 11^{+0} and 13^{+6} weeks using the Gaussian algorithm combining maternal characteristics, mean arterial pressure, uterine arteries pulsatility index, pregnancy-associated plasma protein-A and placental growth factor. Patients with a risk greater than 1/170 were prescribed daily salicylic acid 150 mg

Abbreviations: ASA, salicylic acid; BMI, body mass index; CI, confidence interval; FMF, fetal medicine foundation; ICU, intensive care unit; MAP, mean arterial pressure; OR, odds ratio; PAPP-A, pregnancy-associated plasma protein-A; PE, pre-eclampsia; PlGF, placental growth factor; SGA, small for gestational age; UtAPI, uterine artery pulsatility index.

Pablo Garcia-Manau and Erika Bonacina contributed equally as co-first authors.

Elena Carreras and Manel Mendoza contributed equally as co-last authors.

until 36 weeks. Patients in the reference group did not receive salicylic acid during gestation.

Results: A significant reduction was observed in preterm pre-eclampsia (OR 0.47; 95% CI: 0.30–0.73), early-onset (<34 weeks) pre-eclampsia (OR 0.35; 95% CI: 0.16–0.77), preterm small for gestational age newborn (OR 0.57; 95% CI: 0.40–0.82), spontaneous preterm birth (OR 0.72; 95% CI: 0.57–0.90), and admission to intensive care unit (OR 0.55; 95% CI: 0.37–0.81). A greater treatment adherence resulted in a significant reduction in adverse outcomes.

Conclusions: Routine first-trimester screening for pre-eclampsia with placental growth factor leads to a reduction in preterm pre-eclampsia and other pregnancy complications. Aspirin treatment compliance has a great impact on the effectiveness of this screening program.

KEYWORDS
aspirin, placental growth factor, PlGF, pre-eclampsia, salicylic acid, screening

1 | INTRODUCTION

Pre-eclampsia (PE) affects around 2%–8% of pregnancies and is one of the leading causes of maternal and perinatal morbidity and mortality,[1] being the most frequent cause of maternal admission to intensive care units (ICU) and resulting in significant health care costs.[2,3] For this reason, an optimal screening method has been investigated for years. Currently, the method that combines maternal characteristics (medical history, mean arterial pressure [MAP], uterine artery pulsatility index [UtAPI] and biomarkers placental growth factor [PlGF] and in some cases pregnancy-associated plasma protein-A [PAPP-A]) has the greatest diagnostic accuracy.[4,5] Thus, different scientific organizations recommend universal first-trimester screening for PE using this method.[6,7]

Different algorithms have been developed for identifying women at a high risk for early-onset and preterm PE.[5,8,9] The most used and widely validated algorithm is the one developed by the Fetal Medicine Foundation. Nevertheless, in most Spanish maternities the Gaussian algorithm is used for routine screening in the first trimester, as it allows assessment of the UtAPI by Doppler ultrasound either transabdominally or transvaginally, and measurement of the biomarkers between 8^{+0} and 13^{+6} weeks,[10] rendering it easy to integrate with the first-trimester aneuploidy screening, and highly adaptable in different settings. The Gaussian algorithm was designed to predict early-onset PE; however, it has shown a similar performance to that of the Fetal Medicine Foundation algorithm for predicting preterm PE, early-onset PE and small for gestational age (SGA) fetuses in a Spanish population.[11]

The ASPRE trial showed that daily administration of 150 mg of salicylic acid (ASA) before 16 weeks reduces the incidence of preterm PE by 62% and may also reduce the incidence of early-onset PE, early-onset SGA and preterm SGA by 82%, 40% and 20%, respectively.[12] These favorable findings were observed in a research context; however, a screening strategy may be less effective in real-life clinical practice.[13] For this reason, it is advisable to prospectively assess the clinical impact of a new strategy after being implemented in the clinical practice.[14] The clinical impact of the routine first-trimester combined screening for PE with PlGF has never been investigated. Therefore, the aim of this study was to assess the clinical effectiveness after implementing a routine first-trimester combined screening for PE with PlGF by the Gaussian algorithm.

Key message

Routine first-trimester screening for pre-eclampsia with placental growth factor reduced preterm and early-onset pre-eclampsia, preterm small for gestational age, spontaneous preterm birth and intensive care unit admissions. Aspirin compliance has a great impact on the effectiveness of this screening program.

