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Implementing Preeclampsia Screening in Switzerland (IPSISS): First Results from a Multicentre Registry

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Mini-Summary

What does this study add to current knowledge?

- This multicentre cohort study investigates the performance of screening for preterm preeclampsia (pPE) for the Swiss population according to the Fetal Medicine Foundation (FMF) London algorithm. The different screening parameters for pPE perform well in our population, only pregnancy-associated plasma protein A (PAPP-A) values are higher than expected. The prevalence of pPE in this Swiss cohort is lower than previously described, a fact that we attribute to the screening for pPE and low-dose aspirin prophylaxis in high-risk patients in our cohort.

What are the main clinical implications?

- When using the FMF London algorithm in screening for pPE in the Swiss population, the cut-off should be set rather at 1: ≥75 or lower in order to keep the screen positive rate low at 10–11%. PAPP-A shows a poor performance in screening for pPE and should eventually be excluded for the screening or pPE. Screening of pPE should be recommended to all singleton pregnancies as part of routine first trimester screening.

Keywords
Pre-eclampsia · First trimester pregnancy · Prenatal diagnosis

Abstract
Introduction: The Fetal Medicine Foundation (FMF) London developed a first trimester combined screening algorithm for preterm preeclampsia (pPE) that allows a significantly

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higher detection of pregnancies at risk compared to conventional screening by maternal risk factors only. The aim of this trial is to validate this screening model in the Swiss population in order to implement this screening into routine first trimester ultrasound and to prescribe low-dose aspirin 150 mg (LDA) in patients at risk for pPE. Therefore, a multicentre registry study collecting and screening pregnancy outcome data was initiated in 2020; these are the preliminary results. ***Methods:*** Between June 1, 2020, and May 31, 2021, we included all singleton pregnancies with pPE screening at the hospitals of Basel, Lucerne, and Bern. Multiple of medians of uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP), placental growth factor (PlGF), and pregnancy-associated plasma protein A (PAPP-A) as well as risks were analysed as calculated by each centre's software and recalculated on the FMF online calculator for comparative reasons. Statistical analyses were performed by GraphPad Version 9.1. ***Results:*** During the study period, 1,027 patients with singleton pregnancies were included. 174 (16.9%) had a risk >1:100 at first trimester combined screening. Combining the background risk, MAP, UtA-PI, and PlGF only, the cut-off to obtain a screen positive rate (SPR) of 11% is ≥1:75. Outcomes were available for 968/1,027 (94.3%) of all patients; 951 resulted in live birth. Fifteen (1.58%) developed classical preeclampsia (PE), 23 (2.42%) developed PE according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) definition. ***Conclusion:*** First trimester combined screening for PE and prevention with LDA results in a low prevalence of PE. The screening algorithm performs according to expectations; however, the cut-off of >1:100 results in a SPR above the accepted range and a cut-off of ≥1:75 should be considered for screening. More data are needed to evaluate, if these results are representative for the general Swiss population.

Introduction

Preeclampsia (PE) affects 3–8% of all pregnancies globally and is associated with severe short- and long-term consequences for both mother and child [1–4]. Prevention with low-dose aspirin (LDA) started before 16 weeks of gestation in pregnancies at risk reduces the risk of preterm PE (pPE) requiring delivery before 37 weeks of gestation in women with anamnestic risk factors such as previous PE significantly [5–7]. First trimester screening for pPE by the competing risks model combining background risk with mean arterial pressure (MAP), maternal serum placental growth factor (PlGF), and uterine artery pulsatility index (UtA-PI) allows the detection of 75% of all pregnancies at risk at a false positive rate of 10%, a performance that is superior to screening by background risk alone [8–13]. The Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial demonstrated that LDA at a dose of 150 mg per day initiated before 16 weeks of gestation reduces the risk of pPE by 62–75% in women found to have a risk >1:100 at first trimester combined PE-screening [14, 15]. Further analysis also demonstrated that by screening for pPE and prescribing LDA the incidence of preterm foetal growth restriction (FGR) can be reduced as well [16]. Results from a single-centre study from Switzerland could validate these results; however, several questions remain when planning to implement PE-screening for all pregnant women in Switzerland [17, 18]. Multiple of medians (MoMs) of the different markers need validation as some studies showed an improved performance when they were adapted; the biochemical marker pregnancy-associated plasma protein A (PAPP-A) is often available from aneuploidy screening and its value in PE-screening in our population needs to be assessed [19–21]. The ideal cut-off to consider a pregnancy at risk needs to be evaluated [14, 18]. Further, we need to test the value of two-stage screening, the cost-effectiveness of screening, and the influence of the new definition of PE according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) on the performance of screening. Finally, the screening algorithm for twins needs to be validated [22–27].

