Reducing the Risk of Preterm Preeclampsia: Comparison of Two First Trimester Screening and Treatment Strategies in a Single Centre in Switzerland

Minderung des Risikos für Präeklampsie vor 37 Schwangerschaftswochen: Vergleich zweier Ersttrimesterscreening- und Behandlungsstrategien in einem Zentrum in der Schweiz

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Key words

preeclampsia, first trimester screening, implementation

Schlüsselwörter

Präeklampsie, Ersttrimesterscreening, Durchführung

received	10.11.2020
accepted after revision	7.12.2020
published online	15.7.2021

Bibliography

Geburtsh Frauenheilk 2021; 81: 1354–1361

DOI 10.1055/a-1332-1437

ISSN 0016-5751

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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ABSTRACT

Introduction First trimester screening for preeclampsia (PE) is based on the combined risks model. Recent trials demonstrate that variations in multiple of the medians (MoMs) of the screening markers influence the performance of the algorithm in different populations. The aim of this study is to compare the performance of the algorithm in two cohorts with different prevention strategies.

Material and Methods All first trimester screening tests performed between January 2014 and April 2020 were included. Up to June 2017 pregnancies with a risk > 1 : 200 for early-onset PE (eoPE) were considered at risk and received 100 mg of aspirin (strategy A). From July 2017 onwards, pregnancies with a risk > 1 : 100 for preterm PE (pPE) received 150 mg of aspirin (strategy B). We compared the screen positive rates (SPR) and incidence of PE between the two screening approaches. Statistical analysis were performed with Graphpad 8.0.

Results 3552 pregnancies were included; 1577 pregnancies were screened according to strategy A, 1975 pregnancies according to strategy B. The screen positive rate (SPR) for strategy A and B was 8.9 and 16.9 % respectively ($p < 0.0001$) while the incidence of PE was 1.41 and 1.84 % respectively (p = ns).

Conclusion With a SPR of less than 10 % we achieved a remarkably low rate of PE in our population, no further reduction in PE could be achieved by an increase in the SPR and LDA-prescription during the second screening period. The cut-off to define a pregnancy at risk for PE should be tailored to keep the SPR below 10 % to avoid unnecessary treatment with aspirin.

ZUSAMMENFASSUNG

Einleitung Das Ersttrimesterscreening auf Präeklampsie (PE) basiert auf einem Modell, das Risiken kombiniert. Vor Kurzem durchgeführte Studien haben gezeigt, dass Variationen der MoM-Werte („multiple of the median“) der Screening-Marker

die Leistung des Algorithmus in unterschiedlichen Populationen beeinflussen. Ziel dieser Studie war es, die Leistung des Algorithmus in 2 Kohorten mit unterschiedlichen Präventionsstrategien zu vergleichen.

Material und Methoden Es wurden alle Ersttrimesterscreening-Tests, die zwischen Januar 2014 und April 2020 durchgeführt wurden, in die Studie eingeschlossen. Bis zum Juni 2017 wurden Schwangerschaften mit einem Risiko von > 1 : 200 für eine früh auftretende PE (vor 34 SSW, eoPE) als Risikoschwangerschaft eingestuft und mit 100 mg Aspirin behandelt (Strategie A). Nach Juli 2017 wurden Schwangerschaften mit einem Risiko von > 1 : 100 für eine PE vor 37 SSW (pPE) mit 150 mg Aspirin behandelt (Strategie B). Wir verglichen die Screen-Positiv-Raten (SPR) und die Häufigkeit von PE der beiden Früherkennungsstrategien miteinander. Die statistische Analyse wurde mit Graphpad 8.0 durchgeführt.

Ergebnisse Insgesamt wurden 3552 Schwangerschaften in die Studie aufgenommen; davon wurden 1577 Schwangerschaften gemäß Strategie A und 1975 Schwangerschaften gemäß Strategie B untersucht und behandelt. Die Screening-Positiv-Rate (SPR) für Strategie A bzw. B war 8,9 bzw. 16,9 % ($p < 0{,}0001$), und die Häufigkeit von PE war 1,41 bzw. 1,84 % (p = n. s.).