2 | MATERIAL AND METHODS

This was a multicenter cohort study. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was followed for writing this report.[15] Participants in the reference group were obtained from a secondary analysis of a study for the development of the Gaussian algorithm to predict early-onset PE at the first trimester conducted at Vall d'Hebron University Hospital between October 2015 and September 2017. Data from this cohort of pregnant individuals have previously been published.[5,16] A total of 3777 patients were assessed at the routine first-trimester scan. Of those, 2946 were enrolled; 305 (10.4%) were excluded from all analysis for the following reasons: missing outcome data ($n=86$), major fetal defects ($n=13$), miscarriage <24 weeks ($n=15$), and insufficient

blood sample ($n=191$). In addition to these exclusions, birthweight data were unavailable for an additional 158 (5.4%) patients. Consequently, 463 (15.7%) participants were excluded from the SGA analysis. None of the participants included in the reference group received ASA during gestation, as it was an exclusion criterion. In the study group, 11 586 patients from eight different maternities across Spain attending the first-trimester ultrasound were retrospectively analyzed between March 2019 and May 2021. PE risk was calculated for all as part of their routine prenatal care. Of those, 1121 (10%) were excluded from all analysis for the following reasons: missing outcome data ($n=905$), major fetal defects ($n=110$), and miscarriage <24 weeks ($n=106$). In addition to these exclusions, birthweight data were unavailable for an additional 1332 (11.8%) patients. Consequently, 2453 (21.8%) participants were excluded from the SGA analysis. More details can be seen in the flow chart (Figure 1).

During the first-trimester scan, between 11^{+0} and 13^{+6} weeks, gestational age was confirmed by fetal crown-rump length measurements.[17] Demographic characteristics, obstetric and maternal history and MAP and UtAPI (measured transvaginally or transabdominally) were assessed and recorded for all participants.[18,19] Serum PAPP-A (mU/L) and PlGF (pg/mL) levels were measured in maternal blood samples between 8^{+0} and 13^{+6} weeks[10] by means of the fully automated Elecsys assays on an electrochemiluminescence immunoassay platform (Cobas analyzer; Roche Diagnostics, Rotkreuz, Switzerland). MAP, PlGF and PAPP-A values were then transformed to multiples of the median.[5] All data were introduced in the prenatal screening software SsdwLab6 (SBP Soft 2007 S.L; Girona, Spain), which was already being used for common trisomies screening in all participant sites. PE risk was then calculated in the study group using the Gaussian algorithm by combining maternal characteristics, maternal history, MAP, UtAPI, PAPP-A and PlGF. Women with a risk of early-onset PE ≥1/170[20] were considered at a high risk for PE and referred before 16^{+6} weeks to a specialized clinic where ASA was prescribed at a dose of 150 mg at night (Tromalyt box of 28 tablets; Mylan Pharmaceuticals, S.L; Madrid, Spain) until 36 weeks. Six boxes are usually required to complete treatment and compliance in the study group was checked using pharmacy dispensing records.

PE was defined in both groups according to the criteria of the American College of Obstetricians and Gynecologists.[21] Patients diagnosed with PE with severe features were delivered at 34 weeks and 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 (≤500 mL in 24 h or ≤ 20 mL/h), persistent hypertension despite appropriate antihypertensive therapy (≥2 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 before 34 or 37 weeks, respectively. Term PE (≥37 weeks) was not recorded for that study as ASA treatment has not been proven to reduce the incidence of this condition.[22] All cases diagnosed with early-onset and preterm PE were cross-checked to confirm that diagnosis and elective delivery followed the criteria previously described.

SGA was defined as birthweight below the 10th percentile according to local charts[23] and was considered early-onset if delivery occurred before 32 weeks and preterm if delivery occurred before 37 weeks.

Maternal admission to the ICU was recorded only when the indication was related to PE or its complications (eclampsia or hemorrhage due to placental abruption). Other reasons for maternal ICU admission were not recorded. On the other hand, as participating sites had different neonatal care units and different criteria for admission due to the existence of transitional care units in some of them, neonatal admission to the ICU was not recorded in this study.