A multicentre registry study, the Implementing Preeclampsia Screening in Switzerland Study (IPSISS) trial is therefore planned with the aim to collect data on 10,000 pregnancies from different centres to answer these questions. In order to test the feasibility of such a trial in Switzerland, three tertiary centres agreed to participate in a pilot trial aiming to collect data on 1,000 pregnancies over 1 year. These are the results from this pilot phase.

Materials and Methods

This is a prospective registry study performed at the University Hospitals of Bern and Basel and the Cantonal Hospital of Lucerne. All pregnant women with a singleton pregnancy who opted for PE-screening at their 11–14-week scan at one of the three participating centres and who agreed to participate in this study by written consent were included between June 1, 2020, and May 31, 2021. Multiple pregnancies were excluded from these analyses. Maternal age, height, weight, BMI, parity, and ethnicity, personal history of smoking, pre-existing diabetes, pre-existing hypertension, systemic lupus erythematosus or antiphospholipid antibody syndrome (APS), previous pregnancy with a small for gestational age child 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,

Table 1. Background risk factors distributed among the three participating centres in alphabetic order

	Basel	Bern	Luzern	*p* value
	N = 252	*N* = 677	*N* = 98	
Median maternal age, years	34.0 [30.0–37.2]	32.9 [30.1–36.0]	32.2 [29.3–35.5]	Ns
Median maternal weight, kg	65.0 [58.0–77.0]	64.6 [58.0–73.8]	65.0 [57.5–77.0]	Ns
Median maternal height, cm	165 [161–170]	166 [162–170]	168 [163–172]	Ns
Median maternal BMI at 12 weeks, kg/m^2	23.6 [21.0–27.1]	23.4 [21.0–26.9]	23.2 [21.1–27.3]	Ns
Median foetal CRL, mm	65.1 [60.4–70.1]	65.5 [60.6–70.4]	64.9 [59.2–70.7]	Ns
Ethnicity				
White	212 (84.1)	621 (91.7)	92 (93.9)	<0.005
Black	18 (7.1)	15 (2.2)	1 (1.0)	<0.001
South Asian	13 (5.2)	23 (3.4)	2 (2.0)	Ns
East Asian	5 (2.0)	5 (0.7)	0 (0.0)	Ns
Mixed	4 (1.6)	13 (1.9)	3 (3.1)	Ns
Parity				
Nulliparous	127 (50.4)	355 (52.4)	47 (48.0)	Ns
Parous without prev. PE	123 (48.8)	272 (40.2)	45 (45.9)	<0.05
Parous with previous PE	2 (0.8)	50 (7.4)	6 (6.1)	<0.001
Cigarette smoker	14 (5.6)	35 (5.2)	2 (2.0)	Ns
Family history of PE	8 (3.2)	20 (3.0)	3 (3.1)	Ns
Conception				
Spontaneous	202 (80.2)	626 (92.5)	87 (88.8)	<0.0001
IVF	47 (18.7)	29 (4.3)	11 (11.2)	<0.05
Ovulation drugs	3 (1.2)	22 (3.2)	0 (0.0)	Ns
Chronic hypertension	6 (2.4)	15 (2.2)	5 (5.1)	Ns
Pre-existing diabetes mellitus	4 (1.6)	5 (0.7)	1 (1.0)	Ns
SLE or APS	1 (0.4)	22 (3.2)	0 (0.0)	<0.01

