IMR Press

Systematic Review

Real-world implementation and adaptation to local settings of first trimester preeclampsia screening in Italy: a systematic review

Silvia Amodeo[1,†], Giulia Bonavina[2,†], Anna Seidenari[3], Paolo Ivo Cavoretto[2], Antonio Farina[3,4,*]

[1] *Department of Health Promotion, Division of Obstetrics and Gynecology, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, 90133 Palermo, Italy*

[2] *Gynecology and Obstetrics Department, I.R.C.C.S. San Raffaele Hospital, University Vita-Salute, 20132 Milan, Italy*

[3] *Department of Medical and Surgical Sciences, University of Bologna, 40121 Bologna, Italy*

[4] *Obstetric Unit, IRCCS Azienda Ospedaliero-Universitaria Sant' Orsola-Malpighi, 40121 Bologna, Italy*

*Correspondence: antonio.farina@unibo.it (Antonio Farina)
† These authors contributed equally.

DOI:10.31083/j.ceog4804130

Submitted: 10 April 2021 Revised: 27 April 2021 Accepted: 2 June 2021 Published: 15 August 2021

Background: Preeclampsia (PE) is a multisystem disease of pregnancy representing a major cause of maternal and perinatal morbidity and mortality. Early identification of pregnancies at risk of developing PE is crucial for implementing preventive strategies. The effectiveness of PE screening in the first trimester is widely recognized and endorsed by several guidelines, but unfortunately real-world implementation of this practice within local settings remains difficult. *Methods*: We performed a systematic review of the literature to understand the critical issues hampering the implementation of PE screening procedures in Italy. All studies on first trimester PE screening in the Italian population were eligible for inclusion. Key-concepts relevant for implementation of PE screening in Italy were extracted and analysed qualitatively. *Results*: Nine articles were selected and included. Lack of evidence concerning the topic of PE screening in Italy was shown. Major critical issues found encompassed healthcare personnel education, training of sonographers, economic coverage for biochemical markers and adjustment of algorithms based on population characteristics. *Conclusions*: Identification and adaptation of specific protocols to local settings and population characteristics is critical for successful implementation of early PE screening in Italy. This process has the potential to improve pregnancy outcomes and to save valuable health-care resources, particularly scarce in the COVID-19 era. There is an urgent need for research studies on specific local populations focussing on subtle details capable of maximizing PE screening uptake. This action will likely potentiate PE screening implementation reducing the burden and the cost of perinatal and maternal complications.

Keywords

Preeclampsia; Prediction; Screening; First trimester; Mean arterial pressure; Uterine artery pulsatility index; Placental growth factor; Pregnancy associated plasma protein-A

1. Introduction

Preeclampsia (PE) is a multisystem disease affecting 2–8% of all pregnancies [1]. The definition of PE was recently updated by the International Society for the Study of Hypertension in Pregnancy (ISSHP) [2] and subsequently endorsed by the International Federation of Gynecology and Obstetrics (FIGO) [3] as new-onset hypertension after 20 weeks of gestation accompanied by at least one of the following: proteinuria, other maternal organ dysfunction or uteroplacental dysfunction. PE was classified into early-onset (with delivery at $<34+0$ weeks of gestation), preterm (with delivery at $<37+0$ weeks of gestation), late-onset (with delivery at ≥ 34 weeks of gestation) and term (with delivery at $\geq 37+0$ weeks of gestation) [3].

The clinical relevance of PE is related to the high maternal and perinatal morbidity and mortality. Indeed, PE may cause maternal complications such as placental abruption, HELLP syndrome, acute pulmonary oedema, respiratory distress syndrome, and acute renal failure [4]. On the fetal side, PE is associated with fetal growth restriction (FGR), intra uterine fetal death (IUFD), oligohydramnios, preterm delivery, non-reassuring fetal heart rate (FHR) during labour, risk of caesarean section or instrumental operative delivery, low Apgar scores, and need for NICU admission [5].

The risk of adverse maternal and perinatal outcomes is higher in early-onset PE than late-onset PE [6, 7].

