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Patient-reported preconceptional characteristics in the prediction of recurrent preeclampsia

Rianne C. Bijl [a], Jérôme M.J. Cornette [a], Alina N. Brewer [b,c], Ini F. Zwart [a], Arie Franx [a], Eleni Z. Tsigas [b], Maria P.H. Koster [a,*]

[a] Department of Obstetrics and Gynecology, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands
[b] Preeclampsia Foundation, 3840 W Eau Gallie Blvd 104, Melbourne, FL, United States
[c] Juneau Biosciences, LLC, 2749 East Parleys Way Suite 210, Salt Lake City UT, United States

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ABSTRACT

Objective: To develop a prediction model for recurrent preeclampsia using patient-reported preconceptional characteristics, which can be used for risk stratification of subsequent pregnancies.
Study design: Retrospective cohort study using data from The Preeclampsia Registry™ of 1028 women with a history of preeclampsia and at least one subsequent pregnancy.
Main outcome measures: Candidate predictors were included in a multivariable logistic regression analysis and a backward selection procedure was used to select the final predictors. Internal validation took place by internally validating the model in 500 simulated samples (bootstrapping), which provided a shrinkage factor to create the final model. This final model was evaluated for performance by a calibration plot and the area under the receiver operating curve (AUC). Missing data was handled by multiple imputation.
Results: Recurrent preeclampsia occurred in 467 (45.4%) women. Predictors in the final model were: a history of migraine, first degree relative with cardiovascular disease, first degree relative with placenta-related pregnancy complication, gestational age at delivery of index pregnancy, birthweight of the previous child, history of placental abruption, multiparity, chronic hypertension, interval between index and subsequent pregnancy, paternal non-white ethnicity and maternal age. AUC of the model was 0.63 (95% CI 0.59–0.66). In a subset of women who used aspirin prior or during their subsequent pregnancy, performance of the model was similar (AUC 0.60; 95% CI 0.50–0.71).
Conclusions: In this study we developed a prediction model for recurrent preeclampsia with moderate performance after internal validation. Early risk stratification of subsequent pregnancies that allows for customization of antenatal care and personalized prevention strategies, is not yet possible.

1. Introduction

Preeclampsia occurs in approximately 3–5% of first pregnancies and 15–25% of these women again develop preeclampsia in a subsequent pregnancy [1,2]. Estimating the risk for recurrent disease prior to a subsequent pregnancy, would allow couples to make better informed choices about family planning. Besides, with a discriminative prediction model, it would not only be possible to identify women at high risk for recurrence, but also to identify the 75–85% of women who will not develop recurrent preeclampsia. These women may benefit from a less intensive antenatal visit and testing schedule during the subsequent pregnancy than is currently recommended, let alone the expected stress reduction due to low-risk stratification [3,4].

Numerous prognostic models have been developed to predict preeclampsia, however, so far with limited performance and without implementation in clinical care [5,6]. Most of these models aim to predict preeclampsia during the first and second trimester of pregnancy, only some models are developed for prediction of recurrent preeclampsia prior to a subsequent pregnancy [7–10]. With regard to prevention of pregnancy complications, it is the preconception period that

Abbreviations: AUC, Area under the receiver operating curve; BMI, Body mass index; CI, Confidence interval; IQR, Interquartile range; OR, Odds ratio.

* Corresponding author at: PO Box 2040, 3000 CA Rotterdam, the Netherlands.
E-mail addresses: r.bijl@erasmusmc.nl (R.C. Bijl), j.cornette@erasmusmc.nl (J.M.J. Cornette), alina.brewer@preeclampsia.org (A.N. Brewer), i.f.zwart@erasmusmc.nl (I.F. Zwart), a.franx@erasmusmc.nl (A. Franx), eleni.tsigas@preeclampsia.org (E.Z. Tsigas), m.p.h.koster@erasmusmc.nl (M.P.H. Koster).

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can be considered as a window of opportunity for risk stratification and prevention. Currently, the most important risk factor for recurrent preeclampsia, is a history of preeclampsia, whereas identified modifiable risk factors before conception (eg obesity, untreated hypertension), might be improved to lower the risk for recurrent complications.