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. ART, assisted reproductive technology; SLE, systemic lupus erythematosus; APS, antiphospholipid antibody syndrome. $p < 0.05$ is considered significant (*).

biophysical, and ultrasound parameters were assessed according to the guidelines provided by the Fetal Medicine Foundation (FMF) London (The Fetal Medicine Foundation/education/preeclampsia Screening; https://fetalmedicine.org/education/preeclampsia-screening, accessed August 5, 2022). MAP was measured at the time of the scan between 11 and 14 weeks of gestation with a pregnancy-validated device. Sonographers certified by the FMF London for UtA-PI measurement assessed the UtA-PIs. PlGF was measured on Kryptor Compact Plus from Brahms GmbH between 11+0 and 14+0 weeks of gestation; 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 of gestation. MoMs were calculated by each centre's software, namely, the Viewpoint versions 5.6 and 6 (by GE Healthcare GmbH) and B·R·A·H·M·S Fast Screen pre I plus (by Thermo Fisher), based on the algorithm provided by the FMF London [10, 12]. Additionally, for comparative purposes, all MoMs and risks for pPE by different combinations of markers were recalculated on the FMF website (The Fetal Medicine Foundation/calculators/research tools; https://fetalmedicine.org/research/peRisk, accessed August 5, 2022).

Pregnancies at risk for pPE were prescribed LDA 100–150 mg/day before 16 weeks and until 36 weeks of gestation. To evaluate the effect of LDA, the dosage of LDA prescribed if indicated and the gestational age when it was prescribed were registered.

Historically, PE has been defined as systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg after 20 weeks of gestation occurring together with a significant proteinuria (≥300 mg/24 h urine collection or ≥30 mg protein/mmol creatinine or ≥++ dipstick) [26]. The ISSHP proposed an adapted definition: additionally to hypertension either proteinuria and/or other signs of maternal endothelial dysfunction and/or utero-placental dysfunction with intrauterine growth restriction are applied for the diagnosis [26]. We recorded the following outcome data in all patients: date and gestational age at delivery, mode of delivery, gender of the newborn, birth weight and birth weight percentile, and the occurrence of maternal pregnancy complications such as gestational diabetes mellitus and PE [28]. To specify the diagnosis of PE, maternal hypertension, proteinuria, clinical signs, and laboratory changes were individually recorded. For this study, all