Schlussfolgerung Mit einer SPR von weniger als 10 % konnten wir eine bemerkenswert niedrige PE-Rate bei unseren Patientinnen erzielen. Die PE-Rate wurde nicht weiter gesenkt durch die Erhöhung der SPR und der Aspirindosis im 2. Überwachungszeitraum. Der Schwellenwert für die Klassifizierung einer Schwangerschaft als PE-gefährdet sollte entsprechend so gewählt werden, dass die SPR unter 10 % bleibt, um eine unnötige Behandlung mit Aspirin zu vermeiden.

Introduction

Preeclampsia (PE) affects 1.2–4.5 % of all pregnancies globally and is associated with severe short- and long-term consequences for both mother and child [1 – 4]. Preterm PE (pPE), requiring delivery before 37 weeks of gestation, occurs in 0.7–2.3 % of all pregnancies or around 30–50 % of all pregnancies diagnosed with PE [5 – 9]. The decision to deliver in the late preterm period (after 34 weeks of gestation), is mostly based on local protocols trading off maternal risks against fetal benefits and not due to deterioration of maternal or fetal health, which explains the variation in the incidence of pPE [9]. Delivery is still the only treatment for PE available today, however prevention is possible in high-risk pregnancies with low-dose aspirin (LDA) started before 16 weeks of gestation [10 – 12]. The Fetal Medicine Foundation (FMF) London has developed a first trimester screening algorithm combining background risk factors with placental growth factor (PlGF), mean arterial pressure (MAP) and uterine artery pulsatility index (UtA PI). This allows the identification of more pregnancies at risk for pPE than the previous approach of screening by maternal risk factors alone at the same false positive rate (FPR) of 10 % [6, 13]. The initial publications focussed on screening for early onset preeclampsia (eoPE), with delivery before 34 + 0 weeks of gestation [6, 12]. A cut-off of 1 : 200 for eoPE resulted in an acceptable false-positive rate (FPR) of about 10 % [6, 14]. An international multicentre study validating the FMF screening algorithm, prior to starting the ASPRE trial, demonstrated that to achieve a FPR of 10 % the cut-off had to be set at 1 : 100 for pPE [15].

Most data on combined first trimester screening for PE today originate from prospective studies, little is known about the performance of this PE-screening in a general clinical setting. We introduced screening for PE in our ultrasound department in 2014. Initially we focused on screening for eoPE as described above and prescribed 100 mg of aspirin if the risk was > 1 : 200 for eoPE (strategy A). Following the publication of the ASPRE trial in June 2017, we changed our policy and prescribed 150 mg of aspirin to all women with a risk > 1 : 100 for pPE (strategy B) [12, 15].

The aim of this study was to compare the two screening strategies in our population. As LDA reduced the incidence of pPE, neither the DR nor the FPR are valid parameters in our study, setting to be assessed as measures of quality control. However, the screen-positive rate (SPR) is a valuable parameter not influenced by treatment [13].

Material and Methods

Recruitment and inclusion criteria

This is an observational study with a prospective analysis of retrospective data. All women with singleton pregnancies who opted for screening for PE at the ultrasound department of the university hospital of Bern at their 11 to 14 weeks scan between January 2014 and April 2020 and agreed to further use of their data were included in this study.

Maternal characteristics and screening modality

Maternal age, height, weight, BMI, parity and ethnicity, personal history of smoking, pre-existing diabetes, pre-existing hypertension, systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), previous pregnancy with a small for gestational age child (SGA) or previous PE and family history of PE as well as mode of conception define the background risk and were recorded in all patients. All biochemical, biophysical and ultrasound parameters were assessed according to the guidelines provided by the FMF London [16]. MAP was measured at the time of the scan between 11 and 14 weeks gestation with UEBE Visomat comfort, a pregnancy-validated device. UtA-PI was assessed by sonographers certified by the FMF London on Voluson E8 and E10 machines (GE medical systems). PlGF was measured on Kryptor Compact Plus from Brahms GmbH between 10 + 0 and 14 + 0 weeks gestation [17]; PAPP-A was included in case it was measured for screening for trisomies, it was also assessed on Kryptor Compact Plus from Brahms GmbH between 8 + 0 and 14 + 0 weeks gestation. Multiples of the Medians (MoMs) were calculated by the software provided by Viewpoint 5.6.25.284 (GE healthcare support systems)

▶ **Table 1** Maternal characteristics, personal history and screening parameters grouped according to the two strategies applied.