From this background, the aim of our study was to develop a clinically applicable prediction model for recurrent preeclampsia to be used for risk stratification of subsequent pregnancies.

2. Methods

2.1. Study population

For this study we used data from the Preeclampsia Registry™, an observational, ongoing patient registry since September 1st 2013, initiated by the Preeclampsia Foundation (https://clinicaltrials.gov/ct2/show/NCT02020174). The registry consists of women who experienced preeclampsia or a related hypertensive disorder of pregnancy and who filled out several questionnaires regarding individual characteristics, medication use, family history, obstetric history and child outcomes. After providing informed consent, medical records can be uploaded and a yearly health update is requested.

For this study, we retrospectively subtracted a subset of women with a history of at least one pregnancy complicated by preeclampsia (self-reported preeclampsia, HELLP syndrome, eclampsia and/or superimposed preeclampsia) with at least one subsequent pregnancy thereafter. All miscarriages, molar pregnancies, extra uterine pregnancies, pregnancy losses before 20 weeks gestation, pregnancies after ovum donation and multiple gestation pregnancies were excluded from our subset (Fig. 1). The index pregnancy was defined as the first pregnancy complicated by preeclampsia, the first ongoing pregnancy hereafter was defined as the subsequent pregnancy.

2.2. Data collection

Patient and pregnancy characteristics were collected from the questionnaires of the aforementioned subset of women. Several categories of candidate predictors were distinguished: patient characteristics before the index pregnancy, pregnancy- and delivery characteristics of the index pregnancy, and additional maternal and paternal characteristics before the subsequent pregnancy. Age at the time of delivery was calculated by using the year of birth of the participant and the delivery date. The interval between both pregnancies was calculated by using the delivery date of the index pregnancy and the conception date of the subsequent pregnancy (calculated by subtracting gestational age at delivery from the delivery date of the subsequent pregnancy). The variables concerning a first degree family member with cardiovascular disease, hypertension and/or stroke were combined to a composite determinant of family history of cardiovascular disease. For a family history of placenta-related pregnancy complications, we used the variables of first degree relatives with a history of (pre)eclampsia, HELLP syndrome, other hypertensive disorders of pregnancy and/or fetal growth restriction, combined to a composite determinant.

We made a pre-selection of potential predictors based on a literature search, to limit the possibility of overfitting the prediction model. This selection was based on established risk factors for recurrent preeclampsia and risk factors for cardiovascular disease [7,8,11,12]. All potential predictors and how they were extracted from the questionnaires are reported in Table S1. To assess potential collinearity between candidate predictors, we used Pearson's correlation analysis.

2.3. Missing data and data presentation

The number and percentage of missing cases per variable were identified and significant differences in distribution of patient characteristics and potential predictors between complete cases and cases with at least one missing value were assessed. To account for missing data in the development of our prediction model, multiple imputation (10 times) by a multivariate regression model was applied, using observed patient characteristics [13,14]. Results shown are the pooled results after multiple imputation, unless otherwise specified.

2.4. Model development and internal validation

Continuous variables were assessed for linearity and, if necessary, categorized to improve linearity. The preselected candidate predictors were included in a multivariable logistic regression analysis to assess the association between the predictors and the recurrence of preeclampsia. A backward selection procedure was used to select the final predictors by $p < 0.20$. The results of this analysis are reported as regression coefficients and odds ratios (OR) with 95% confidence intervals (95% CI). To adjust the final model for overfitting, we automatically resampled our dataset to create 500 simulated random samples (bootstrapping), wherein the accuracy of the model was tested. This resulted in a shrinkage factor to adjust the final model's regression coefficients [15].