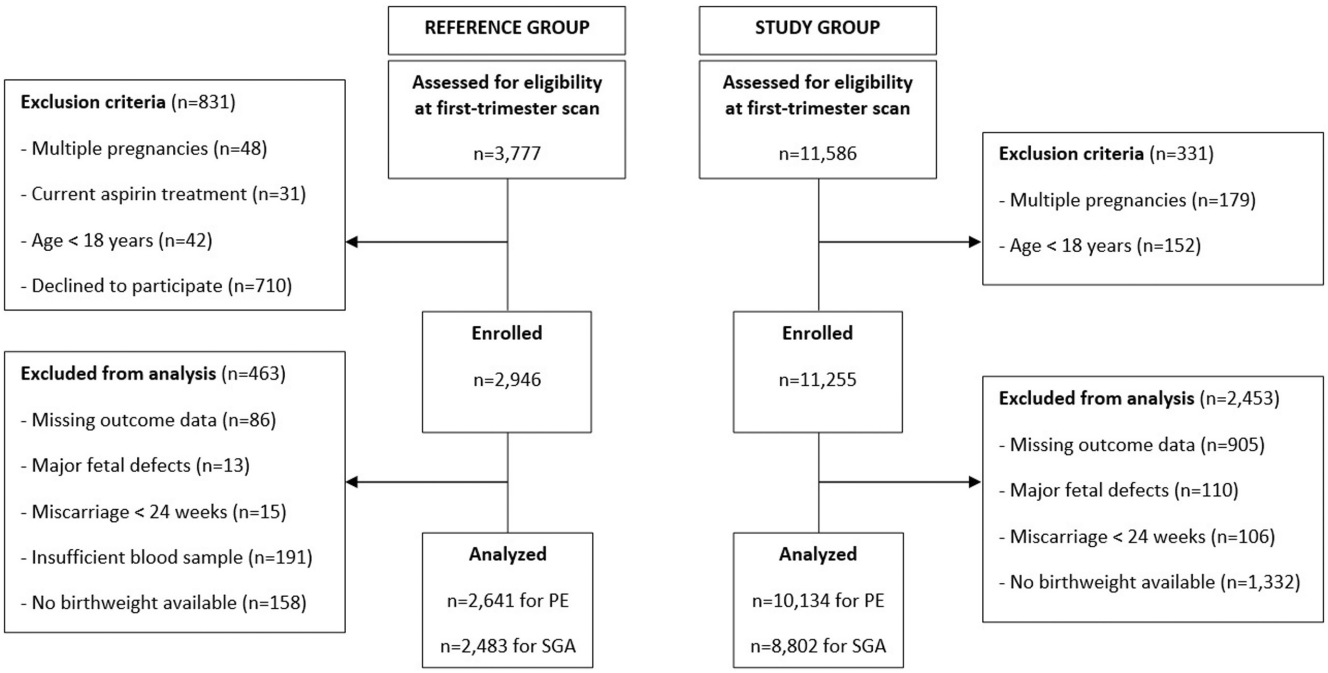

FIGURE 1 Recruitment flow chart.

Categorical data are reported as frequency and percentage and continuous data as mean and standard deviation or as median and interquartile range. Comparisons between groups were estimated by chi-squared or Fisher's tests, as appropriate. Mann–Whitney U test was used to assess differences between groups. Treatment effect was quantified as the odds ratio (OR) with a 95% confidence interval (CI) in the study group. The statistical software R Commander, R package version 2.3–1, was used for data analyses. Statistical significance level was set at $p < 0.05$.

The incidence of preterm PE in our population before implementation of routine first-trimester PE screening was 1.14%.[10] Sample size calculation was based on an expected reduction in the incidence of preterm PE by 62% (from 1.14% to 0.43%),[22] with a statistical power of 80% and an estimated dropout rate of 5%. Therefore, in order to detect such reduction at a significance level of 5%, 2546 women had to be recruited for each group. Since untreated controls with UtAPI and PlGF assessed at the first trimester are no longer available in our region and as we aimed to investigate the effect of aspirin treatment on the incidence of rarer complications such as early-onset PE, we decided to include more cases than controls in a 4:1 ratio, which is the maximum accepted ratio for case–control studies.[24]

2.1 | Ethics statement

The study protocol was approved by the Institutional Review Board at each participating site (PR-AMI-147/2021) on March 23, 2021. All participants in the untreated group signed the written informed consent. For the retrospective cohort of treated participants (study group), written informed consent was waived.

3 | RESULTS

Baseline characteristics in the untreated and treated groups were significantly different for age, body mass index, assisted reproductive technique with ovarian stimulation, obstetric history, MAP, UtAPI, PAPP-A and PlGF (Table 1).

Preterm PE occurred in 30 of 2641 participants (1.14%) in the untreated group vs 54 of 10 134 patients (0.53%) in the treated group (OR 0.47; 95% CI: 0.30–0.73; $p < 0.001$). Early-onset PE occurred in 11 patients (0.42%) in the untreated group vs 15 patients (0.15%) in the treated group (OR 0.35; 95% CI: 0.16–0.77; $p = 0.009$). Preterm SGA occurred in 44 of 2483 patients (1.77%) in

TABLE 1 Baseline characteristics of the study population.

