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MATERNAL-FETAL MEDICINE

Comparison of two "a priori" risk assessment algorithms for preeclampsia in Italy: a prospective multicenter study

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Abstract

Purpose To compare the performance of the algorithms proposed by the Fetal Medicine Foundation in 2012 and BCNatal in 2013 in an Italian population.

Methods A multicentric prospective study was carried out which included pregnancies at 11–13 weeks' gestation from Jan 2014 through May 2017. Two previously published algorithms were used for the calculation of the "a priori" risk of preeclampsia (based on risk factors from medical history) in each individual.

Results In a study population of 11,632 cases, 67 (0.6%) developed early preeclampsia and 211 (1.8%) developed late preeclampsia. The detection rates (95% CI) for early and late preeclampsia were 58.2% (45.5–70.2) vs. 41.8% (29.6–54.5) (p value < 0.05) and 44.1% (37.3–51.1) vs. 38% (31.3–44.8) (p value < 0.05) for the Fetal Medicine Foundation and BCNatal, respectively (at a 10% false positive rate). The associated risk was 1:226 and 1:198 (p value ns) for early PE, and 1:17 and 1:24 (p value ns) for late PE for the Fetal Medicine Foundation and BCNatal, respectively.

Conclusions The Fetal Medicine Foundation screening for preeclampsia at 11–13 weeks' gestation scored the highest detection rate for both early and late PE. At a fixed 10% false positive rate, the estimated "a priori" risks of both the Fetal Medicine Foundation and the BCNatal algorithms in an Italian population were quite similar, and both were reliable and consistent.

Keywords Screening for preeclampsia · A priori risk · ROC curves · Detection rate

Introduction

Preeclampsia (PE) is a multisystem pregnancy disorder characterized by hypertension and proteinuria. It affects approximately 2–8% of pregnancies [1] and is a significant contributor to iatrogenic preterm birth [2]. It remains a major cause of maternal and perinatal morbidity and mortality [3, 4], and is responsible for approximately 15% of all pregnancy-related deaths [5]. Furthermore, women affected by this disorder are more likely to develop cardiovascular disease, type 2 diabetes mellitus and cognitive impairment later in life [6–9].

The traditional approach to screening PE is to identify risk factors from maternal demographic characteristics and medical histories. Many professional organizations including the National Institute for Health and Care (NICE), the World Health Organization (WHO) and the American College of Obstetricians and Gynecologists (ACOG) have proposed simple score methods for detecting women at a higher "a

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priori" risk of developing PE. Many new algorithms, based solely on maternal characteristics as reviewed by Al-Rubaie [10], have also been prospectively validated. More specifically, Al-Rubaie [10] showed that simple models using routinely collected maternal characteristics in the prenatal setting can be used to identify women at high risk of PE.

To date, however, the Fetal Medicine Foundation (FMF) algorithm has been demonstrated to have the best performance and, when compared with the NICE guidelines, has produced an approximately 10% higher detection rate (DR) [11, 12]. Recent evidence has shown the efficiency of the competing risks model (if also biophysical and biochemical markers rather than demographics and medical history alone are included) and the administration of anti-platelet dose aspirin to the high-risk group in more than halving the incidence of the preterm form of PE [13].

All the models are based on maternal characteristics, and biophysical and biochemical markers and their predictive value is population dependent, assuming that they are measured using the same standardized methods as those suggested, for example, by the FMF [14, 15]. However, the influence of the population and/or the statistical model on the "a priori risk" estimation, which could represent a major source of discrepancy [16, 17], seems not to have ever been properly evaluated before.

Furthermore, in a number of settings, many women (including low social status women, immigrants and refugees) did not undergo a proper screening program for PE in the first trimester. Unfortunately, many of these women, including those who are black, and those from South and Southeast Asia, are those at higher risk of PE and have, for example, a higher prevalence of type 1 and type 2 diabetes with respect to the Caucasian population [18]. In addition, evidence that lower rates of black women, obesity and chronic hypertension are present in Southern European countries than in the UK has been reported by Tunstall-Pedoe [19]. It is evident, therefore, that the performance of a predictive algorithm would be affected by the characteristics of the local population.