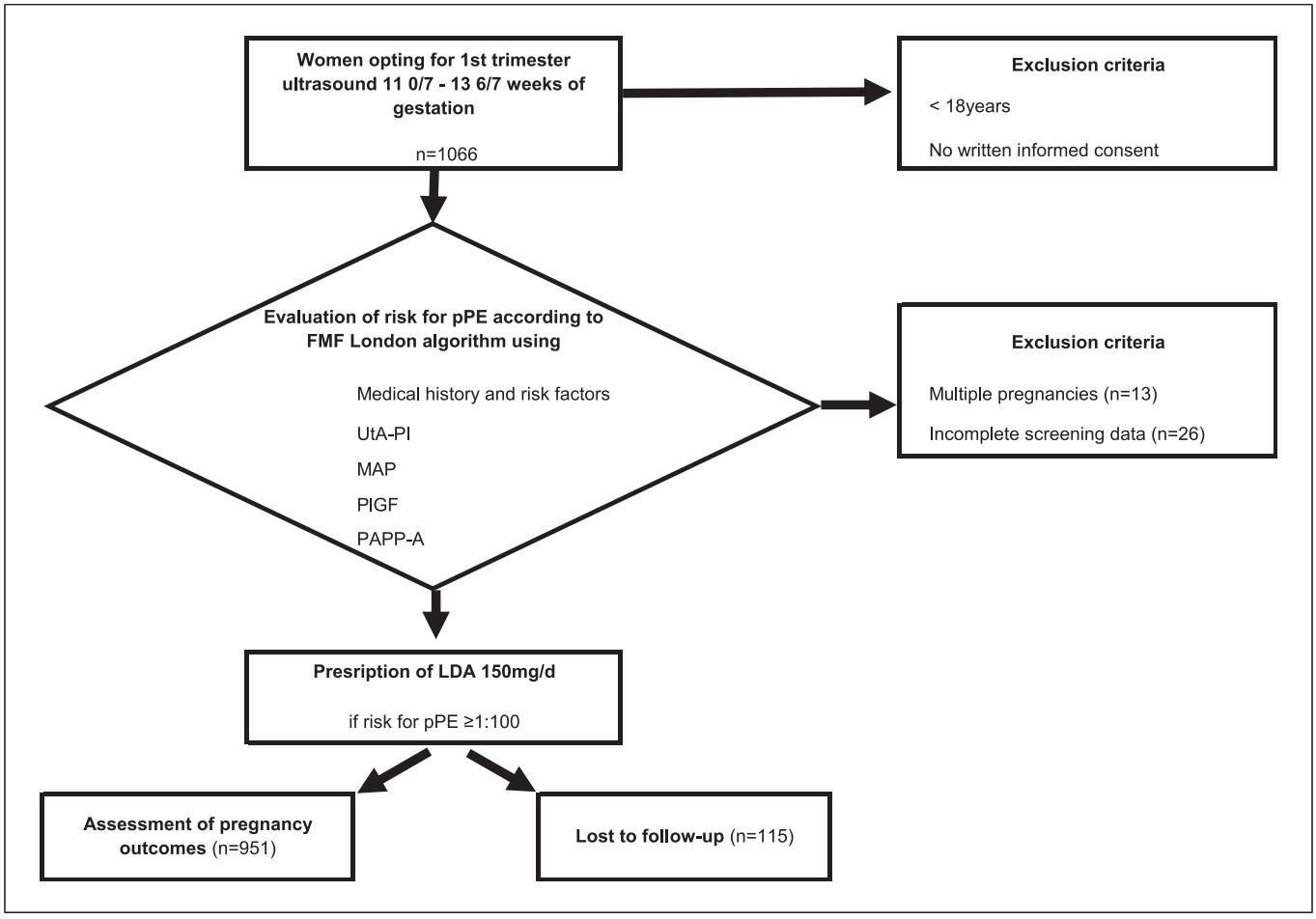

Fig. 1. Flow chart of patient inclusion.

pregnancies without pre-existing renal disease diagnosed with hypertension and proteinuria were considered as "classical" PE, and all cases (including those with classical PE) fulfilling the new ISSHP criteria as "ISSHP PE." Deliveries after 37+0 weeks of gestation were considered as term deliveries, whereas deliveries before 37+0 weeks of gestation were named preterm birth. Neonates born with a birth weight below the 5th percentile according to the birth weight charts of the FMF London are classified as FGR [28]. In order to assess the implications of the new ISSHP definition of PE on the prevalence of PE in the Swiss population, we compared our data to historical data on the prevalence of PE [29].

Statistical analyses were performed with GraphPad version 9.1 for Windows (GraphPad Software, San Diego, CA, USA). 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's *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. This study protocol was reviewed and approved by the Ethics Committees of Bern and Northwestern and Central Switzerland, approval number 2020-00429, date of decision June 9, 2020.

Results

Between June 1, 2020, and May 31, 2021, 1,066 patients were included in this trial. Thirteen twin pregnancies and 26 pregnancies with incomplete screening data were excluded, and 1,027 singleton pregnancies remained for further analysis. 252 (24.5%) patients were screened in Basel, 677 (65.9%) in Bern, and 98 (9.5%) in Lucerne. The background risk factors are depicted in Table 1. There are significant differences in ethnicity, mode of conception, and history of previous PE among the participating centres. The cut-off at a fixed screen positive rate (SPR) of 10% or 11% for the background risk alone excluding MAP, UtA-PI, PlGF, and PAPP-A is 1:62 and 1:68, respectively.