Characteristic	Reference group ($n = 2641$)	Study group ($n = 10\,134$)	p-value
Age in years, median (IQR)	32.0 (28.0–36.0)	32.8 (28.5–36.6)	<0.001
BMI in kg/m^2, median (IQR)	23.8 (21.3–27.5)	24.5 (21.8–28.4)	<0.001
Ethnicity			0.444
Other	2569 (97.3)	9884 (97.5)	
Black	72 (2.7)	250 (2.5)	
Smoking status	312 (11.8)	1039 (10.3)	0.073
ART with ovarian stimulation	78 (3.0)	219 (2.2)	0.020
Medical history			
Chronic Hypertension	29 (1.1)	132 (1.3)	0.645
Diabetes mellitus	36 (1.4)	130 (1.3)	0.773
Obstetric history			
Nulliparous	1232 (46.6)	4155 (41.0)	0.002
Previous pre-eclampsia	35 (1.3)	229 (2.3)	0.005
Biophysical variables			
GA at first-trimester ultrasound in weeks, median (IQR)	12.6 (12.1–13.0)	12.6 (12.3–13.0)	0.472
MoM MAP, median (IQR)	1.05 (0.97–1.14)	1.09 (1.00–1.18)	<0.001
MoM UtAPI, median (IQR)	1.03 (0.84–1.26)	1.01 (0.82–1.21)	<0.001
Biochemical variables			
GA for PAPP-A and PlGF measurement, median (IQR)	10.6 (10.0–11.3)	10.7 (10.0–11.9)	<0.001
MoM PAPP-A, median (IQR)	1.05 (0.73–1.50)	1.02 (0.72–1.46)	0.040
MoM PlGF, median (IQR)	0.96 (0.75–1.19)	0.98 (0.77–1.22)	0.008

Note: Categorical data are reported as frequency and percentage. Continuous data are reported as the median and interquartile range.

Abbreviations: ART, assisted reproductive technique; BMI, body mass index; GA, gestational age; IQR, interquartile range; MAP, mean arterial pressure; MoM, multiples of median; PAAP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; UtAPI, uterine artery pulsatility index.

the untreated group vs 89 of 8802 women (1.01%) in the treated group (OR 0.57; 95% CI: 0.40–0.82; $p = 0.003$). Spontaneous preterm birth (SPB) <37 weeks occurred in 104 patients (3.9%) in the untreated group vs 287 (2.8%) in the treated group (OR 0.72; 95% CI: 0.57–0.90; $p = 0.005$). More details can be found in Figure 2. Admission to the ICU was required in 37 women (1.40%) in the untreated group vs 78 participants (0.77%) in the treated group (OR 0.55; 95% CI: 0.37–0.81; $p = 0.003$) and the total number of days at the ICU was 133 in the untreated group versus 270 in the treated group (OR 0.53; 95% CI: 0.43–0.65; $p < 0.001$). We would like to clarify that despite 270 days was more than 133 days, since the treated group was approximately four times larger, the OR was <1. Other adverse outcomes, such as incidence of early-onset SGA, SPB <34 weeks, placental abruption and stillbirth, were not significantly different between both groups (Table 2).