An effective screening tool is essential for guiding clinicians in correctly identifying women at high risk of developing PE. In this paper, the predictive performance of two models for the "a priori" risk calculation of early and late PE was compared in a Northern Italian population: the 2012 Fetal Medicine Foundation algorithm [20] and the 2013 BCNatal algorithm [21]. In the "a priori" risk estimation, the biophysical and biochemical markers which play an essential role in improving and determining the screening performance of both algorithms were excluded.

Materials and methods

Study design and population

This was a multicentric prospective observational cohort study conducted from January 2014 through May 2017 in singleton pregnancies in which women underwent a routine first trimester admission visit and/or routine first trimester screening at 11–13 weeks' gestation at four Northern Italy Centers (Sant'Anna Hospital, Torino; San Raffaele Hospital, Milano; Buzzi Hospital, Milano; Sant'Orsola Hospital, Bologna). The local ethics committee of each hospital approved the study protocol, and each patient provided written informed consent. The study was carried out following the ethical rules of each hospital in which the study took place (the local ethics committee approval code is DBPP13EPP).

Women who were seen in the hospitals which participated in the study were recruited. Informed consent was given by the patients before their data were entered into a dedicated database. The data were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

The eligibility criteria were: a singleton pregnancy, maternal age > 18 years, live fetus at 11–13 weeks' gestation and written informed consent. The participants were selected if a complete follow-up of the pregnancy (stored in the electronic database Viewpoint, GE Healthcare Italia) was available. The exclusion criteria were: a lack of follow-up recorded in the electronic database, multiple gestation, fetal congenital anomalies and miscarriage at < 24 weeks' gestation. The gestational age was confirmed by ultrasound measurement of the crown-rump length.

The primary outcome was comparison of DR, at FPR of 5% and 10%, of two algorithms [20, 21]. The secondary outcome was the comparison, by means of a linear calibration, of the estimated risks for early and late PE obtained from the two algorithms, and evaluation of the DR and the false positive rate (FPR) at specific risk cut-off categories. Briefly calibration establishes a linear relationship to predict a value from an instrument response.

Maternal history and characteristics

The patients were asked to complete a questionnaire regarding maternal age, racial origin (Caucasian, Afro–Caribbean, South Asian, East Asian, South American and mixed), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy (yes or no), history of

chronic hypertension (yes or no), history of type 1 or type 2 diabetes mellitus (yes or no), history of systemic lupus erythematosus or antiphospholipid syndrome (yes or no), the presence of any known congenital thrombophilia (yes or no), the presence of renal diseases (yes or no), family history of PE in the mother of the patient (yes or no), obstetric history including parity (parous or nulliparous if no previous pregnancies at or after 24 weeks) and previous pregnancy with PE (yes or no). Maternal weight and height at the time of enrollment were also measured. No information about the use of aspirin was taken at the time of enrolment.

The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy [22]: systolic blood pressure of > 140 mm Hg and/or the diastolic blood pressure of > 90 mm Hg on at least two occasions 4 h apart developing after 20 weeks of gestation in previously normotensive women, and proteinuria of > 300 mg in 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h collection is available. In PE superimposed on chronic hypertension, significant proteinuria (as defined above) developed after 20 weeks of gestation in women with known chronic hypertension.

Sample size

A power analysis was carried out using Power Analysis Sample Size (PASS) software (Kaysville, UT, USA) and was conducted before the enrollment started. It was estimated that, for a receiver operating characteristic (ROC) curve analysis (given the sample allocation ratio = 1:200 or 0.5%) 50 + 10,000 cases would be needed to validate an area under the curve (AUC) ≥ 0.62 with a power of 80% and a Type 1 error of 5%. Moreover, at the same allocation ratio and the same number of cases, a difference of at least 10% in the comparison of two AUC curves would be properly detected, given the same conditions of power and type 1 error.