Outcomes were available for 968/1,027 (94.3%) of all patients. 15/968 (1.5%) resulted in a second trimester miscarriage or termination of pregnancy, 2/968 (0.2%)

Table 2. Pregnancy outcomes of all live births

	Live births (*N* = 951)
Gestational age, weeks	39.4 [38.6–40.3]
PTB <34+0 weeks	10 (1.0)
PTB 34+0–36+6 weeks	43 (4.4)
Term deliveries	915 (94.5)
Mode of delivery	
Spontaneous	482 (50.7)
Vaginal operative	114 (12.0)
CS	353 (37.1)
Unknown	2 (0.2)
Gender	
Male	499 (52.5)
Female	445 (46.8)
Unknown	7 (0.7)
Birth weight, g	3,310 [2,995–3,600]
Birth weight percentile	46 (21–70)
<5th percentile	75 (7.9)
<10th percentile	120 (12.6)
GDM	158 (16.6)
Classic PE	15 (1.58)
pPE	3 (0.32)
Term PE	12 (1.26)
ISSHP PE	23 (2.42)
pPE	6 (0.63)
Term PE	17 (1.79)

Figures in parentheses are percentages; figures in brackets are interquartile ranges. PTB, preterm birth; CS, Caesarean section; GDM, gestational diabetes mellitus. Classic PE, hypertension and proteinuria; ISSHP PE, hypertension and proteinuria and/or maternal endothelial dysfunction and/or utero-placental dysfunction.

were diagnosed with an intrauterine foetal death after 24+0 weeks of gestation, both unrelated to PE (Fig. 1). Pregnancy outcomes of the 951 live births are summarized in Table 2.

MoMs of MAP, PlGF, and UtA-PI

The performances of the different screening parameters by the different centres are shown in Table 3. Overall, the median MoMs of the different parameters vary insignificantly when recalculated on the FMF website: the median (IQR) MAP-MoM is 1.01 (0.96–1.07) each, the median (IQR) PlGF-MoM is 1.03 (0.77–1.34) and 1.01 (0.74–1.30), respectively (p = 0.09), and the median (IQR) UtA-PI-MoM calculated during the study period is 0.94 (0.75–1.13) and 0.91 (0.74–1.10) by the FMF (p = 0.06). The means ± SD of the MoMs between 11 and 14 weeks are all in the acceptable range (Fig. 2a–c).

Value of PAPP-A

Median (IQR) PAPP-A is 3.04 mU/L (1.57 mU/L–5.15 mU/L), the median (IQR) PAPP-A-MoM is 1.15 (0.80–1.56) and significantly higher if calculated on the FMF website with 1.25 (0.84–1.72) (p = 0.0039) (Fig. 2d). 721/1,027 (70.2%) of all pregnancies had a PAPP-A value measured, 94/721 (13.0%) were at risk >1:100 for pPE if PAPP-A was included into the algorithm, while 96/721 (13.3%) were at risk >1:100 when the calculation was performed without PAPP-A (p = 0.65).

Screen Positive Rates

Using a cut-off of >1:100 for pPE, 174/1,027 (16.9%) pregnancies were considered screen positive during the study period. 151/174 (86.8%) of them were treated with LDA 150 mg. 23/174 (13.2%) did not receive LDA for various reasons, mostly due to differences in local cut-off policies and aspirin intolerance; none of the latter developed PE. A SPR between 10% and 11% is obtained at a cut-off of ≥1:53 to ≥1:57 during the study period for the combined screening. When the risks are calculated on the FMF website however, combining the background risk with MAP, UtA-PI, and PlGF only, the cut-off for the same SPRs is found at ≥1:69 to ≥1:76.

Implication of New Definition of PE according to ISSHP [26, 27]

15/951 (1.58%) developed classical PE; according to the extended ISSHP definition, however 23/951 (2.42%) women were diagnosed with PE. Of those additionally diagnosed with PE, 4/8 developed hypertension solely associated with FGR, while the other 4/8 had a combination of clinical signs and laboratory changes additional to hypertension.

Six/951 (0.63%) developed pPE according to ISSHP, only 3/951 (0.32%) were diagnosed with classical pPE. Seven/15 (46.7%) of the women with classical and 6/8 (75%) of the women only diagnosed according to ISSHP had a risk >1:100 for pPE, all 13 were prescribed LDA. Only 1/6 pPE had a risk <1:100 at first trimester screening, and the diagnosis was based on hypertension and FGR.