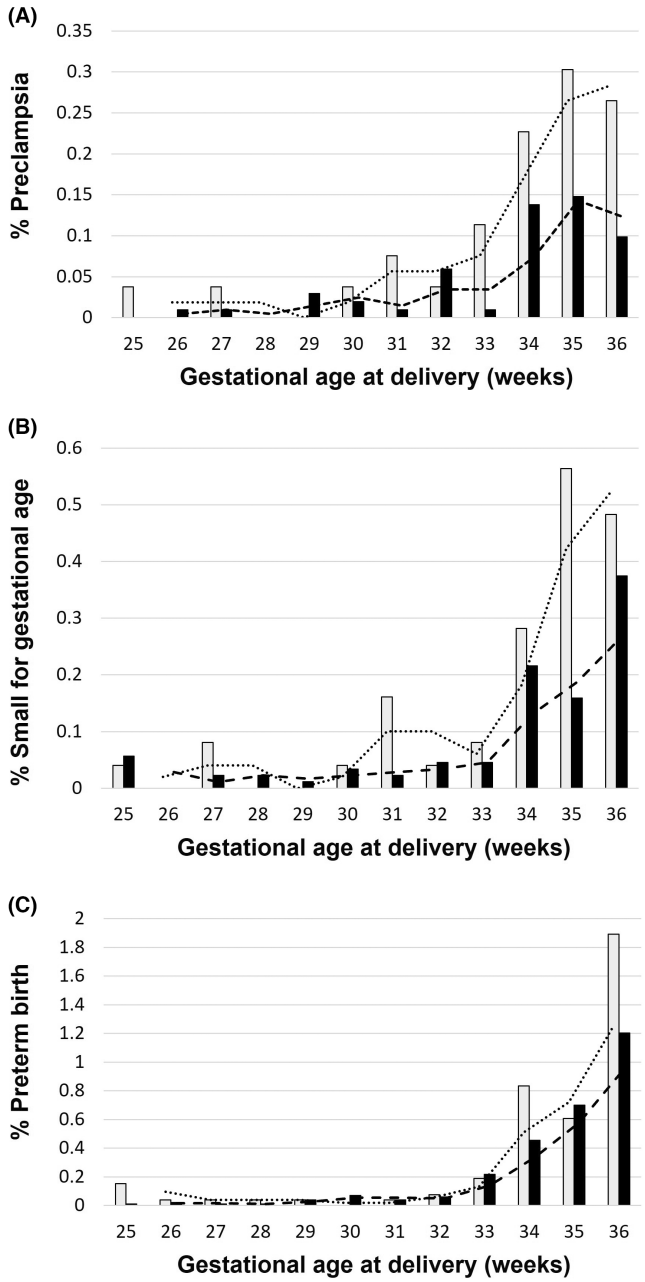

FIGURE 2 Proportion of women developing (A) pre-eclampsia, (B) small-for-gestational-age newborns, or (C) spontaneous preterm birth according to gestational age at delivery in the treated and the untreated cohorts (untreated cohort, gray bars and dotted line; treated cohort, black bars and dashed line).

During the study period, 1520 patients (15.0%) were at a high risk for PE. Of those, 1406 (92.5%) took ASA; in 39 patients (2.6%) treatment could not be confirmed and 75 patients (4.9%) did not take ASA due to the following reasons: ASA was not prescribed (10), allergy or contraindications (18), treatment was refused by the patient (28), patient did not attend the medical appointment before 16 weeks (16) and other (3). Among the 1363 patients that took ASA, compliance was >50% in 1292 (94.8%) and > 90% in 1183 (86.8%).

The 1393 patients with verified ASA treatment compliance in the treated group were classified into three groups according to treatment adherence during the study period: <50%, ≥50% and ≥90% of tablet intake. The risk for PE and baseline characteristics did not differ significantly between women with a compliance <50% and ≥50%, except for maternal age and UtAPI (Table S1). When comparing the occurrence of adverse outcomes between participants with treatment compliance <50% and those with treatment compliance ≥50% and ≥90%, we observed that greater treatment compliance resulted in a significant reduction of adverse outcomes, especially when compliance was ≥90% (Table 3).

4 | DISCUSSION

In this study, routine first-trimester combined screening for PE with PlGF and subsequent aspirin treatment resulted in a significant reduction of preterm PE by 53%, early-onset PE by 65%, preterm SGA by 43%, SPB by 28%, maternal ICU admission by 45% and length of stay in the ICU by 47%. On the other hand, this screening program did not show any significant impact on the incidence of early-onset SGA, placental abruption or stillbirth.

One of the main strengths of this study was the large sample size from eight maternity hospitals across Spain, which increases the external validity of our findings. Additionally, the favorable results of our study demonstrate the effectiveness of the first-trimester combined screening for PE also in real-life conditions and the importance of ASA treatment compliance for the screening to be effective.

We acknowledge some limitations to this study. First, participants in the treated group were recruited from eight different sites, while patients in the untreated group were obtained from a single site. This may have resulted in groups not being comparable. However, differences in baseline characteristics, such as biophysical and biochemical markers, were small and therefore may not be clinically relevant. Regarding obstetric history and maternal characteristics; maternal age, body mass index and nulliparity rate, previous PE and assisted reproductive technique were significantly different

TABLE 2 Adverse pregnancy outcomes in the study population.

Outcome	Reference group ($n = 2483$ for SGA, $n = 2641$ for other outcomes)	Study group ($n = 8802$ for SGA, $n = 10\,134$ for other outcomes)	Odds ratio (95% CI)
Early-onset adverse outcomes			
SGA newborn <32 weeks	8 (0.32)	15 (0.17)	0.53 (0.22–1.25)
Pre-eclampsia <34 weeks	11 (0.42)	15 (0.15)	0.35 (0.16–0.77)
Spontaneous preterm birth <34 weeks	16 (0.61)	67 (0.66)	1.09 (0.63–1.89)
Adverse outcomes <37 weeks			
Pre-eclampsia	30 (1.14)	54 (0.53)	0.47 (0.30–0.73)
Spontaneous preterm birth <37 weeks	104 (3.9)	287 (2.8)	0.72 (0.57–0.90)
SGA newborn <37 weeks	44 (1.77)	89 (1.01)	0.57 (0.40–0.82)
Other adverse outcomes			
Stillbirth	10 (0.38)	29 (0.29)	0.76 (0.37–1.55)
Placental abruption	13 (0.49)	39 (0.38)	0.78 (0.42–1.47)
Maternal ICU admission			
ICU admission	37 (1.40)	78 (0.77)	0.55 (0.37–0.81)
Total days in ICU	133	270	0.53 (0.43–0.65)

Note: Data are reported as *n* (%).