Statistical analysis

The Student's *t* test, χ^2 test and *z* test for comparison of two proportions were carried out to make univariate comparisons of quantitative and qualitative variables, respectively, between subgroups.

Receiver operating characteristic (ROC) curves were carried out to analyze model discrimination, which were expressed as DRs for 5% and 10% FPRs. The DRs and FPRs at fixed cut-off risk categories were also calculated using the same ROC curves. For comparison purposes, the PE cases delivering at < 34 weeks were excluded from the ROC curve generated for evaluating the DRs for late PE. This strategy was indicated since, in the FMF algorithm, the risk for PE is expressed as < 42 weeks which also includes the PE cases delivering at < 34 weeks. On the contrary, the BCNatal algorithm uses a more traditional logistic regression approach, considering just PE cases > 34 weeks. No statistical adjustment for the use of aspirin was performed.

IBM SPSS Statistics for Windows, Version 23.0. (Armonk, NY, USA) IBM Corp. with specific extension bundles was used for all the analyses.

The equation of Wright et al. [20] (including age, height, weight, ethnicity, previous history of PE, mother with PE, mode of conception, systemic lupus erythematosus or antiphospholipid syndrome, chronic hypertension, type 1 diabetes mellitus) was used to estimate the "week at delivery with PE" and the associated risk of PE occurring within 42 weeks of gestation. The estimation of the "week at delivery with PE" is a main assumption of the competing risks model proposed by the FMF in London.

Briefly, if the pregnancy were to continue indefinitely, all women would develop PE, and competition would occur between delivery with PE and delivery for other reasons. Therefore, under this statistical assumption, a theoretical and abnormally high week at delivery (up to 70 weeks) was observed, as reported by Wright [20]. By estimating the distribution of PE occurrence for an individual patient, it is possible to derive the probability of disease before or at any given gestation. Since the study began in January 2014, we could not use the latest FMF algorithm that was presented in 2015 [11].

The Scazzochio et al. equation [21] was used to calculate the risk of early and late PE requiring delivery < 34 or > 34 weeks, respectively, according to the BCNatal algorithm [including previous PE, multiparity, body mass index (BMI), chronic hypertension, diabetes mellitus, thrombophilic condition, renal disease].

To assess the agreement between the predicted risk and the prevalence of PE, the population screened was ranked according to the predicted risk of PE with the FMF and the BCNAtal algorithms, and was then divided into groups with a roughly similar number of cases of PE as suggested by Wald et al. [23]. For each group, the expected number of cases of PE was calculated as the sum of each pregnancy's individual risk. The observed prevalence of PE was also calculated for each group. For each group, the predicted and observed prevalences were compared (using a *z* test).

Results

Demographics

Between January 2014 and May 2017, women who underwent routine first trimester admission visit and/or screening for Down's syndrome, were also screened for PE in the first trimester; all delivered by 31 January 2018. During this

period, 12,284 singleton pregnancies were collected. There were 11,632 cases (94.7%) which fulfilled the inclusion criteria. Sixty-seven (0.6%) cases experienced early PE (requiring delivery < 34 weeks) and 211 (1.8%) experienced late PE (requiring delivery at 34–42 weeks). Baseline demographics, and clinical characteristics are presented in Table 1.

Primary outcome: ROC curves

Table 2, and Fig. 1a and b show the ROC curves obtained with the FMF and BCNatal algorithms. The DRs (95% CI) for early and late PE were 58.2% (45.5–70.2) vs. 41.8% (29.6–54.5) (p value < 0.05) and 44.1% (37.3–51.1) vs. 38% (31.3–44.8) (p value < 0.05) for the FMF and the BCNatal algorithms, respectively (at a 10% FPR). Despite a difference in the DRs, the associated risks were quite similar, namely 1:226 and 1:198 (p value ns) for early PE, and 1:17 and 1:24 (p value ns) for late PE, respectively. The DRs at 5% FPR are also reported in Table 2. It is interesting that a similar difference between the two algorithms performance (+ 17% for early PE and + 7% about for late PE) was found at 5% and 10% FPR.