	Strategy A (n = 1577)	Strategy B (n = 1975)	p
Median maternal age, years	31.0 [27.0–35.0]	33.0 [29.0–36.0]	p < 0.0001
Median maternal weight, kg	62.6 [56.0–71.6]	64.4 [58.0–74.0]	p < 0.0001
Median maternal height, cm	165.0 [160.0–169.0]	165.0 [160.0–169.7]	ns
Median maternal BMI at 12 weeks, kg/m^2	22.8 [20.6–26.1]	23.7 [21.4–27.0]	p < 0.0001
Median fetal CRL, mm [IQR]	64.7 [59.6–70.6]	65.0 [59.9–70.2]	ns
Gestational age, weeks [IQR]	12.7 [12.3–13.0]	12.6 [12.3–13.0]	ns
Ethnicity:			
▪ Caucasian	1184 (75.1)	1670 (84.6)	p < 0.0001
▪ Black	199 (12.6)	113 (5.7)	p < 0.0001
▪ South asian	82 (5.2)	79 (4.0)	ns
▪ East asian	70 (4.4)	48 (2.4)	p = 0.0013
▪ Mixed	40 (2.5)	65 (3.3)	ns
Parity:			
▪ Nulliparous	805 (50.9)	1028 (52.1)	ns
▪ Parous without previous PE	725 (46.2)	860 (43.5)	ns
▪ Parous with previous PE	47 (2.9)	87 (4.4)	p = 0.027
Cigarette smoker	138 (8.8)	128 (6.5)	p = 0.012
Family history of PE	23 (1.5)	26 (1.3)	ns
Mode of conception:			
▪ Spontaneous	1434 (90.9)	1776 (89.9)	ns
▪ Ovulation induction	60 (3.8)	77 (3.9)	ns
▪ IVF	83 (5.3)	122 (6.2)	ns
Chronic hypertension	34 (2.2)	51 (2.6)	ns
Preexisting diabetes mellitus	9 (0.6)	19 (1.0)	ns
SLE or APS	10 (0.6)	21 (1.1)	ns
Median MAP	84.8 [80.4–89.9]	85.5 [80.8–90.6]	0.017
Median MAP-MoM	1.003 [0.953–1.060]	1.004 [0.953–1.064]	ns
Median UtA	1.51 [1.22–1.87]	1.50 [1.20–1.88]	ns
Median UtA-MoM	0.946 [0.764–1.160]	0.935 [0.761–1.168]	ns
Median PlGF	38.1 [29.4–51.0]	38.6 [29.0–52.0]	ns
Median PlGF-MoM	0.971 [0.766–1.231]	0.986 [0.751–1.268]	ns

Figures in parentheses are percentages; figures in brackets are interquartile ranges. SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome. Comparisons between each outcome group and unaffected controls: Fisher's exact test for categorical variables and Mann-Whitney test for continuous variables. $p < 0.05$ is considered significant.

[6]. The same software was also used to calculate the risks for eoPE, pPE and term PE (tPE) [6]. Pregnancy outcomes up to December 2018 were obtained from our clinical data system or from referring doctors and hospitals.

Aspirin was prescribed according to the two different screening strategies described in the Introduction. Few women with a low risk at screening but with previous PE and/or SGA, chronic hypertension, pre-existing diabetes, SLE, APS and/or chronic kidney disease received a prescription of LDA (usually 100 mg) despite their screening result by our outpatient's clinic or their private gynaecologist. Compliance was not tested in this study.