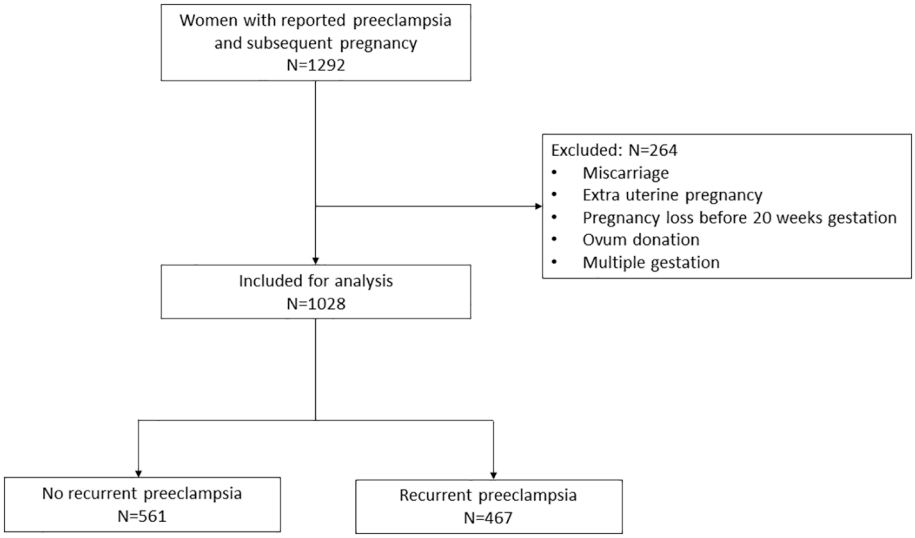

Fig. 1. Selection of cases. Flowchart depicting the selection of included cases.

2.5. Model performance

Calibration of the prediction model was assessed based on the predicted probabilities versus the observed probabilities. A prediction model can be considered as well-calibrated if the slope of the plot is close to one with an intercept of zero.

The model's discriminative performance was assessed using the area under the receiver operating curve (AUC), where the sensitivity was plotted against 1-specificity (false negatives). An AUC of 0.5 indicates no discrimination by the model; an AUC of 1 indicates perfect discrimination. Furthermore, we tested the model's performance separately in the group of women who used aspirin prior or during the subsequent pregnancy.

For clinical application of the final model we examined several cut-off levels of the predicted risk probabilities resulting from the model and subsequently calculated the sensitivity and specificity. Also, predicted probabilities were assessed for the ability to predict preeclampsia with necessary delivery before 32 weeks gestation and, again, sensitivity and specificity were calculated.

Analyses were performed in the Statistical Package of the Social Sciences (IBM SPSS, version 25, Armonk, NY) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) in combination with RStudio (RStudio PBC, v.1.3.1093, Boston, MA, USA).

2.6. Etical approval

Study protocols regarding human subjects included in the Preeclampsia registry™ were approved by Advarra Institutional Review Board. All participants provided written informed consent at enrollment with the Preeclampsia Registry™ through an online process.

3. Results

3.1. Patient population

Questionnaires of 1028 women were available for analysis and 467 (45.4%) developed recurrent preeclampsia. The missing rate per individual variable was generally <10%, except for maternal birthweight (23%), maternal BMI before index pregnancy (10%) and maternal BMI before subsequent pregnancy (14%) (Table S2). Baseline characteristics of complete cases and cases with one or more missing values were similar, except for the occurrence of pregnancy complications in first degree relatives and the occurrence of gestational diabetes in the index pregnancy, both higher in the complete cases, and perinatal death in the index pregnancy, which was lower in the complete cases.

The median maternal age of the total study population at the start of the index pregnancy was 27 (IQR 24–30) years, median maternal BMI was 23.7 (IQR 20.9–28.1) kg/m2, this pregnancy ended at a median gestational age at delivery of 248 days (35^{+3} weeks) and perinatal death occurred in 123 (12%) neonates (Table 1). The median interval between the index and subsequent pregnancy was two years, with 500 (48.6%) of the subsequent pregnancies occurring within one year after the index pregnancy. Prophylactic aspirin use was reported by 120 (11.7%) women, either before and/or during the subsequent pregnancy.