The difference in the two AUCs for early PE was significant (p value < 0.001) and met the criteria adopted for

Table 1 Epidemiological and clinical characteristics of the study population according to study group

Characteristics	No PE (n = 11,354)	PE (n = 278)	p value*
Mean (SD) maternal age, years	32.4 (4.68)	34.3 (4.70)	< 0.001
Maternal BMI	22.61 (3.92)	24.88 (4.88)	< 0.001
Racial origin (%)			
Caucasian	97.2 (11,036)	87.4 (243)	< 0.01
Afro–Caribbean	0.9 (102)	2.2 (6)	< 0.01
South-East Asian	2 (227)	4 (11)	< 0.05
Other	2.2 (250)	0 (0)	< 0.05
Nulliparous (%)	65.7 (7460)	70.9 (197)	0.073
Parous with previous PE (%)	2.9 (329)	35.3 (98)	< 0.01
Family history of PE (%)	2.6 (295)	3.9 (11)	< 0.01
Family history of hypertension (%)	29.8 (3383)	35.4 (98)	< 0.05
Conception (%)			
Spontaneous	96.5 (10,957)	87.1 (242)	< 0.01
Assisted	3.5 (397)	12.9 (36)	< 0.01
History of chronic hypertension (%)	0.5 (57)	14.4 (40)	< 0.01
History of type 1 or 2 diabetes mellitus (%)	3.1 (352)	6.1 (17)	< 0.01
History of SLE or APLS autoimmune disease (%)	0.4 (45)	1.4 (4)	< 0.01
Renal disease (%)	1.4 (159)	3.6 (10)	< 0.01
Known congenital thrombophilia (%)	2.4 (272)	2.9 (8)	0.0536

Data are expressed as means (standard deviation or SD) or percentages (%) (number of cases)

PE preeclampsia, *BMI* body mass index, *SLE* systemic lupus erythematosus, *APLS* antiphospholipid antibody syndrome

*Student t test or χ^2 test

Table 2 Receiver operating characteristic (ROC) curve output. Performance of screening for delivery with early (<34 weeks) and late (34–42 weeks) preeclampsia

Algorithm	AUC	SE	DR (95% CI) at 5% FPR	DR (95% CI) at 10% FPR	p value	AUC 95% CI	
Early preeclampsia < 34 weeks							
FMF	0.764	0.037	47.8 (35.4–60.3)	58.2 (45.5–70.2)	< 0.001	0.692	0.836
BCNatal	0.686	0.037	30.0 (19.3–42.3)	41.8 (29.6–54.5)	< 0.001	0.614	0.758
Late preeclampsia 34–42 weeks							
FMF	0.730	0.020	37.0 (30.4–43.9)	44.1 (37.3–51.1)	< 0.001	0.690	0.770
BCNatal	0.729	0.019	30.0 (22.4–38.6)	38.0 (31.3–44.8)	< 0.001	0.692	0.766

Area under the curve (AUC) standard error (SE) and associated detection rate (DR) at fixed false positive rates (FPRs) of 5% and 10% of the two algorithms for early PE < 34 and late PE 34–42 weeks