The prediction of PE in the first trimester of pregnancy may allow the introduction of prophylactic treatments as demonstrated by the ASPRE trial [8]. This study provided major evidence that applying a combined screening test including maternal demographic characteristics and measurements of maternal biomarkers level (mean arterial pressure, uterine artery Doppler pulsatility index, serum concentra-

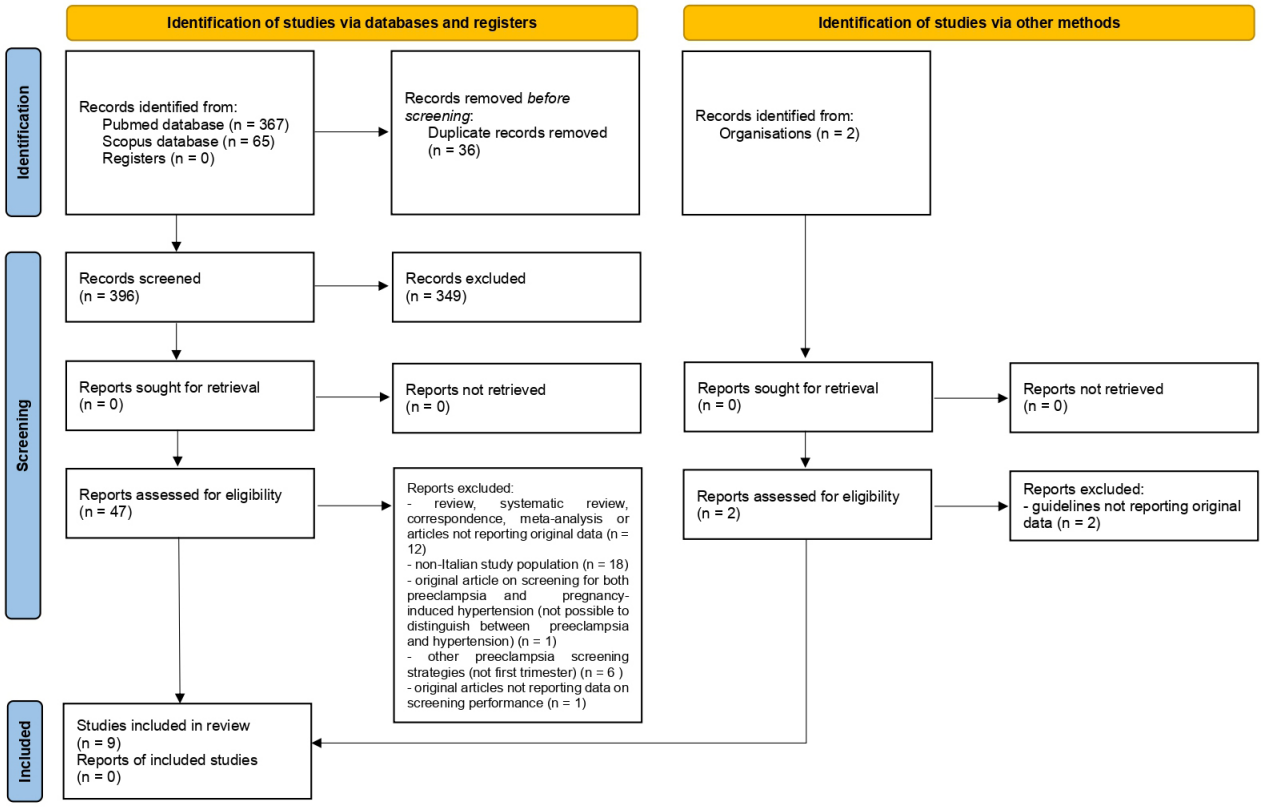

Fig. 1. PRISMA 2020 flow diagram of systematic review search.

tions of pregnancy associated-plasma protein A, placental growth factor) and performing in women at high-risk Aspirin prophylaxis (150 mg/day; from 11–14 weeks until 36 weeks of gestation) the risk of developing preterm PE reduced by 60% [8]. Relevant international guidelines [3], as well as the Italian association of preeclampsia (AIPE) [9], recently supported and recommended the introduction of universal screening for PE.

The aim of this study was to examine the available literature on first trimester PE screening implementation within local settings in Italy, including aspects related to peculiar characteristics of local populations and health systems, in order to identify potential critical issues hampering the diffusion of the screening program.

2. Materials and methods

2.1 Literature search strategy

A systematic review of the literature was conducted through PubMed and Scopus databases, according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [10]. The search was carried out from the inception of each database to February 2021 using the following keywords alone or in combination with Boolean operators AND, OR: "preeclampsia screening"; "Italy"; "first trimester"; "placental growth factor"; "pregnancy associated plasma protein-A"; "uterine arteries Doppler"; "uterine artery pulsatility index"; "risk factors". We also searched Google for the guidelines of the main Italian scientific societies. The available literature was considered in English or Italian language.