PE definition

Historically PE was defined as systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg after 20 weeks of gestation occurring together with a significant proteinuria (≥ 300 mg/24 h urine collection or ≥ 30 mg protein/mmol creatinin or ≥++ dipstick) [18]. The International Society for the Study of Hypertension in Pregnancy (ISSHP) proposed an adapted definition: Additionally to hypertension either proteinuria and/or other signs of maternal endothelial dysfunction and/or uteroplacental dysfunction with intrauterine growth restriction are required for the diagnosis [18]. We considered all pregnancies without pre-existing renal disease diagnosed with hypertension and proteinuria as "classical" PE, and all cases fulfilling the new ISSHP

▶ **Table 2** Pregnancy outcomes.

	Strategy A (n = 1507/1577 [95.6%])	Strategy B (n = 942/983 [95.8%])	p
Misscarriages/TOP (%)	21 (1.4)	18 (1.9)	ns
IUFD after 24 weeks (%)	3 (0.2)	0 (0.0)	ns
Live birth (%)	1483 (98.4)	924 (98.1)	ns
Gestational age [IQR]	39.6 [38.4–40.4]	39.4 [38.4–40.3]	ns
▪ PTB < 34 weeks (%)	18 (1.2)	17 (1.8)	ns
▪ PTB 34–37 weeks (%)	72 (4.9)	50 (5.4)	ns
▪ Term birth (%)	1393 (93.9)	857 (92.7)	ns
Mode of delivery			
▪ Spontaneous	750 (50.6)	488 (52.8)	ns
▪ Vaginal operative	181 (12.2)	82 (8.9)	p = 0.011
▪ CS	550 (37.1)	354 (38.3)	ns
▪ Unknown	2 (0.1)	0 (0.0)	ns
Gender			
▪ Male	749 (50.5)	459 (49.7)	ns
▪ Female	734 (49.5)	465 (50.3)	ns
Birth weight g [IQR]	3313 [2990–3600]	3260 [2965–3589]	ns
▪ < 5%ile (%) FMF	100/1476 (6.8)	64/916 (7.0)	ns
▪ < 10%ile (%) FMF	183/1476 (12.4)	113/916 (12.3)	ns
Classic PE	21 (1.41)	17 (1.84)	ns
▪ eoPE	5 (0.34)	4 (0.43)	ns
▪ pPE	7 (0.47)	8 (0.87)	ns
▪ tPE	14 (0.94)	9 (0.97)	ns
New definition PE	29 (1.96)	20 (2.16)	ns
▪ eoPE	5 (0.34)	4 (0.43)	ns
▪ pPE	9 (0.61)	9 (0.97)	ns
▪ tPE	20 (1.35)	11 (1.19)	ns
Screen positive pPE, negative eoPE			
▪ pPE with LDA	1/90 (1.1)	2/80 (2.5)	ns

Figures in parentheses are percentages; figures in brackets are interquartile ranges. Comparisons between each outcome group and unaffected controls: Fisher's exact test for categorical variables and Mann-Whitney test for continuous variables. $p < 0.05$ is considered significant.

criteria as "ISSHP-new" PE. Neonates born with a birth weight below the 5th percentile according to the birth weight charts of the FMF London are classified as FGR [14].

Statistical analysis

Statistical analyses were performed with GraphPad version 8.0 for Windows (GraphPad Software, San Diego CA). Spearman rank correlation and linear regression were used to analyse the correlation between the individual markers and gestational age. Continuous variable were analysed using the Student t-test or Mann-Whitney U-test while proportions were evaluated utilizing the Fisher's exact test or χ^2 test. Statistical significance was considered achieved when p was less than 0.05.

The Ethics Committee of the University of Bern approved the study.

Results

During the study period, 3552 pregnancies were included. 1577 screening tests were performed up to June 2017 (strategy A) and 1975 between July 2017 and April 2020 (strategy B). The background risk factors and screening parameters of both screening periods are depicted in ▶ **Table 1**. The various outcome parameters are shown in ▶ **Table 2**. The incidence of classical PE and pPE respectively was 1.58% (38/2407) and 0.62% (15/2407) of all live births while the incidence of ISSHP-new PE and pPE was 2.04% (49/2407) and 0.75% (18/2407).