95% CI 95% confidence intervals

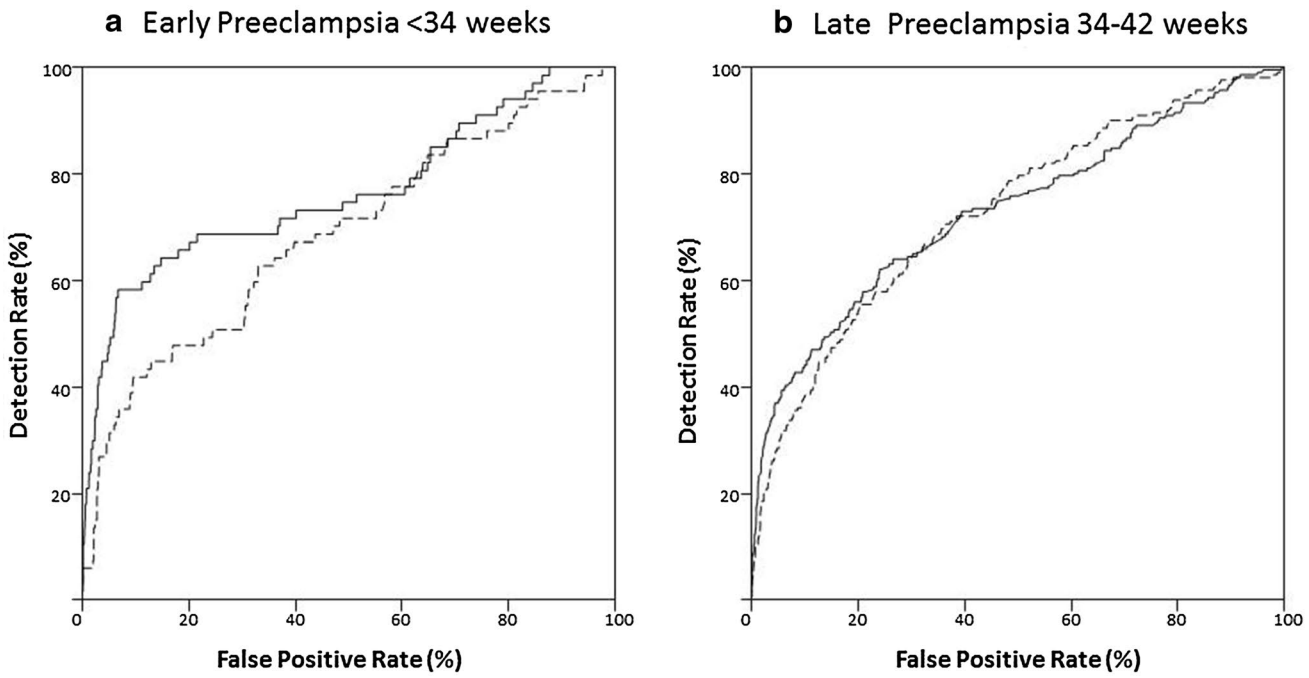

Fig. 1 Receiver operating characteristic (ROC) curves for the prediction of preeclampsia (PE) requiring delivery: (**a** < 34 weeks; **b** 34–42 weeks) according to the FMF (solid line) and BCNatal (dotted line) algorithms

sample size validation, i.e., a difference > 10%. Instead, no statistical difference between the two AUCs was demonstrated for late PE, the difference being almost zero.

Table 3 reports the DRs and FPRs of the two algorithms in early (panel a) and late (panel b) PE for the FMF and the BCNAtal algorithms at fixed risk cut-offs. It was also shown that the actual risk values of the two models were quite similar, and had a very strong correlation (p value < 0.001) for both early and late PE) (data available on request).

Secondary outcome: calibration

Table 4 reports the observed and predicted prevalence of PE for each risk category according to the FMF and BCNAtal algorithms. The results of early and late PE are reported in panels a and b, respectively, and are also graphically expressed in Fig. 2a and b. As shown, both algorithms underestimated the early PE risk. Instead, late PE risk estimation resulted in a better performance for both the algorithms.

Table 3 Diagnostic performance for early (panel a) and late (panel b) preeclampsia expressed as detection rate (DR) and false positive rate (FPR) at cut-off categories for preeclampsia

Risk category	DR for FMF	FPR for FMF (Fetal Medicine Foundation)	DR for BCNatal	FPR for BCNatal
(panel a) Early preeclampsia < 34 weeks				
> 1:20	17.9	0.5	6.0	1.7
> 1:50	20.9	1.2	19.4	2.8
> 1:100	34.3	2.5	26.9	3.7
> 1:300	65.7	18.4	62.7	34.9
(panel b) Late preeclampsia 34–42 weeks				
> 1:10	30.8	2.7	18.0	1.8
> 1:20	52.1	16.6	30.8	5.5
> 1:50	90.5	76.9	56.9	22.9
> 1:100	99.5	98.2	95.7	86.1