2.2 Study selection

All studies on first trimester PE screening in the Italian population were eligible for inclusion. We excluded studies dealing with PE screening in second or third trimester, studies performed in non-Italian populations as well as all types of reviews or meta-analysis and correspondence articles. After elimination of duplicates, two reviewers (SA and GB) independently screened all identified articles and selected relevant articles by mutual agreement. Disagreement was resolved by discussion with a third senior reviewer (PIC or AF).

2.3 Study analysis

Limitations, problems, and specific issues related to study groups or populations where the screening was applied were extracted and added in Table 1. A narrative review was carried out selecting relevant key-points to be highlighted in order to facilitate implementation of the process of PE screening in Italy.

3. Results

The systematic search yielded 432 papers. After excluding duplicates and inappropriate citations, 47 full-text articles were assessed for eligibility. Fig. 1 shows the flow chart of study selection. Thirty-eight studies were excluded for the

following reasons: review, systematic review, meta-analysis, correspondence, or articles not reporting original data (n = 12), original articles of non-Italian study population (n = 18), original articles about screening for both PE and pregnancy-induced hypertension (n = 1), original articles about other PE screening strategies that excluded the first trimester (n = 6), and original articles not reporting data on screening performance (n = 1). Finally, nine articles were included in this review [11–16, 18–20] (Fig. 1).

The results of this systematic review with critical points and suggested actions are summarized in Table 1.

Rizzo *et al.* [11] proposed the first PE screening model at 11–14 weeks in the Italian population. The authors evaluated a dichotomic detection rate (DR) of uterine artery Doppler velocimetry pulsatility index >95th centile and three-dimensional ultrasound placental volume <5th centile for PE on 348 nulliparous, including 16 cases of PE. The detection rate of Doppler and placental volume were 50% and 56.3% at a false positive rate of 2–5% about, which increased to 66.7% for both markers for PE requiring delivery <32 weeks. While this screening model is based exclusively on ultrasound parameters, other studies evaluated the efficacy of screening based on biochemical markers in the first trimester. D'Anna *et al.* [12] evaluated PAPP-A and neutrophil gelatinase-associated lipocalin (NGAL) at 9–11 weeks in 111 pregnancies, including 37 cases of PE. NGAL showed for prediction of late-onset PE a DR of 33.3%, with a false-positive rate of 6.7%.

Youssef *et al.* [13], in a study of 528 pregnancies including 13 late-onset PE, concluded that a combined screening model that included PlGF, sFlt-1 and NGAL has a DR for PE of 77% at a 10% FPR. Gesuita *et al.* [18], combining the plasma concentration of high temperature requirement factor A1 (HtrA1) at 12 weeks of gestation with pre-pregnancy BMI, obtained a DR of 40% about at a FPR of 10% (this data was extrapolated from the visual inspection of the ROC curve reported by the authors in their paper). Gestational age at delivery (with a mean of 39 weeks for both case and control groups) was also added to the model but its contribution to DR seems very low.

Di Lorenzo *et al.* [15], using chronic hypertension plus free-βhCG and PlGF, found a DR of 75% for early onset PE at 10% FPR. Conversely, late PE was better predicted by the use of Uterine Doppler PI uterine artery PI yielding a DR of 31% at same 10% FPR.

Following various experiences in other countries, models combining these parameters were evaluated in Italy as well. Farina *et al.* [14] first used screening models that combined maternal characteristics, biophysical and biochemical parameters. The authors applied eight different logistic regression models and compared their DR with that of the original studies. The models proposed by Onwudiwe [21] and Poon [22] showed the best DRs in the study population, respectively of 74.4% and 84.6% at a FPR of 10%.

Di Martino *et al.* [16] compared the performance of the a priori risk algorithms proposed by FMF [23] in 2012 and BCNatal [17] in an Italian population of 11,632 singleton pregnancies, including 67 cases of early PE and 211 cases of late PE. At a 10% FPR, the DR was 58.2% vs. 41.8% for early PE and 44.1% vs 38% for late PE for the FMF and the BCNatal algorithms, respectively. Therefore, the FMF algorithm showed better performance in this study population. Furthermore, the authors highlighted that the number of observed PE cases was higher than predicted with both algorithms, demonstrating that both algorithms underestimated the risk of early PE.

Brunelli *et al.* [20] assessed the optimal screening tool for PE in an Italian population considering maternal characteristics in nulliparous pregnant women. The study included 73 preterm PE cases and 7546 controls (including 101 term PE). The authors carried out an external validation study of the simple risk score developed by Sovio and Smith [24] and based on maternal characteristics, whose regression coefficients was derived from the algorithm used by the FMF. This approach showed a low performance on the Italian population of the study, with a DR of 32.9 at a FPR of 8.8% (approximately 40%, lower as compared to the population in Sovio and Smith's paper). Furthermore, by applying the Sovio and Smith risk score and the FMF algorithm to the same population of the study, the latter showed better performance in predicting PE, with an SDR of 50% about a FPR of 10%.