Abbreviations: CI, confidence interval; ICU, intensive care unit; SGA, small for gestational age.

TABLE 3 Effect of aspirin compliance in the incidence of complications.

Outcome	Compliance <50% $n = 71$	Compliance ≥50% $n = 1292$	Odds ratio (95% CI)[a]	Compliance ≥90% $n = 1183$	Odds ratio (95% CI)[a]
Early-onset PE	4 (5.6%)	4 (0.31%)	0.06 (0.01–0.22)	4 (0.34%)	0.06 (0.01–0.25)
Preterm PE	6 (8.5%)	21 (1.6%)	0.19 (0.08–0.49)	18 (1.5%)	0.18 (0.07–0.47)
SPB at <37 weeks	2 (2.8%)	52 (4.0%)	1.43 (0.34–5.98)	47 (4.0%)	1.41 (0.34–5.92)
Preterm SGA	1 (1.4%)	34 (2.6%)	1.87 (0.25–13.85)	31 (2.6%)	1.86 (0.25–13.83)
ICU admission	6 (8.5%)	31 (2.4%)	0.28 (0.11–0.70)	26 (2.2%)	0.26 (0.10–0.65)
ICU stay (days)	20	124	0.33 (0.19–0.56)	108	0.32 (0.19–0.55)

Note: Data are reported as *n* (%).

Abbreviations: CI, confidence interval; ICU, intensive care unit; PE, pre-eclampsia; SGA, small for gestational age; SPB, spontaneous preterm birth.

[a]Compared to compliance <50%.

between groups. However, some of these risk factors were more prevalent in the untreated group and vice versa, thereby rendering groups still comparable. Second, the fact that the treated group was recruited retrospectively and with respect to the untreated group, and not simultaneously, may limit the internal validity of our findings. For this reason, we cannot exclude the possibility that changes in the characteristics of the population or in the clinical practice may have influenced the results. Third, birthweight was not available in 19.9% (2237/11255) of participants in the treated group, which may have influenced our results regarding the effect of ASA treatment to prevent SGA newborns. Finally, criteria for neonatal admission were different among the different hospitals, rendering these findings not comparable.

No previous studies have evaluated the clinical impact of performing routine combined screening for PE with PlGF using the Gaussian algorithm in clinical practice. A recent study has assessed the clinical benefit of incorporating PlGF to the Gaussian algorithm but only in a subgroup of medium-risk patients using a contingent scheme. That study showed that measuring PlGF only in 21.5% of the screened patients allows to reduce PE by 68.4% and reduce costs.[25] However, sample size in that study was too small as to drive any solid conclusions and the incidence of preterm PE (1.9%) was slightly higher than expected in our population (1.1%).[26] Another previous study evaluated the effectiveness of the first-trimester combined screening for PE using the Gaussian algorithm with all markers except PlGF, showing a moderate reduction in preterm PE of 45% and in maternal ICU admission of 43%. Unfortunately, that study was underpowered and failed to show any impact in the rates of early-onset PE, SGA, preterm birth, placental abruption or stillbirth.[26] Regarding the Fetal Medicine Foundation algorithm, its effectiveness in clinical practice with PlGF has not been yet assessed. Nevertheless, three studies have evaluated the clinical impact of such algorithm without PlGF. Two studies were conducted by the same group and in the same

cohort of participants. They compared the incidence of PE and SGA in a cohort of 4841 women screened for PE using the Fetal Medicine Foundation algorithm without PlGF and treated with daily ASA 150 mg with the incidences in a cohort of 7720 women screened according to the NICE criteria and treated with daily ASA 75 mg. They showed that aspirin treatment compliance increased from 28.9% to 99% and the combined screening strategy resulted in a significant reduction of 23% in PE incidence and 45% in term SGA incidence.[27,28] The third study was conducted in a small cohort of 1272 women showing a significant reduction of 68% of early-onset PE, compared to untreated controls.[29]

As in previous studies, treatment compliance in our study was high (≥90% in >85% of women) after implementing the combined screening for PE.[27,29] However, 12.2% (185/1520) of women at high risk for PE did not take aspirin or compliance was <50% or unknown. By contrast, in a secondary analysis of the ASPRE trial, treatment compliance was <50% in only 5% of participants.[30] We also show that despite baseline risk for PE being the same in both groups, the reduction of PE and other related complications was greater in women with compliance ≥50% and particularly when compliance was ≥90% as compared with women with a compliance <50%. These findings agree with a previous study;[30] however, the effect of treatment compliance in the clinical practice had not been previously confirmed. Since aspirin treatment compliance has a great impact on the effectiveness of the screening, a greater proportion of patients with unknown or poor compliance (<50%) in our study as compared to the ASPRE trial may partly account for the lower reduction in preterm PE in our study (53% vs. 62%).