Table 4 Observed and predicted prevalence of early (panel a) and late (panel b) preeclampsia in a population screened by the Fetal Medicine Foundation (FMF) and BCNatal

Risk category	FMF						Risk category	BCNatal					
	N	Observed number of cases	Observed prevalence	Predicted number of cases	Predicted prevalence	*p* value*		*N*	Observed number of cases	Observed prevalence	Predicted number of cases	Predicted prevalence	*p* value*
(panel a) Early preeclampsia < 34 weeks													
> 1:30	90	13	1:7	8	1:12	0.246	> 1:50	321	13	1:24	32	1:10	< 0.01
1:30–1:100	213	13	1:16	3	1:62	< 0.05	1:51–1:200	881	13	1:67	5	1:166	0.057
1:101–1:200	569	13	1:44	4	1:155	< 0.05	1:201–1:300	2820	13	1:216	11	1:259	0.681
1:201–1:600	5542	13	1:426	13	1:411	1	1:301–1:400	4815	13	1:370	13	1:354	1
< 1:600	5007	15	1:333	4	1:1152	< 0.05	< 1:400	2584	15	1:172	6	1:434	< 0.05
(panel b) Late preeclampsia 34–42 weeks													
> 1:5	154	42	27.3%	51	33%	0.258	> 1:5	119	42	35.3%	30	25.2%	0.091
1:6–1:15	812	42	1:19	58	1:14	0.099	1:6–1:35	1253	42	1:30	59	1:21	0.083
1:16–1:20	1253	42	1:30	66	1:19	< 0.05	1:36–1:50	1407	42	1:34	32	1:44	0.238
1:21–1:30	3535	42	1:84	136	1:26	< 0.001	1:51–1:65	2597	42	1:62	44	1:58	0.825
< 1:30	5811	43	1:135	129	1:45	< 0.001	< 65	6189	43	1:144	77	1:81	< 0.001