4. Discussion

Traditionally, the National Institute for Health and Clinical Excellence (NICE) [25] and the American College of Obstetricians and Gynaecologists (ACOG) [26, 27] recommended to assess the risk of PE based exclusively upon maternal risk factor. The Fetal Medicine Foundation (FMF) proposed an alternative screening tool that allows to estimate individual patient-specific risk through the use of Bayes theorem, which combines *a priori* risk (determined by maternal characteristics and medical history) with mean arterial pressure (MAP), mean uterine artery pulsatility index (UtA-PI) and two first-trimester biochemical markers, placental growth factor (PlGF) and pregnancy-associated plasma protein A (PAPP-A) [28, 29].

A prospective multicentre validation study confirmed that FMF's algorithm detection rates are superior: 100%, 75% and 43%, at a FPR of 10.0% for delivery with PE <32, <37 and ≥37 weeks' gestation, respectively [30]. Moreover, the SPREE study compared diagnostic accuracy of early screening of PE based upon the NICE guidelines with that of the FMF. The NICE method showed poor performance and low compliance. The performance of screening was substantially improved by a method combining maternal factors with biomarkers [31].

Based on the evidence above, the International Federation of Gynecology and Obstetrics (FIGO) endorsed FMF's algorithm and recommended its use for preterm PE screening in

Table 1. Summary of observational, case-control studies on first trimester screening for preeclampsia: critical points and suggested solutions for implementation at the local-level setting.

Author	Area	Study design	Study population	Screening methods	Limitations	Suggested actions
Rizzo *et al.*, 2007 [11]	Middle-Italy	Prospective	6 PE (6 early-PE)	*Uterine artery Doppler PI*	Expertise of sonographers, technique standardization, no dedicated software, local settings inadequacies	Use of rapid and easy-to-reproduce ultrasound parameters
			332 controls	*Three-dimensional ultrasound placental volume*	Inclusion criteria limited to nulliparous (prevalence of PE higher than in previous studies)	Extend inclusion criteria to enhance potential application in clinical practice
					Small sample size	Wider sample size to reduce prevalence of PE
D'Anna *et al.*, 2009 [12]	Southern Italy	Retrospective	37 PE	*Biochemical markers (PAPP-A and NGAL)*	Efficacy evaluated only in late-onset PE	Include variables to assess risk of early-onset PE
			74 controls		Early GA (9–11 w) at PAPP-A blood sampling	Blood sampling later GA (11–14 w)
					Heterogeneity of GA at delivery and in birth weight	Define population-based test performances and adjust the test for local settings
Youssef *et al.*, 2011 [13]	Northern Italy	Prospective	13 late-PE	*Maternal history*	Efficacy evaluated only in late-onset PE	Include variables to assess risk of early-onset PE
			515 controls	*hUtA-PI*	Tertiary level center with high prevalence of PE (selection bias)	Consider community hospitals to avoid selection bias
				Biochemical markers (PAPP-A, PIGF, s-Flt-1, P-selectin and NGAL)	Small sample size	Wider sample size to reduce prevalence of PE
					Study population almost exclusively Caucasian (population bias), difference in demographic characteristics in terms of parity and birth weight	Define population-based test performances and adjust the test for local settings
Farina *et al.*, 2011 [14]	Northern Italy	Prospective	39 late-PE	*Eight different logistic regression-based statistical models*	Efficacy evaluated only in late-onset PE	Include variables to assess risk of early-onset PE
			515 controls		Demographic differences affect test performance (parity, BMI, family history of PE, smoking)	Define population-based test performances and adjust the test for local settings
					Small sample size	With a wider sample size, the estimated DR would be closer to the original
					Using different logistic regression-based statistical models prospectively on a different population, rarely yields the same results as in retrospective analysis (different DR)	Retrospective data collection
					Rate of mild versus severe PE could not be the same in all populations (the risk of estimation could be skewed to an unknown degree)	Define mild to severe PE through strict criteria
					Heterogeneity in definition of PE	Strive a universal definition of PE
					Criteria defining the degree of risk (low vs high) in a given population are not uniform and too model-dependent	Define reproducible criteria for the level of risk

Table 1. Continued.