3.2. Model development and internal validation

In Table 2 the final multivariate model after backward selection procedure is reported with corresponding OR per predictor. The final model included the following predictors for recurrent preeclampsia:

- *Patient characteristics before the index pregnancy*: a history of migraine (OR 1.34 [95% CI 0.98–1.83]), first degree relative with cardiovascular disease (OR 1.22 [95% CI 0.95–1.59]), first degree relative with placenta-related pregnancy complication (OR 1.29 [95% CI 0.96–1.73]);
- *Pregnancy- and delivery characteristics of the index pregnancy*: gestational age at delivery (OR 0.98 [95% CI 0.97–0.99]), birthweight of the child (OR 1.71 [95% CI 1.27–2.31]), placental abruption (OR 1.48 [95% CI 0.84–2.61]);
- *Additional patient characteristics before the subsequent pregnancy*: multiparity (OR 1.49 [95% CI 0.83–2.69]), chronic hypertension (OR 1.82 [95% CI 1.11–2.98]), interval between index and subsequent pregnancy (reference group < 1 year; 1–2 years OR 1.10 [95% CI 0.79–1.52]; 2–3 years OR 1.24 [95% CI 0.83–1.86]; >3 years OR 1.58 [95% CI 1.08–2.31]), paternal non-white ethnicity (OR 1.17 [95% CI 0.99–1.39]), maternal age (reference group < 25 years; 25–30 years OR 0.74 [95% CI 0.50–1.08]; 30–35 years OR 0.63 [95% CI 0.43–0.92]; >35 years OR 0.69 [95% CI 0.42–1.12]).

3.3. Model performance

Fig. 2 shows the calibration plot with a visually good agreement between predicted and observed risks of recurrent preeclampsia; the AUC was 0.63 [95% CI 0.59–0.66], which indicates moderate discrimination (Fig. S1 shows the receiver operating characteristic (ROC) curve). The mean predicted risk for recurrent preeclampsia in our cohort was 45% (range 18% to 85%). In the subset of women who used aspirin prior or during the subsequent pregnancy (n = 120), the AUC was slightly lower (0.60 [95% CI 0.50–0.71]). After bootstrapping for interval validation, the regression coefficients of the final predictors were multiplied with a shrinkage factor of 0.79 (Table 2).

In Table 3a clinical application of the model was simulated by describing several potential cut-off levels for the predicted probabilities of the women in our cohort, none of the cut-off levels achieved an optimal sensitivity and specificity. For example, when a cut-off probability of 0.4 is used, sensitivity is 75.2% with a specificity of 43.1%. In a subset of women who delivered before 32 weeks gestation (n = 95), no optimal cut-off level was identified (Table 3b).

4. Discussion

When using patient-reported characteristics to predict recurrent preeclampsia in this cohort with high recurrence rates (45.2%), recognition of women at risk was insufficient (AUC = 0.63). Identification of women at low-risk for recurrent disease, who may benefit from less intensified antenatal surveillance, is not yet possible and individual counseling about risks in future pregnancies remains challenging.

The predictors for recurrent preeclampsia in our model are partially compliant with previous reported prediction models by van Kuijk et al. (chronic hypertension, gestational age at delivery of index pregnancy, birthweight child of index pregnancy; AUC 0.65) and van Oostwaard et al. (chronic hypertension, longer interpregnancy interval, ethnicity; AUC 0.69) [7,10]. We could not confirm the association with higher maternal BMI, although the proportion of women with BMI > 30 kg/m^2 before the subsequent pregnancy was higher in the recurrent preeclampsia group (30% vs. 23.9%) compared to the non-recurrent preeclampsia group. Additionally, we observed higher odds for multiparous women compared to primiparous women, women with a history of migraine, women with placental abruption in the index pregnancy, women with a burdened family history of cardiovascular disease and a family history of pregnancy complications; lower odds were observed for women aged 30–35 years in the subsequent pregnancy. Found associations were in the expected direction with unfavorable characteristics leading to a higher risk for recurrent preeclampsia, except for women who delivered a child with higher birthweight in the index pregnancy. These women seemed to be at higher risk for recurrence of preeclampsia, which is in accordance to the model of van Kuijk et al., who observed lower odds of recurrence when a woman previously delivered a small for gestational age neonate.

Associations between migraine and the development of preeclampsia during pregnancy have been previously described, mainly in case-

Table 1
Baseline characteristics.