Performance of the screening parameters

Over the total study period median MAP was significantly higher in women who developed pPE compared to uneventful pregnancies (94.1 mmHg [81.5–104.5] vs. 84.8 mmHg [80.4–89.8] ($p < 0.05$). Median PlGF was significantly lower (17.4 ng/ml

▶ **Table 3** Comparison of our population to the population investigated by O'Gorman et al prior to starting the ASPRE trial [13].

	Bern (n = 3552)	O'Gorman (n = 8775)	p
Median maternal age, years	32.0 [28.0–35.0]	31.5	
Median maternal weight, kg	63.4 [57.0–73.0]	66.4	
Median maternal height, cm	165.0 [160.0–169.0]	165.0	
Median BMI at 12 weeks, kg/m^2	23.4 [21.0–26.7]	24.6	
Gestational age (weeks)	12.6 [12.3–13.0]	12.7	
Ethnicity:			
▪ White	2854 (80.3)	6883 (78.4)	p = 0.0191
▪ Black	312 (8.8)	1090 (12.4)	p < 0.0001
▪ South asian	161 (4.5)	462 (5.3)	ns
▪ East asian	118 (3.3)	154 (1.8)	p < 0.0001
▪ Mixed	107 (3.0)	186 (2.1)	p = 0.004
Parity:			
▪ Nulliparous	1833 (51.6)	4127 (47.0)	p < 0.0001
▪ Parous without previous PE	1585 (44.6)	4459 (50.8)	p < 0.0001
▪ Parous with previous PE	134 (3.8)	189 (2.2)	p < 0.0001
Cigarette smoker	266 (7.5)	732 (8.3)	ns
Family history of PE	49 (1.8)	458 (5.2)	p < 0.0001
Conception:			
▪ Spontaneous	3210 (90.4)	8484 (96.7)	p < 0.0001
▪ ART	342 (9.6)	291 (3.3)	p < 0.0001
Chronic hypertension	85 (2.4)	100 (1.1)	p < 0.0001
Preexisting diabetes mellitus	28 (0.8)	68 (0.8)	ns
SLE or APS	31 (0.9)	32 (0.4)	p = 0.0007

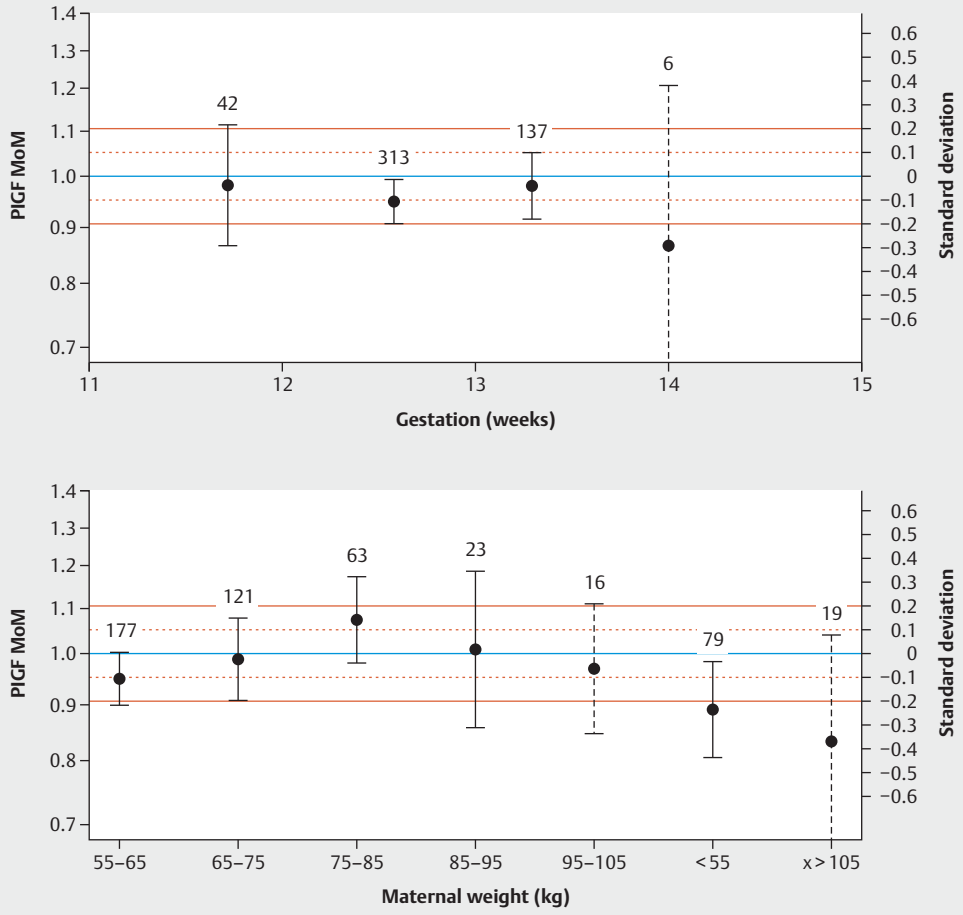
Figures in parentheses are percentages; figures in brackets are interquartile ranges. ART: assisted reproductive technology; SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome. Comparisons between each outcome group and unaffected controls: Fisher's exact test for categorical variables and Mann-Whitney test for continuous variables. p < 0.05 is considered significant.