The screen-positive rate was 15.0% which was only 2% higher than the percentage of 13% expected in our population using a cutoff of 1/170.[20] Usually, screening for PE using combined algorithms include cutoffs that correspond to a 10% false-positive rate. However, PE screening performance in non-black women is poorer than in black women and therefore, screen-positive rates should be higher for a predominantly white population so as to achieve adequate detection rates.[31] Given that >90% of our population are of Caucasian or Latin-American origin, a screen-positive rate of around 15% is probably more appropriate.

This study has important clinical implications as it shows that routine combined screening for PE with PlGF is feasible in a public healthcare setting, resulting in high treatment compliance and a significant reduction of PE, SGA, SPB and maternal ICU admission. As treatment compliance has a great impact on the effectiveness of the screening program, an adequate pre- and post-screening counseling should be provided to all patients in order to achieve optimal compliance and enhance ASA benefits.

5 | CONCLUSION

Routine first-trimester combined screening for PE with PlGF using the Gaussian algorithm can be implemented in a public healthcare setting and leads to a significant reduction of preterm PE by 53%, early-onset PE by 65%, preterm SGA by 43%, SPB by 28%, maternal ICU admission by 45% and length of stay in the ICU by 47%. As ASA treatment compliance has a great impact on the effectiveness of this screening program, an adequate pre- and post-screening counseling may improve compliance to ASA treatment and its preventive effect.

AUTHOR CONTRIBUTIONS

MM and EC had full access to all study data and accept responsibility for the integrity of such data and the accuracy of data analysis. MM and EC conceived and designed the study. PG-M, EB, BS, SC, MR, EL-Q, ÀV, ML, SC, MD, EDB, AH, MM, MSJ, MA-A and EC contributed to the literature research and data collection and confirmation. PG-M, EB, EC and MM contributed to the data analysis and data interpretation. PG-M and EB were responsible for writing the draft of the manuscript. MM and EC made substantial revisions to the manuscript. All authors contributed to revision of the manuscript, and read and approved the submitted version.

ACKNOWLEDGMENTS

We thank all the physicians who facilitated the recruitment at all participating sites and Roche Diagnostics for providing the reagents used in this study.

FUNDING INFORMATION

This study had no funding. Roche Diagnostics provided the placental growth factor used in this study.

CONFLICT OF INTEREST STATEMENT

MM received lecture fees from Roche Diagnostics. The remaining authors report no conflict of interest.

ORCID

Pablo Garcia-Manau https://orcid.org/0000-0002-2415-1626
Erika Bonacina https://orcid.org/0000-0002-8042-8247
Berta Serrano https://orcid.org/0000-0002-1264-9195
Ester Del Barco https://orcid.org/0000-0002-1484-9027
Manel Mendoza https://orcid.org/0000-0002-3030-3833

REFERENCES

1. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol*. 2009;33:130-137.
2. Tang LC, Kwok AC, Wong AY, Lee YY, Sun KO, So AP. Critical care in obstetrical patients: an eight-year review. *Chin Med J (Engl)*. 1997;110:936-941.
3. Hao J, Hassen D, Hao Q, et al. Maternal and infant health care costs related to preeclampsia. *Obstet Gynecol*. 2019;134:1227-1233.
4. Tan MY, Wright D, Syngelaki A, et al. 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.
5. Serra B, Mendoza M, Scazzocchio E, et al. A new model for screening for early-onset preeclampsia. *Am J Obstet Gynecol*. 2020;222:608.e1-608.e18.
6. de Paco-Matallana K, Llurba-Olivé E. *Guía de Asistencia Práctica SEGO: trastornos hipertensivos en la gestación*. Accessed June 19,