Author	Area	Study design	Study population	Screening methods	Limitations	Suggested actions
Di Lorenzo *et al.*, 2012 [15]	Northern Italy	Prospective	25 PE (12 early-PE and 13 late-PE)	*Maternal history*	Low prevalence of PE in the study population probably due to the low prevalence of Black women in the cohort	Define population-based test performances and adjust the test for local settings, reproducibility
			2093 controls	*Uterine artery Doppler* *Biochemical markers (free b-HCG, PAPP-A, PIGF, PP-13)*	Not recorded maternal blood pressure at the first prenatal visit	Record maternal blood pressure at the first prenatal visit to improve the screening performance
Di Martino *et al.*, 2019 [16]	Northern Italy	Prospective, multicenter	278 PE (67 early-PE and 211 late-PE)	*FMF algorithm* [22, 28, 29]	In evaluating late-PE performance, the two algorithms were not fully comparable: cases delivering at <34 had to be excluded	Consider and compare algorithms in both early and late PE
			11354 controls	*BCNatal algorithm* [17]	Study population not fully representative of the Northern Italian population: an unknown percentage of high-risk women have been lost to the screening program and many of them were Black or Asian, and were at higher risk of PE	Define population-based test performances and adjust the test for local settings, reproducibility
					Approximately 4% of the women received low dosage aspirin but no specific indications regarding the duration of treatment or the week the therapy began were available	Exclude chronic aspirin-users
Gesuita *et al.*, 2019 [18]	Middle-Italy	Prospective	14 PE 144 controls	*Prepregnancy BMI* *Biochemical marker (Htra1)*	Not widely used in clinical practice, expensive	Use more available and low cost markers
Masturzo *et al.*, 2019 [19]	Northern Italy	Prospective	83 early-PE	*Maternal age*	Data about the ovulatory status of recipient women is not available. In particular, we are not able to know how many patients suffered from POF as a possible extra risk factor for PE	Define and stratify the population based on gynecological comorbidities and risk factors
			11545 controls		Data on ART procedure and on donor characteristics are not available (all OD treatments had been performed abroad)	Include only women who underwent ART treatment in Italy
				Type of conception	In the reference population there are very few cases of advanced maternal age (>46 years)	Consider a study population balanced by age
				Number of fetuses	No twin pregnancies are available in the reference group	Include twin pregnancies in order to evaluate possible differences in the PE risk in spontaneous twin pregnancies vs. twin pregnancies obtained by OD
Brunelli *et al.*, 2020 [20]	Northern Italy	Retrospective, multicenter	73 preterm PE cases	*Maternal factor*	Statistical models influence the different performance of the test in various populations	Define the best statistical model for each specific population
			7546 controls (including 101 term PE)		Inclusion criteria limited to nulliparous	Extend inclusion criteria to enhance potential application in clinical practice

Table legend: hUtA PI, Highest UtA pulsatility index; POF, Premature ovarian failure; OD, Oocyte donation.

the first trimester [3]. However, where resources are limited, FIGO recommends screening by maternal factors and MAP in all pregnancies and subsequent measurements of PlGF and UtA-PI for the subgroup at risk.

While the Italian Association of PE (AIPE) suggests PE screening proposed by the FMF in centres with adequate professional, laboratory skills and resources [9], we are not aware of clear endorsements of this method by other Italian scientific societies. Unfortunately, despite robust scientific evidence in support of PE screening, the test is not widely adopted within the first trimester.

Validation studies are required before the introduction into clinical practice of new predictive risk models. In fact, their performance can be affected by various factors including differences in statistic models, healthcare systems, methods of measurement and patient characteristics [32].

4.1 Demographic characteristics

We highlighted that the main limitation of PE screening is linked to heterogeneity of population' characteristics. Indeed, demographic and ethnic factors in the first place, but also others such as the proportion of non-spontaneous conception, could affect the performance of screening tests.

The competing risks model proposed by the FMF achieved the best performances in terms of prediction and reproducibility in external studies, including the Japanese population [33].

Di Lorenzo *et al.* [15] reported a lower prevalence of PE in the Italian population than that reported in the literature (1.18% vs 2–3%), probably as a consequence of the lower prevalence of Afro-Caribbean ethnicity (0.70%). Similarly, the demographic characteristics of the Italian population studied by Di Martino *et al.* [16] showed sensible differences in the ethnic distribution compared to the FMF group data [23, 28, 29]. In the Italian study, Caucasians represent 94.7% and Afro-Caribbean ethnicity $<1\%$, while in the population studied by FMF were approximately 70% and 16–18%, respectively. As the risk of PE increases by 20–50% in the Afro-Caribbean population [34, 35], the different ethnic distribution could partly explain the discrepancy in the risk estimation.