*Z test for two independent proportions

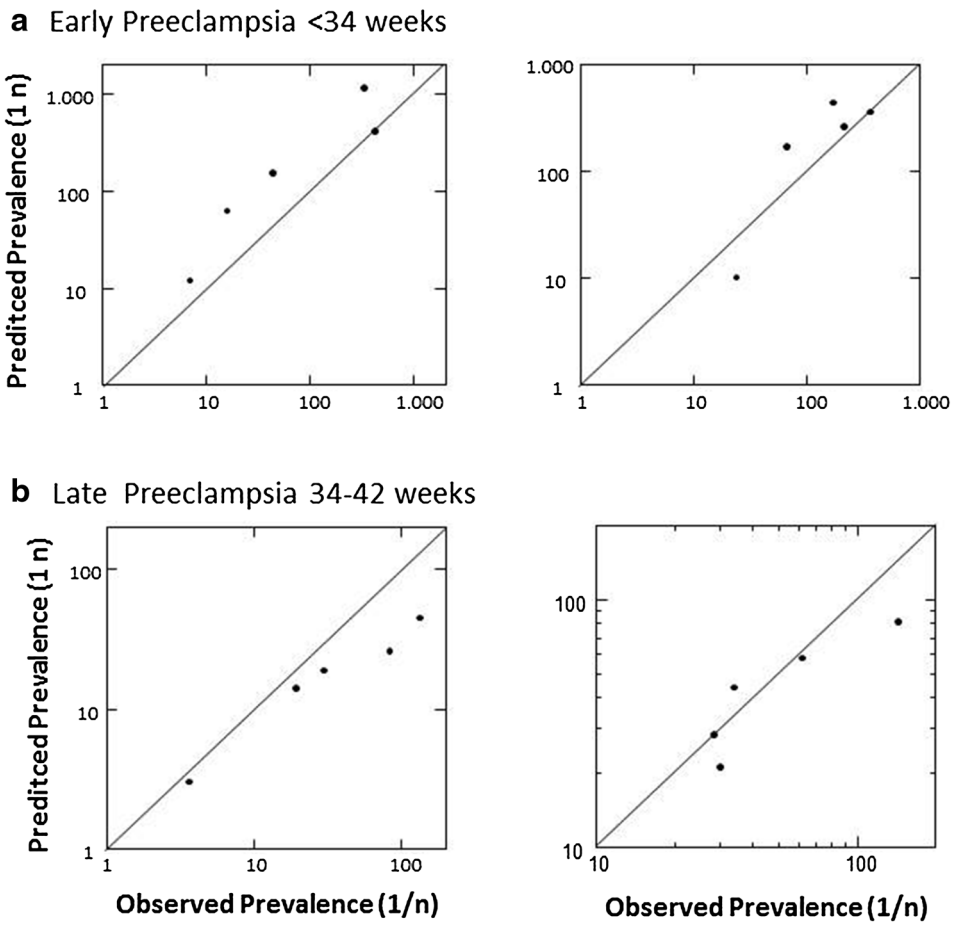

Fig. 2 Comparison of the observed prevalence of preeclampsia and the predicted prevalence of preeclampsia (**a** < 34 weeks and **b** 34–42 weeks) in a population screened by the Fetal Medicine Foundation (left) and BCNatal (right) algorithms. The diagonal line is the line of identity between the predicted and the observed prevalences

Discussion

This study was the first Italian observational study which evaluated and compared two multifactorial first trimester screening algorithms for the evaluation of the "a priori" risk of PE. Thanks mainly to the FMF algorithm; it was possible to introduce a new concept in screening performance, i.e., the rate "population specific" of PE occurring < 42 weeks in a higher risk population which is not necessarily the same for the various populations. This concept should be applied to any specific geographic area, and taken into consideration for a more proper testing of the screening performance.

The follow-up loss in the study was 5.3%. Not delivering in one of the participating hospitals was the major reason of the cases loss.

The incidence of late PE (1.8%) was somewhat lower than commonly expected for the Italian population [25] which was probably due to the loss of some PE cases which did not undergo the first trimester screening. This is, however, an expected result for every screening program where the accessibility and population uptake can be suboptimal.

The main findings of this study showed that, in this study population, the FMF algorithm had a better performance for early PE detection (+ 17% at both 5% and 10% FPR); Also for late PE the FMF resulted in a slight better performances (+ 7% at both 5% and 10% FPR) when compared with BCNAtal algorithm.

As for calibration, both the FMF and the BCNAtal algorithms underestimated the risk of early PE, the number of observed PE cases being higher than that predicted (Table 4a). This paralleled the lower risk of PE occurring at or before 42 weeks, and should have been taken into account in the planning of the clinical application of the algorithms in the population in this study. As concerns late PE, the BCNatal appeared to be somewhat more accurate than the FMF algorithm (lower percentage of discordance between the observed and predicted incidence) but again, in this case, both underestimated prevalence (data available on request).

It must, however, be pointed out that prediction with "a priori risk" alone is still not sufficient, and the addition of biophysical and biochemical markers could improve the DRs of both algorithms, up to 80% for early PE, and lower the FPRs.

The comparison between the two algorithms for late PE was, however, not straightforward since the FMF algorithm treats gestation at the time of delivery for PE as a

continuous variable while the BCNatal algorithm uses two different logistic equations for early and late PE risk estimations. In the FMF algorithm, the risk for PE is expressed as < 42 weeks which also includes the PE cases delivering at < 34 weeks. On the contrary, the BCNatal algorithm uses a more traditional logistic regression approach, considering just PE cases > 34 weeks. Therefore, for comparison purposes, the PE cases delivering at < 34 weeks were excluded from the ROC curve generated for evaluating the DRs for late PE. Moreover, FMF algorithm treats deliveries for reasons other than PE as censored observations. We did not considered censor cases in our study design, and this could result is an overestimation of the risk for late PE and raising the number of cases wrongly classified as positives.