Discussion

This study demonstrates that a multicentre registry study in Switzerland is feasible; we recorded the data of over 1,000 patients with 94% outcomes within a year in only three centres. As previous results from a single centre in Switzerland and trials from other countries demonstrated, the strategy to screen for PE in the first trimester

Table 3. Screening markers in the whole study population and in comparison among the three centres

	All (*N* = 1,027)	Basel (*N* = 252)	Bern (*N* = 677)	Luzern (*N* = 98)	*p* value
MAP	86.5 (81.3–91.9)	85.1 (78.2–92.1)	86.7 (82.0–91.6)	89.0 (84.6–94.2)	<0.0001
MAP-MoM					
IPSISS	1.01 (0.96–1.07)	0.99 (0.92–1.06)	1.02 (0.97–1.07)	1.03 (0.99–1.08)	<0.0001
FMF London	1.01 (0.96–1.07)	0.99 (0.93–1.06)	1.01 (0.97–1.06)	1.04 (1.00–1.09)	<0.0001
UtA-PI	1.50 (1.20–1.80)	1.50 (1.20–1.80)	1.51 (1.21–1.81)	1.53 (1.21–1.78)	Ns
UtA-PI-MoM					
IPSISS	0.94 (0.75–1.13)	0.90 (0.72–1.12)	0.95 (0.76–1.14)	0.95 (0.78–1.13)	Ns
FMF London	0.91 (0.74–1.10)	0.89 (0.72–1.11)	0.91 (0.75–1.09)	0.93 (0.75–1.11)	Ns
PlGF	40.7 (29.9–53.8)	40.1 (28.8–55.4)	41.2 (30.0–53.7)	39.7 (30.4–48.3)	Ns
PlGF-MoM					
IPSISS	1.03 (0.77–1.34)	1.03 (0.73–1.31)	1.04 (0.77–1.37)	1.01 (0.85–1.29)	Ns
FMF London	1.01 (0.74–1.30)	1.02 (0.73–1.29)	1.01 (0.74–1.32)	1.00 (0.81–1.21)	Ns
PAPP-A	3.04 (1.57–5.15)	4.00 (2.36–5.67)	2.66 (1.26–4.87)	3.67 (2.34–5.35)	<0.0001
PAPP-A-MoM					
IPSISS	1.15 (0.80–1.56)	1.15 (0.82–1.61)	1.17 (0.80–1.58)	0.95 (0.73–1.25)	Ns
FMF London	1.25 (0.84–1.72)	1.15 (0.81–1.64)	1.27 (0.86–1.74)	1.29 (0.85–1.74)	Ns

MoMs were analysed as calculated in each centre (IPSISS) as well as calculated on the FMF website. Figures in parentheses are interquartile ranges. MAP, mean arterial pressure; MoM, multiple of the median; UtA-PI, uterine artery pulsatility index; PAPP-A, pregnancy-associated plasma protein A; PlGF, placental growth factor. $p < 0.05$ is considered significant (*).

and prescribe LDA results in a low prevalence of PE of 1.58% compared to the historically described 2.31 and a very low prevalence of classical pPE of 0.32% [29]. While differences in background risk do not allow a direct statistical comparison of the two Swiss cohorts, both cohorts are yet too small to analyse the effect of LDA on pPE, especially seen the different management strategies of PE between 34 and 37 weeks of gestation [30]. Whether the expenses of combined screening in a generally low-risk population are justified remains a question we will address once the IPSISS cohort of 10,000 patients is complete.