Another demographic difference that affects screening performance is the rate of *in vitro* fertilization (IVF) in women who developed PE: from 12.9% to 27.5% in Italian population [16, 20] versus 2–5% of the English population [23, 28, 29]. A recent study from our group observed that pregnancies obtained from oocyte donation have a higher risk of early PE [19]. Furthermore, the risk increases according to number of fetus and in direct proportion to the increase in maternal age. Finally, current major evidences showed lower UtA-PI in IVF/ICSI pregnancies from frozen blastocyst transfer and oocyte donations throughout pregnancy, from the first to the third trimester [36, 37]. This new knowledge, in adjunct to previous evidences showing lower PAPP-A and higher free-βhCG concentrations in IVF/ICSI pregnancies, confirms that populations with higher rate of these pregnancies should be screened to correct these risk factors [38].

Given the significant and growing rate of conceptions from assisted reproductive technology (ART) in Italy, adjustments of UtA-PI values and serum biochemistry in these pregnancies should be considered to improve risk prediction, as suggested by the Fetal Medicine Foundation, and even more in light of these new evidences [36, 37].

In order to favour the implementation and to maximize performance of PE screening in local settings, it is desirable to calibrate the statistical model in relation to the demographic characteristics of the population and to define population-based test performances.

4.2 Health systems organization

In addition to demographic characteristics, the organization of health systems and their economic resources should be emphasized because they play a key role in the spread of PE screening.

The screening model proposed by the FMF has been demonstrated to be the most appropriate effective and reproducible. However, the statistical model is very complicated and requires specific softwares and sonographers who received the appropriate training with certification of competence from the Fetal Medicine Foundation (FMF). Again, there are no independent studies that compared the value of each variable to predict the PE occurrence. It should be noted that in Italy there are 1189 health professionals accredited for aneuploidy screening, while only 263 are certified for PE screening (http://www.fetalmedicine.org; Accessed: 3 April 2021). This discrepancy is also observed in other countries. Therefore, it is necessary that health systems and scientific societies invest in the training of operators to guarantee competent screening for the entire population.

In our opinion, limits to the spread of PE screening in Italy are the lack of complete economic coverage by the national health system for serum biochemistry and training of operators. Moreover, important risk factors often coexist in the less wealthy social group, including immigrants, particularly women of Afro-Caribbean ethnic group.

Unfortunately, we could not find published studies on health economic analysis of first trimester PE screening performed specifically in the Italian setting. However, this topic was object of analysis by leading groups at international level with demonstration of high cost-effectiveness of the PE screening procedure [39–42]. This was predominantly due to the reduction in the number of early preterm deliveries with PE and related costs [43].

Therefore, the strategy to implement PE screening should be three-fold: (1) raising awareness among the population, politics, individual physicians, and scientific societies on the importance of prediction and prevention of PE; (2) ensuring the economic coverage for training operators and providing free biochemical reagents for PE screening; (3) developing

validation research projects simultaneously to implementation processes, in order to adapt the FMF methods to specific local settings and populations.

5. Conclusions

Our systematic review showed lack of evidence concerning the topic of PE screening within the Italian local setting. We found only a few studies, which unfortunately enrolled a relative small number of cases. Overall, statistics is quite rudimentary if compared to the FMF algorithm, and no custom applications of such algorithm to Italian population are available. While it is already established that PE screening should be clinically implemented at a global level, this review shows the importance of identifying optimal implementation methods for specific clinical settings, and adjusting algorithms for local population characteristics. Specific issues related to populations and health system characteristics will suggest specific strategies to optimize implementation of the screening process. Although the competing risk model proposed by the FMF showed high quality evidence to promote implementation of PE screening globally, research studies on specific local populations are still desirable to focus on subtle details capable of maximizing screening uptake and performance at a local level. This will likely consolidate the effectiveness of screening, whilst also contributing to improve pregnancy outcome and to save valuable health-care system resources.

Author contributions

AF and PIC designed the research study and carried out critical revision. SA and GB performed the literature search, data extraction and qualitative analysis, drafted the paper. AS performed critical revision for important intellectual content and text editing including English language. All authors contributed to writing, editing and revising the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This study received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Duley L. The global impact of pre-eclampia and eclampsia. Semin Perinatol. 2009; 33: 130–137.

[2] Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, *et al.* Hypertensive Disorders of Pregnancy. Hypertension. 2018; 72: 24–43.

[3] Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, *et al.* The international Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia. A pragmatic guide for first-trimester screening and prevention. International Journal of Gynecology & Obstetrics. 2019; 145: 1–33.