[13.7–27.3] vs. 38.1 ng/ml [29.2–51.8] (p < 0.001) and UtA-PI significantly higher (1.99 [1.71–2.10] vs. 1.50 [1.20–1.86] (p < 0.001) in pregnancies with pPE. Throughout the whole study period, the median MAP-MoM was 1.003 [0.953–1.062], the median PlGF-MoM was 0.981 [0.757–1.247], and the median UtA-PI MoM measured 0.940 [0.761–1.164]. In comparison to the study population included in the ASPRE trial, in our cohort the background risk is significantly higher in regard to obstetrical risk factors, chronic hypertension, SLE and APS as well as a higher prevalence of pregnancies conceived by assisted reproductive technologies (ART). The ethnic background is similar in both populations, only the family history for PE was lower in our cohort (▶ **Table 3**) [15].

Comparison of the two different screening strategies

In regard of the background risk, women assessed during the second screening period (strategy B) were significantly older and had a higher BMI. The ethnicity changed to more Caucasian women and instead less black women attending for screening during strategy B. The screening parameters performed similarly, only the median MAP was significantly higher in the second screening period (▶ **Table 1**), a finding that did not reflect significantly on the calculated median MAP-MoMs. The SPR during the first study period (strategy A) was much lower with 8.9% (141/1577) compared to the SPR during the second study period (strategy B) with 16.9% (334/1975) (p < 0.0001). This resulted in a much higher LDA-prescription rate during the second screening period. In both study periods all women with a risk for eoPE > 1:200 also had a risk for pPE > 1:100. During strategy A 99 (6.2%) of all women had an increased risk for pPE > 1:100 but no increased risk for eoPE > 1:200; during strategy B 149 (7.5%) were in this intermediate risk group.

The incidence of PE did not vary significantly between the two screening strategies (1.41% in strategy A vs. 1.84% in strategy B [p = ns]) (▶ **Table 2**). In addition, no significant difference in the incidence of pPE, eoPE, or any PE according to the new ISSHP-definition could be demonstrated. Finally no difference of pPE was found in the women with a risk for pPE > 1:100 but not for eoPE > 1:200 (1.1% [1/90] vs. 2.5% [2/80], p = ns) despite a much lower rate of LDA-prescription during strategy A compared to B (25.3 vs. 86.6%, p < 0.0001).



▶ **Fig. 1** PlGF MoM distributions of the first 500 patients by alphabetical calculated by Viewpoint 5.6.25.824. The measurements are within 0.1 SD from the expected [6, 16].

Screening positive rate

Considering the whole study population the SPR is 9.2% if the cut-off > 1 : 200 for eoPE is chosen and 16.2% if the cut-off > 1 : 100 for pPE is used. Vice versa, in our population a SPR of 10–11% is achieved using a cut-off for pPE set at 1 : 60 (SPR of 10% at 1 : 57, SPR of 11% at 1 : 64).