	Total cohort		Non-recurrent preeclampsia		Recurrent preeclampsia	
	1028		561	54.6%	467	45.4%
Individual characteristics	N / median	%/IQR	N / median	%/IQR	N / median	%/IQR
White ethnicity	977	95.0	537	95.8	440	94.2
Born ≥37 weeks gestation	928	90.3	513	91.4	416	89.0
Birth weight mother – grams	3357	2994–3674	3357	2999–3720	3357	2969–3674
Education level						
High school or less and technical/vocational school	113	11.0	63	11.3	50	10.6
(Some) college	607	59.1	324	57.8	283	60.6
Graduate school	308	29.9	173	30.9	134	28.8
First degree cardiovascular disease	581	56.5	303	54.0	278	59.5
First degree diabetes mellitus	216	21.0	119	21.3	97	20.7
First degree placenta-related pregnancy complication	249	24.2	124	22.2	125	26.7
Index pregnancy characteristics						
Maternal age	27	24–30	28	24–31	27	23–30
<25	376	36.6	185	33.0	191	40.9
25–30	396	38.5	229	40.8	167	35.7
30–35	218	21.2	125	22.3	93	19.8
>35	38	3.7	22	3.9	16	3.5
Maternal BMI – kg/m^2	23.7	20.9–28.1	24	20.9–27.7	24	20.9–28.4
<20	165	16.0	92	16.3	73	15.6
20–25	449	43.7	255	45.4	194	41.6
25–30	231	22.5	121	21.5	110	23.5
>30	184	17.9	94	16.7	90	19.2
Married or in relationship	983	95.6	547	97.5	436	93.3
Paternal age – years	29	26–32	30	26–32	29	26–32
<25	225	21.9	115	20.5	110	23.6
25–30	407	39.6	226	40.3	181	38.8
30–35	274	26.7	149	26.5	126	26.9
>35	121	11.8	71	12.7	50	10.7
Paternal White ethnicity	946	92.0	526	93.8	420	89.9
Nulliparity	977	95.0	539	96.0	439	93.9
Assisted reproductive techniques	74	7.2	39	7.0	35	7.4
Gestational age at delivery – days	248	222–263	248	223–264	247	221–262
Sex of the child						
Male	509	49.5	276	49.3	233	49.8
Female	519	50.5	285	50.7	234	50.2
Birth weight child – grams	2359	1451–3084	2313	1440–3031	2449	1451–3175
Stillbirth or subsequent death of child	123	12.0	69	12.4	54	11.5
Placental abruption	56	5.4	26	4.6	30	6.4
Gestational diabetes	47	4.5	25	4.4	22	4.8
Stress during pregnancy	536	52.2	285	50.8	251	53.8
Postpartum depression	135	13.1	69	12.4	65	13.9
	Total cohort		**Non-recurrent preeclampsia**		**Recurrent preeclampsia**	
Characteristics before subsequent pregnancy	N / median	%/IQR	N / median	%/IQR	N / median	%/IQR
Maternal age – years	31	27–34	31.0	27–34	30.0	27–33
<25	166	16.1	80	14.3	86	18.4
25–30	345	33.6	187	33.3	158	33.9
30–35	387	37.6	224	40.0	163	34.8
>35	130	12.6	70	12.4	60	12.9
Maternal BMI – kg/m^2	25.1	22.0–30.3	25	21.7–29.1	26	22.5–30.8
<20	106	10.3	60	10.6	47	10.0
20–25	400	38.9	237	42.2	164	35.0
25–30	247	24.1	130	23.2	117	25.0
>30	274	26.7	134	23.9	140	30.0
Chronic hypertension	80	7.8	31	5.4	50	10.6
High cholesterol	46	4.5	26	4.5	21	4.4
Migraine	218	21.2	103	18.4	114	24.5
Depression	155	15.1	78	13.9	78	16.6
Assisted reproductive techniques	71	6.9	42	7.4	30	6.4
Vitamins before and/or during pregnancy	384	37.4	211	37.6	173	37.1
Aspirin use before and/or during pregnancy	120	11.7	63	11.2	57	12.2
Smoking	54	5.2	25	4.4	29	6.2
Interval between pregnancies – years	2	1–3	1	1–2.25	2	1–3
<1	500	48.6	287	51.1	214	45.7
1–2	243	23.6	135	24.1	108	23.1
2–3	127	12.4	68	12.1	59	12.6
>3	158	15.4	71	12.7	87	18.5
Multiparity	52	5.1	23	4.2	29	6.1
Married or in relationship	1003	97.5	545	97.1	458	98.0
Same father as index pregnancy	942	91.6	522	93.0	420	89.9
Paternal age – years	31	28–35	31	28–35	31	27–35
<25	134	13.0	72	12.8	62	13.3

