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

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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 focusing 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 ≥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 ASPIRE 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-
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 dichotomous 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 PI GF, 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 PI GF, 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 Onwudie [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 BCSNatal [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 (PI GF) 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
| 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 pla cental 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) Define population-based test performances and adjust the test for local settings |
|                 |                    |              |                  |                                          | Heterogeneity of GA at delivery and in birth weight |                                                                                |
| Youssef et al., 2011 [13] | Northern Italy    | Prospective  | 13 late-PE       | Maternal history hUck-PI                  | Efficacy evaluated only in late-onset PE | Include variables to assess risk of early-onset PE                              |
|                 |                    |              | 515 controls     |                                          | 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                             |
| Author et al., 2012 | Area | Study design | Study population | Screening methods | Limitations | Suggested actions |
|-------------------|------|-------------|------------------|------------------|-------------|------------------|
| Di Lorenzo et al. | 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 Biomedical 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. | 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 | Middle-Italy | Prospective | 14 PE | Prepregnancy BMI Biomedical marker (Htra1) | Not widely used in clinical practice, expensive | Use more available and low cost markers |
| Masturzo et al., 2019 | 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 | Northern Italy | Retrospective, multicenter | 73 preterm PE cases | Maternal factor | Statistical models influence the different performance of the test in various populations Inclusion criteria limited to nulliparous | Define the best statistical model for each specific population |
|                   |       |             | 7546 controls (including 101 term PE) |                  |                  | 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 PIGF 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 fetuses 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-/hCG 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

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Conflict of interest

The authors declare no conflict of interest.

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