The IPSISS trial was initiated to optimise PE-screening in Switzerland; this pilot phase of the trial provides preliminary results to the research questions raised. A multicentre Asian study demonstrated that MoMs needed adjustments to improve the performance of PE-screening compared to the values obtained in the multicultural population assessed in London [19]. In our population, like previously described, MAP and PlGF perform according to expectations, their median MoMs are nearly 1.0 and the performance is maintained throughout the complete first trimester (Table 3; Fig. 2a, c) [18]. The UtA-PI-MoMs are lower than expected, a problem described previously by others and us; however, the values are still within the tolerated range (Fig. 2b) [17, 18, 31]. These results demonstrate once more the importance of training and regular feedback when assessing the UtA-PI [31]. It has been shown that PAPP-A levels are decreased during the first trimester in pregnancies that later develop PE [12]. The value of PAPP-A in screening for PE has been extensively discussed; including PAPP-A into routine screening for pPE does not improve the performance of screening [12, 20, 21]. Screening for aneuploidies is offered to all pregnant women in Switzerland and there is a high acceptance for such screening [32]. PAPP-A is therefore often obtained for aneuploidy screening and routinely included into PE-screening. The poor performance of PAPP-A in this study not only questions the inclusion of this marker in PE-screening but also points out the importance of validating its value in screening for trisomies. These preliminary results do not yet answer the question, whether the inclusion of PAPP-A might even deteriorate the performance of PE-screening in Switzerland; however, due to the raised values in our cohort, fewer pregnancies are screen positive when PAPP-A is included into the algorithm. To further address this question, we plan to analyse the best performance of combined screening in our population by comparing different combinations of markers as well as a two-step approach to screening in the full IPSISS cohort once it is completed.

As previously described, the cut-off of >1:100 to consider a pregnancy at risk results in a SPR above the accepted range [18]. The cut-off is dependent on the algorithm used, with the latest algorithm provided by the FMF London it seems reasonable to propose a cut-off of ≥1:75 in our population. Besides from the ASPRE trial, where a cut-off of >1:100 was proposed, a cut-off of >1:70 at a SPR of 10–11% was also found in most other publications [9, 10, 12, 17, 18]. The