(*continued on next page*)

Table 1 (*continued*)

Characteristics before subsequent pregnancy	Total cohort		Non-recurrent preeclampsia		Recurrent preeclampsia	
	N / median	%/IQR	N / median	%/IQR	N / median	%/IQR
25–30	319	31.0	166	29.6	153	32.8
30–35	358	34.9	209	37.3	149	31.9
>35	216	21.1	114	20.3	103	22.0
Paternal White ethnicity	941	91.6	526	93.7	416	89.0
Subsequent pregnancy characteristics						
Gestational age at delivery – days	266	251–274	273	263–278	252	230–264
Sex of the child						
Male	517	50.3	293	52.1	224	48.0
Female	511	49.7	268	47.9	243	52.0
Birth weight child – grams	3221	2540–3629	3402	3079–3750	2722	1905–3311
Stillbirth or subsequent death of child	39	3.8	9	1.6	30	6.5
Hypertension in pregnancy	606	58.9	139	24.8	467	100.0
Placental abruption	24	2.3	10	1.7	14	3.1
Gestational diabetes	105	10.2	58	10.3	47	10.1
Stress during pregnancy	408	39.7	199	35.5	209	44.7
Postpartum depression	146	14.2	68	12.1	79	16.8

Data after multiple imputation.
Abbreviations: BMI = body-mass index; IQR = interquartile range.

Table 2
Model development.

Predictors – final model	Odds ratio	95% CI-lower	95% CI-upper	Regression coefficient[a]
Gestational age at delivery (days, continuous)	0.98	0.97	0.99	−0.01
Birthweight of child (kg, continuous)	1.71	1.27	2.31	0.43
Multiparity	1.49	0.83	2.69	0.32
Chronic hypertension	1.82	1.11	2.98	0.47
Migraine	1.34	0.98	1.83	0.23
Paternal non-White ethnicity	1.17	0.99	1.39	0.13
Placental abruption	1.48	0.84	2.61	0.31
First degree placenta-related pregnancy complication	1.29	0.96	1.73	0.2
First degree cardiovascular disease	1.22	0.95	1.59	0.16
Interval between pregnancies				
<1 year	ref			
1–2 years	1.10	0.79	1.52	0.07
2–3 years	1.24	0.83	1.86	0.17
>3 years	1.58	1.08	2.31	0.36
Maternal age				
<25 years	ref			
25–30 years	0.74	0.5	1.08	−0.24
30–35 years	0.63	0.43	0.92	−0.37
>35 years	0.69	0.42	1.12	−0.3
Intercept	6.48	1.02	41.33	1.44
	AUC	**95% CI-lower**	**95% CI-upper**	
	0.63	0.59	0.66	

[a] Adjusted by shrinkage factor 0.79 after bootstrapping 500 times.