[4] Zhang J, Meikle S, Trumble A. Severe maternal morbidity associated with hypertensive disorders in pregnancy in United States. Hypertens Pregnancy. 2003; 22: 203–212.

[5] Yücesoy G, Ozkan S, Bodur H, Tan T, Calişkan E, Vural B, *et al.* Maternal and perinatal outcome in pregnancies complicated with hypertensive disorder of pregnancy: a seven year experience of a tertiary care center. Archives of Gynecology and Obstetrics. 2005; 273: 43–49.

[6] Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. American Journal of Obstetrics and Gynecology. 2013; 209: 544.e1–e2.

[7] Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph KS. Maternal morbidity associated with early-onset and late-onset preeclampsia. Obstetrics and Gynecology. 2014; 124: 771–781.

[8] Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, *et al.* Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. New England Journal of Medicine. 2017; 377: 613–622.

[9] Associazione Italiana Preeclampsia (Australian Institute of Professional Education). I disordini ipertensivi in gravidanza: classificazione, diagnosi e terapia. Raccomandazioni di buona pratica clinica. 2020. (In Italian)

[10] Page M, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. British Medical Journal. 2021; 372: n71.

[11] Rizzo G, Capponi A, Cavicchioni O, Vendola M, Arduini D. First trimester uterine Doppler and three-dimensional ultrasound placental volume calculation in predicting pre-eclampsia. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2008; 138: 147–151.

[12] D'Anna R, Baviera G, Giordano D, Russo S, Dugo N, Santamaria A, *et al.* First trimester serum PAPP-A and NGAL in the prediction of late-onset pre-eclampsia. Prenatal Diagnosis. 2009; 29: 1066–1068.

[13] Youssef A, Righetti F, Morano D, Rizzo N, Farina A. Uterine artery Doppler and biochemical markers (PAPP-A, PIGF, sFlt-1, P-selectin, NGAL) at 11 + 0 to 13 + 6 weeks in the prediction of late (>34 weeks) pre-eclampsia. Prenat Diagn. 2011; 31: 1141–1146.

[14] Farina A, Rapacchia G, Freni Sterrantino A, Pula G, Morano D, Rizzo N. Prospective evaluation of ultrasound and biochemical-based multivariable models for the prediction of late pre-eclampsia. Prenatal Diagnosis. 2011; 31: 1147–1152.

[15] Di Lorenzo G, Ceccarello M, Cecotti V, Ronfanu L, Monasta L, Vecchi Brumatti L, *et al.* First trimester maternal serum PIGF, free β-Hcg, PAPP-A, PP-13, uterine artery Doppler and maternal hystory for the prediction of preeclampsia. Placenta. 2012; 33: 495–501.

[16] Di Martino D, Masturzo B, Paracchini S, Bracco B, Cavoretto P, Prefumo F, *et al.* A comparison of two "a priori" risk assessment algorithms for preeclampsia in Italy: a prospective multicentre study. Archives of Gynecology and Obstetrics. 2019; 299: 1587–1596.

[17] Scazzocchio E, Figueras F, Crispi F, Meler E, Masoller N, Mula R, *et al.* Performance of a first-trimester screening of preeclampsia in a routine care low-risk setting. American Journal of Obstetrics and Gynecology. 2013; 208: 203.e1–203.e10.

[18] Gesuita R, Licini C, Picchiassi E, Tarquini F, Coata G, Fantone S, *et al.* Association between first trimester plasma htra1 level and subsequent preeclampsia: a possible early marker? Pregnancy Hypertension. 2019; 18: 58–62.

[19] Masturzo B, Di Martino D, Prefumo F, Cavoretto P, Germano C, Gennarelli G, *et al.* Higher rate of early-onset preeclampsia in pregnancies following oocyte donation according to increasing