Discussion

The introduction of first trimester combined screening for PE into routine practice with prescription of LDA to women considered at risk resulted in a remarkably low rate of classical PE of 1.58% and preterm classical PE of 0.62% in our population compared to the incidence of 2.31% previously stated in Switzerland or 3.8% in Europe [2, 19]. The increase in SPR from 8.9 to 16.9% by changing the cut-off between the two study periods resulted in no further reduction of PE or pPE, despite the higher rate of LDA-prescriptions and even an increased dosage of LDA in the second screening period after the publication of the ASPRE trial [12].

The importance of a certified assessment of the different screening parameters has been stressed in many publications, more recently, it was demonstrated that multiple of the medians especially of PlGF differ for example in the Asian population. As a result adaption is necessary for an optimal performance of PE-screening [7, 20]. In our population, the screening parameters perform as previously described: MAP and the UtA-PI are higher, while PlGF is lower in women who later develop PE [21 – 23]. MAP performs according to expectations with a median MAP-MoM of 1.003 and remains at a very stable level independent of the algorithm used to calculate MoMs. UtA-PI and PlGF are both parameters that are more variable. The most operator-dependant marker is the uterine artery pulsatility index (UtA-PI). Our results demonstrate that the median UtA-PI-MoMs are below 1.0 throughout the whole study period but also that they are significantly different when compared by the different calculators applied. Several studies demonstrated that training and regular feedback improve the performance [24, 25], and eventually also changing to transverse scanning through the cervix instead of the sagittal approach might improve the results [26]. However, in our population despite regular feedback, we find no significant change over the years in the median UtA-PI MoM. These findings might contradict the assumption that in general practice a very good performance

of UtA-PI is achievable. On the other hand, the stable results over the years could also signify that UtA-PIs are generally lower in our population and an adjustment of the MoMs could be considered. Median PlGF-MoMs, unlike in the Asian population, are within the expected range in our cohort (▶ **Fig. 1**) [7, 20].

In the development of the PE-screening algorithm, a fixed false-positive rate (FPR) was used to calculate the detection rate (DR). Ideally a high DR is achieved at a low FPR, generally a FPR of 5–10% is accepted [5, 6, 15, 27–30]. Given that the incidence of pPE is about 1% in a general population without intervention, the FPR of 10% is comparable to a SPR of 11%. In the ASPRE trial, a cut-off of 1:100 for pPE was used, however in our population that cut-off resulted in a SPR of 16.2%, much higher than expected [15]. An explanation for the high SPR could be a higher background risk in our population, as MAP and PlGF perform according to expectations and the UtA-PIs are lower than expected, reducing rather than increasing the SPR [12, 15, 31]. In the original publication of the FMF London, a FPR of 10% for pPE was achieved using a cut-off in screening for pPE of 1:67 [6]. In our population, we found a SPR of 11% at a cut-off of 1:64 for pPE, which is very consistent with the finding of Akolekar et al. [6]. Therefore another explanation for the high SPR could be that the cut-off proposed by the ASPRE trial group is simply too high. One might argue that a high FPR also increases the overall DR, however the safety of LDA in lower-risk populations has not been proven so far and our results demonstrate no further reduction in PE despite the significant increase in LDA-prescription during the second study period [32]. Especially in the group of women with an intermediate risk (> 1:100 for pPE but < 1:200 for eoPE) there was no higher incidence of pPE despite the much lower rate of LDA-prescription during the first study period. It seems therefore safe to withhold LDA in those pregnancies.

Conclusion

Overall, this study demonstrates a good performance of first trimester combined screening for PE in our population using the FMF algorithm. While previous studies focused on improving the performance of individual screening parameters and adjusting MoMs, our results further demonstrate the importance of defining an ideal cut-off to consider a pregnancy at risk. By applying the cut-off of 1:100 for pPE proposed by the ASPRE trial we nearly doubled the SPR compared to our previous screening approach without any further reduction of the incidence of PE. These results prompt us to reconsider the cut-off for defining a pregnancy at risk for pPE and for treating with aspirin to 1:60.

Conflict of Interest

The authors declare that they have no conflict of interest.

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