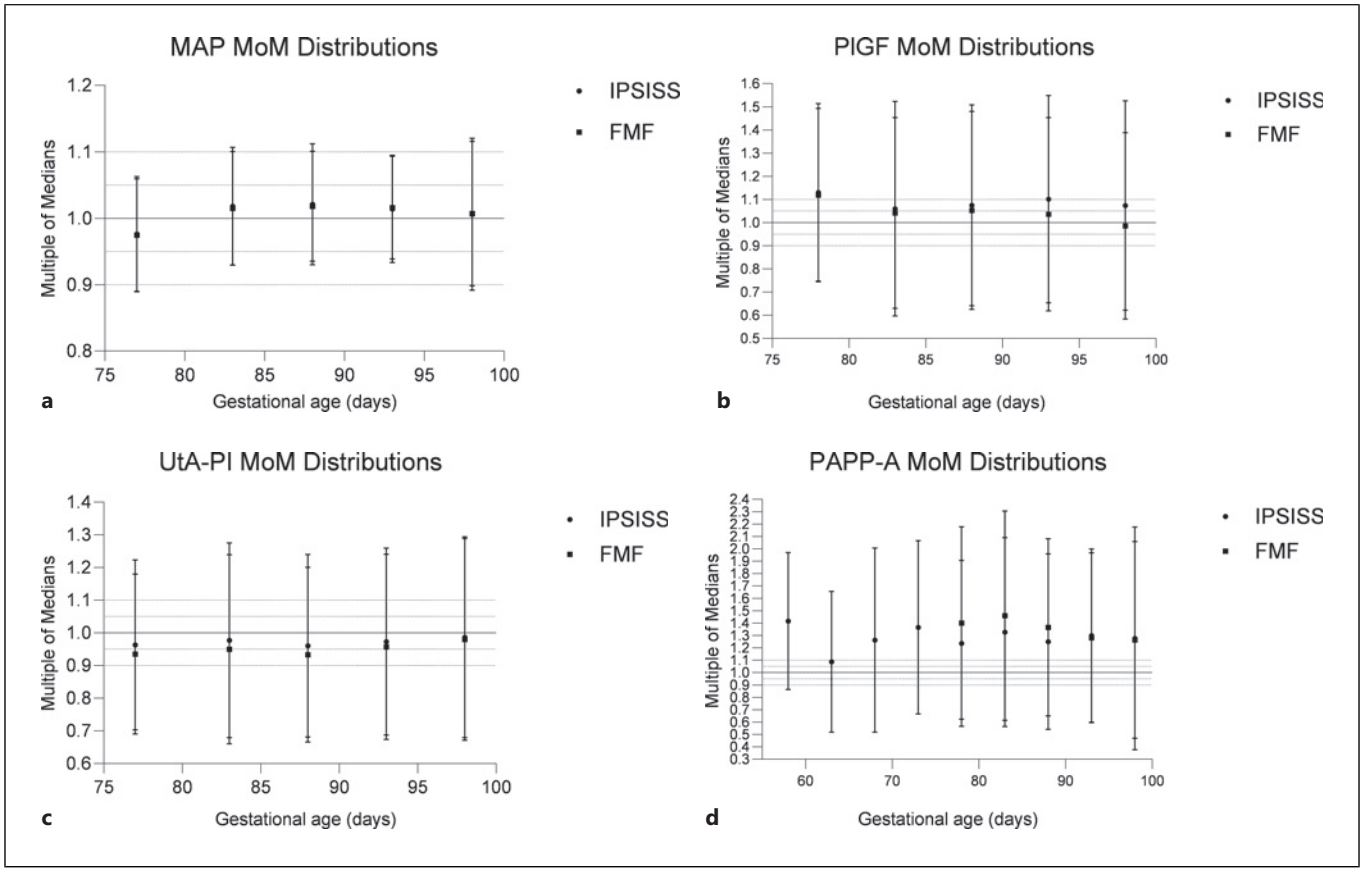

Fig. 2. a MAP-MoMs at 11–14 weeks of gestation. **b** PlGF-MoMs at 11–14 weeks of gestation. **c** UtA-PI-MoMs at 11–14 weeks of gestation. **d** PAPP-A-MoMs at 11–14 weeks of gestation.

performance of PE-screening depends on the background risk of the population analysed, the background risk in this trial is identical to the one described by Tan et al. [12] which confirms again the results obtained [18]. It remains however to be evaluated, if the population analysed so far represents the general Swiss pregnant population.

By extending the diagnostic criteria for preeclampsia as proposed by the ISSHP, the incidence of PE increases [26, 27]. This leads to a change in management like an increase of induction of labour and indication for delivery at earlier gestational ages for non-proteinuric PE, but may also prevent deterioration of the clinical situation [33]. Khan et al. [27] could demonstrate that the first trimester combined screening algorithms perform similarly in the detection of PE according to the new ISSHP definition [26]. In our population, we find a higher percentage of women that develop PE according to ISSHP despite LDA prevention than classical PE; however, the numbers so far are too small to draw meaningful conclusions. These preliminary results need to be confirmed or contradicted by further studies, also only a larger cohort will be able to demonstrate if the outcome is improved with the extended definition. The value of LDA dose, the questions about cost-effectiveness, and the performance of PE-screening in twin pregnancies cannot yet be answered by this pilot phase of the IPSISS trial [6, 23–25].

Conclusion

These preliminary results obtained in a multicentre cohort with real-world data demonstrate a low incidence of classical PE, a fact we attribute to the prescription of LDA to pregnancies considered at risk. We can further demonstrate that the performance of PAPP-A does not meet the expectations and should eventually be explicitly excluded when screening for PE. If only background risk, MAP, PlGF, and UtA-PI are included into screening a cut-off of ≥1:75 results in a SPR of 11%. More data are needed to confirm all these findings.

Statement of Ethics

All participants signed the general informed consent, which allows further use of their data. The Ethical Committee of Bern and of Northwestern and Central Switzerland approved the study (No. 2020-00429, date June 9, 2020).

Conflict of Interest Statement

The authors declare no conflict of interest.

Funding Sources

No external funding was received for this study.

Author Contributions

Fabienne Trottmann: data collection and manuscript writing and editing. Pauline Challande, Sara Ardabili, Irene Hösli, Heidrun Schönberger, Sofia Amylidi-Mohr, Joachim Kohl, and Markus Hodel: data collection. Gwendolin Manegold-Brauer: data collection and Manuscript editing. Daniel Surbek and Luigi Raio: manuscript editing. Beatrice Mosimann: data collection, manuscript writing and editing, and statistical analysis.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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