maternal age. Archives of Gynecology and Obstetrics. 2019; 300: 861–867.
[20] Brunelli E, Seidenari A, Germano C, Prefumo F, Cavoretto P, Di Martino D, *et al.* External validation of a simple risk score based on the ASPRE trial algorithm for preterm pre-eclampsia considering maternal characteristics in nulliparous pregnant women: a multicentre retrospective cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 2020; 127: 1210–1215.
[21] Onwudiwe N, Yu CK, Poon LC, Spiliopoulos I, Nicolaides KH. Prediction of pre-eclampsia by a combination of maternal history, uterine artery Doppler and mean arterial pressure. Ultrasound in Obstetrics and Gynecology. 2008; 32: 877–883.
[22] Poon LC, Stratieva V, Piras S, Piri S, Nicolaides KH. Hypertensive disorders in pregnancy: combined screening by uterine artery Doppler, blood pressure and serum PAPP-A at 11–13 weeks. Prenatal Diagnosis. 2010; 30: 216–223.
[23] Wright D, Akolekar R, Syngelaki A, Poon LC, Nicolaides KH. A competing risks model in early screening for preeclampsia. Fetal Diagnosis and Therapy. 2012; 32: 171–178.
[24] Sovio U, Smith GCS. Evaluation of a simple risk score to predict preterm preeclampsia using maternal characteristics: a prospective cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 2019; 126: 963–970.
[25] National Collaborating Center for women's and Children's Health (UK). Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy. London: Royal College of Obstetricians and Gynaecologists Press. 2010.
[26] Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstetrics and Gynecology. 2013; 122: 1122–1131.
[27] ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstetrics & Gynecology. 2019; 133: e1–e25.
[28] Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. American Journal of Obstetrics and Gynecology. 2015; 213: 62.e1–e10.
[29] O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, Wright A, *et al.* Accuracy of competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation. Ultrasound in Obstetrics & Gynecology. 2017; 49: 751–755.
[30] O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, de Alvarado M, *et al.* Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation: comparison with NICE guidelines and ACOG recommendations. Ultrasound in Obstetrics & Gynecology. 2017; 49: 756–760.
[31] Tan MY, Wright D, Syngelaki A, Akolekar R, Cicero S, Janga D, *et al.* Comparison of diagnostic accuracy of early screening for preeclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. Ultrasound in Obstetrics & Gynecology. 2018; 51: 743–750.
[32] Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. British Medical Journal. 2009; 338: b605.
[33] Farina A, Cavoretto PI. Comment on "Accuracy of the FMF Bayes theorem-based model for predicting preeclampsia at 11–13 weeks of gestation in a Japanese population". Hypertension Research. 2021; 44: 720–721.
[34] Knuist M, Bonsel GJ, Zondervan HA, Treffers PE. Risk factors for preeclampsia in nulliparous women in distinct ethnic groups: a prospective cohort study. Obstetrics and Gynecology. 1998; 92: 174–178.
[35] Caughey AB, Stotland NE, Washington AE, Escobar GJ. Maternal ethnicity, paternal ethnicity, and parental ethnic discordance: predictors of preeclampsia. Obstetrics and Gynecology. 2005; 106: 156–161.
[36] Cavoretto PI, Farina A, Gaeta G, Sigismondi C, Spinillo S, Casiero D, *et al.* Uterine artery Doppler in singleton pregnancies conceived after in-vitro fertilization or intracytoplasmic sperm injection with fresh vs frozen blastocyst transfer: longitudinal cohort study. Ultrasound in Obstetrics & Gynecology. 2020; 56: 603–610.
[37] Cavoretto PI, Farina A, Miglio R, Zamagni G, Girardelli S, Vanni VS, *et al.* Prospective longitudinal cohort study of uterine arteries Doppler in singleton pregnancies obtained by IVF/ICSI with oocyte donation or natural conception. Human Reproduction. 2020; 35: 2428–2438.
[38] Cavoretto P, Giorgione V, Cipriani S, Viganò P, Candiani M, Inversetti A, *et al.* Nuchal translucency measurement, free β-hCG and PAPP-a concentrations in IVF/ICSI pregnancies: systematic review and meta-analysis. Prenatal Diagnosis. 2017; 37: 540–555.
[39] Karaki H, Khazaal J, Chahine R, Kharoubi M, Cuckle H. Cost-Effectiveness of first Trimester Screening for Preterm Preeclampsia in Lebanon. Journal of Fetal Medicine. 2020; 7: 119–123.
[40] Ortved D, Hawkins TL, Johnson J, Hyett J, Metcalfe A. Cost-effectiveness of first-trimester screening with early preventative use of aspirin in women at high risk of early-onset pre-eclampsia. Ultrasound in Obstetrics & Gynecology. 2019; 53: 239–244.
[41] Shmueli A, Meiri H, Gonen R. Economic assessment of screening for pre-eclampsia. Prenatal Diagnosis. 2012; 32: 29–38.
[42] Wertaschnigg D, Reddy M, Mol BWJ, Rolnik DL, da Silva Costa F. Prenatal screening for pre-eclampsia: Frequently asked questions. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2019; 59: 477–483.
[43] Wright D, Rolnik DL, Syngelaki A, de Paco Matallana C, Machuca M, de Alvarado M, *et al.* Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit. American Journal of Obstetrics and Gynecology. 2018; 218: 612.e1–612.e6.