2023. https://sego.es/documentos/progresos/v63-2020/n4/GAP-Trastornos%20hipertensivos%20gestacion.pdf
7. Poon LC, Shennan A, Hyett JA, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. *Int J Gynaecol Obstet*. 2019;145(Suppl 1):1-33.
8. Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. *Fetal Diagn Ther*. 2013;33:8-15.
9. Scazzocchio E, Figueras F, Crispi F, et al. Performance of a first-trimester screening of preeclampsia in a routine care low-risk setting. *Am J Obstet Gynecol*. 2013;208:203.e1-203.e10.
10. Mendoza M, Garcia-Manau P, Arévalo S, et al. Diagnostic accuracy of first-trimester combined screening for early-onset and preterm preeclampsia at 8–10 weeks compared to 11–13 weeks gestation. *Ultrasound Obstet Gynecol*. 2021;57:84-90.
11. Serrano B, Bonacina E, Rodo C, et al. First-trimester screening for pre-eclampsia and small for gestational age: a comparison of the gaussian and Fetal Medicine Foundation algorithms. *Int J Gynaecol Obstet*. 2023;160:150-160.
12. Tan MY, Poon LC, Rolnik DL, et al. Prediction and prevention of small-for-gestational-age neonates: evidence from SPREE and ASPRE. *Ultrasound Obstet Gynecol*. 2018;52:52-59.
13. Zarbin M. Real life outcomes vs. clinical trial results. *J Ophthalmic Vis Res*. 2019;14:88-92.
14. Cohen S, Farrington J, Corbex M, Lasierra-Losada M, World Health Organization. Regional Office for Europe. *Screening Programmes: a short guide. Increase effectiveness. Maximize Benefits and Minimize Harm*. World Health Organization. Regional Office for Europe; 2020:39-42. Accessed December 19, 2022. https://apps.who.int/iris/handle/10665/330829
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12:1495-1499.
16. Mendoza M, Serrano B, Bonacina E, et al. Diagnostic accuracy of the gaussian first-trimester combined screening for pre-eclampsia to predict small-for-gestational-age neonates. *Int J Gynaecol Obstet*. 2022;156:322-330.
17. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. *Br J Obstet Gynaecol*. 1975;82:702-710.
18. Martin AM, Bindra R, Curcio P, Cicero S, Nicolaides KH. Screening for pre-eclampsia and fetal growth restriction by uterine artery doppler at 11–14 weeks of gestation. *Ultrasound Obstet Gynecol*. 2001;18:583-586.
19. Gómez O, Figueras F, Fernández S, et al. Reference ranges for uterine artery mean pulsatility index at 11–41 weeks of gestation. *Ultrasound Obstet Gynecol*. 2008;32:128-132.
20. Mendoza M, Tur H, Garcia-Manau P, et al. Cut-off values for Gaussian first-trimester screening for early-onset preeclampsia with maternal history, biochemical markers and uterine artery doppler. *J Gynecol Obstet Hum Reprod*. 2021;50:101827.
21. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. *Obstet Gynecol*. 2013;122:1122-1131.
22. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med*. 2017;377:613-622.
23. Carrascosa A, Yeste D, Copil A, Almar J, Salcedo S, Gussinyé M. Anthropometric growth patterns of preterm and full-term newborns (24–42 weeks' gestational age) at the hospital Materno-Infantil Vall d'Hebron (Barcelona) (1997–2002). *An Pediatr (Barc)*. 2004;60:406-416.
24. Gail M, Williams R, Byar DP, Brown C. How many controls? *J Chronic Dis*. 1976;29:723-731.
25. Trilla C, Mora J, Ginjaume N, et al. Reduction in preterm preeclampsia after contingent first-trimester screening and aspirin prophylaxis in a routine care setting. *Diagnostics (Basel)*. 2022;12:1814.
26. Mendoza M, Bonacina E, Serrano B, et al. Implementation of routine first-trimester combined screening for preeclampsia based on the Gaussian algorithm: a clinical effectiveness study. *Int J Gynaecol Obstet*. 2022;159:803-809.
27. Guy GP, Leslie K, Diaz Gomez D, et al. Implementation of routine first trimester combined screening for pre-eclampsia: a clinical effectiveness study. *BJOG*. 2021;128:149-156.
28. Guy GP, Leslie K, Diaz Gomez D, et al. Effect of routine first-trimester combined screening for pre-eclampsia on small-for-gestational-age birth: secondary interrupted time series analysis. *Ultrasound Obstet Gynecol*. 2022;59:55-60.
29. Lourenço I, Gomes H, Ribeiro J, Caeiro F, Rocha P, Francisco C. Screening for preeclampsia in the first trimester and aspirin prophylaxis: our first year. *Rev Bras Ginecol Obstet*. 2020;42:390-396.
30. Wright D, Poon LC, Rolnik DL, et al. Aspirin for evidence-based preeclampsia prevention trial: influence of compliance on beneficial effect of aspirin in prevention of preterm preeclampsia. *Am J Obstet Gynecol*. 2017;217:685.e1-685.e5.
31. 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.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Garcia-Manau P, Bonacina E, Serrano B, et al. Clinical effectiveness of routine first-trimester combined screening for pre-eclampsia in Spain with the addition of placental growth factor. *Acta Obstet Gynecol Scand*. 2023;102:1711-1718. doi:10.1111/aogs.14687