Comparison with the original studies

The DRs found in this study were in line with those reported in the original papers [11, 20, 24, 26] for the FMF and the BCNAtal algorithms [21], respectively.

The major differences between the studies published by the FMF group and this study were related to the rate of Caucasian ethnicity, which was 94.7% in this study vs. approximately 70% in the FMF data, and < 1% of Afro–Caribbean women in the present study which, instead, represented approximately 16–18% in the FMF data [11, 20, 24, 26]. Moreover, this study, with respect with those published by the FMF group, had a much higher rate of in vitro fertilization (IVF) (approximately 12.9% vs. approximately 5%) and a similar rate of chronic hypertension.

The very different rate of black ethnicity is probably the major source of discordance in FMF risk estimation. This difference poses the need for a customized model to have a more accurate risk estimation in the Italian population, which appears to be at lower risk of PE with respect to the UK population. This result is, however, consistent with the enrollment of the population to which the screening is offered, which partially excludes some high-risk categories as described above.

The demographic characteristics in this study were, instead, more homogeneous than those reported by Scazzocchio et al. [21]. However, the ethnic mix in the study of Scazzocchio et al. was again different from that in the present study, having a very high rate of South American women. Even if ethnicity was not considered a predictive variable in the BCNatal algorithm, a higher rate of both early and late PE in various ethnic groups, including the South American group, was reported when compared with controls. This could, therefore, be a possible source of the difference in the PE risk estimation between Spanish and Italian populations. It should be noted that Wright [20] and Scazzocchio [21] had a similar rate of Caucasians. The overall rate of renal disease was also higher in the population in this study (0.17% in Scazzocchio vs. 1.4% in these data) but the rate in PE cases was 3 times lower in the population in this study (11.5% vs. 3.6%).

Strength of the study

This is the first multicentric prospective Italian study having an adequate sample size which compared two different algorithms and validated the risk estimation. For the first time, the risk of PE occurring at or before a given gestational age for an Italian population was compared with that calculated for the UK population.

Limitations of the study

There are some limitations which need to be considered. In evaluating late PE performance, the two algorithms were not fully comparable since the FMF algorithm calculates a cumulative risk of PE < 42 weeks, and the BCNatal algorithm, instead, includes only cases delivering between 34 and 42 weeks. Therefore, for comparison purposes the PE cases delivering at < 34 weeks had to be excluded, introducing a bias of unknown degree.

The population in this study was not fully representative of the Northern Italian population since, at the present time, an unknown percentage of high-risk women have been lost to the screening program, probably reducing the actual performance of the screening and the effectiveness of preventive intervention for PE. Many of these women who did not undergo a screening program were black, and from South and Southeast Asia, and were at higher risk of PE, having, for example, a higher prevalence of type 1 and type 2 diabetes. Approximately 4% of the women received low dosage aspirin (100 mg) but no specific indications regarding the duration of treatment or the week the therapy began were available. A possible impact of aspirin intake could result in an increase in the FPR.

Conclusions

In this study, the FMF and BCnatal algorithms yielded the expected DRs and furnished a reliable calculation of the "a priori" risk for early and late PE. In Italy, the rate of PE is quite similar to that expected in other Countries, such as Spain and the UK. However, a discrepancy in the population to which the screening is offered has been noted between the Italian higher risk population and that enrolled in the FMF and BCNatal algorithms. Caution should be used, however, in the comparison with the FMF algorithm as the high-risk group has been defined with slightly different criteria.

Author contributions DDM protocol/project development, data collection, manuscript writing. BM protocol/project development, data collection. SP, BB, FG, VG, GP and LC data collection. PC protocol/project development, data collection, Manuscript writing. FP protocol/project development, data collection, manuscript writing, data analysis. CG data collection, manuscript writing. DM protocol/project development, manuscript writing. FF data collection, manuscript writing. MC, TT and NR manuscript writing. AF protocol/project development, data collection, manuscript writing, data analysis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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