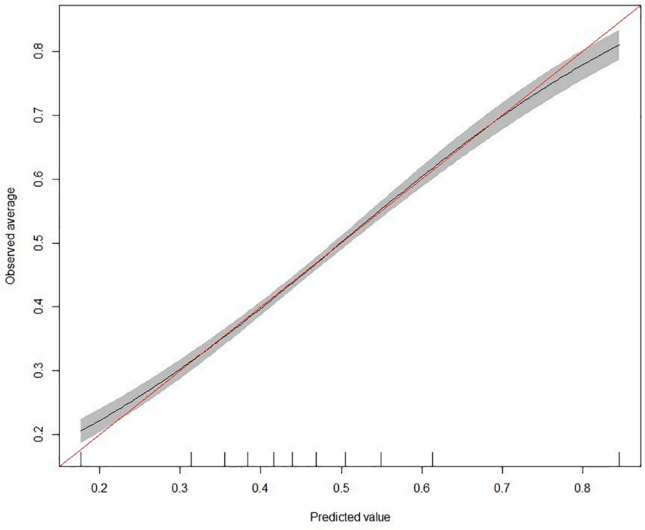

Fig. 2. Calibration plot. Calibration plot of the predicted value versus the observed average values of the prediction model.

control studies, in which migraine was more prevalent amongst women who developed preeclampsia [16]. Although exact pathophysiological mechanisms remain to be determined, a potential explanation may be common pathophysiologic pathways, such as enhanced endothelial reactivity and increased systemic inflammatory substrates [16]. Within our cohort, prevalence of self-reported migraine (21.4%) is in accordance with the prevalence amongst women of reproductive age, although when compared between women with and without recurrent preeclampsia, prevalence was higher in the recurrent preeclampsia group (24.5% vs 18.4%) [17].

The difficulty in the prediction of (recurrent) preeclampsia might be explained by the heterogeneous phenotypes of preeclampsia (e.g., early vs. late preeclampsia and preeclampsia with or without severe features), which make preeclampsia by definition a clinical syndrome that can develop through different pathophysiologic pathways, rather than a monocausal disease entity [18]. Hereby it can be hypothesized that any pregnancy has the potential to end in preeclampsia, with maternal and pregnancy characteristics being able to increase or decrease this risk [19]. Since preeclampsia is still insufficiently understood, prospective collection of potential (bio)markers for recurrent preeclampsia in large cohorts of women with all subtypes of preeclampsia is needed, but it needs to be considered that a functional prediction model for simplified recurrent or non-recurrent preeclampsia might never be developed.

Some limitations of our study should be addressed. First, with a recurrence rate of approximately 45%, our cohort might not be representative for the general population. Potentially, selection bias has occurred, since women with more severe preeclampsia are more likely to be eager to participate in research and thus to participate in the Preeclampsia Registry™. However, since in this high risk cohort discrimination between high and low risk of recurrent preeclampsia is already difficult, in a more general population with lower recurrence rates, discrimination most likely will be even more challenging. Second, recall bias might limit the full potential of the patient reported data we have used. However, a previous study by Gammill et al. showed very high concordance between self-reported diagnosis of preeclampsia in

Table 3
Sensitivity and specificity per clinical cut-off levels of predicted probabilities for recurrent preeclampsia.

(a). All recurrent preeclampsia

Cut off probability	Sensitivity (%)	Specificity (%)
0.25	99.8	1.8
0.30	97.1	8.6
0.35	88.8	24.4
0.40	75.2	43.1
0.45	54.3	61.6
0.50	41.1	76.0
0.55	26.7	85.9
0.60	16.8	92.8

(b). Recurrent preeclampsia with delivery before 32 weeks gestation

Cut off probability	Sensitivity (%)	Specificity (%)
0.25	98.2	2.8
0.30	94.2	9.2
0.35	89.1	21.0
0.40	79.5	37.0
0.45	67.6	54.7
0.50	54.0	69.8
0.55	42.5	80.8
0.60	30.5	88.9

the Preeclampsia Registry™ and medical records [20]. Third, a subset of women (N = 120) in our cohort indicated to have used aspirin prior or during the subsequent pregnancy, hereby potentially introducing bias by the protective effect of aspirin [21]. However, the recurrence rate of preeclampsia in this subset was similar compared to the total cohort. Probably, these women had the highest chance of recurrence since they had preeclampsia with more severe features (shorter gestational age at delivery and lower neonatal birthweight; *data not shown*) in the index pregnancy compared to the women without aspirin use. With aspirin more commonly being used over the last five years, new patient cohorts should clearly document aspirin use to evaluate the effect of aspirin in existing and new prediction models.

5. Conclusion

The developed prediction model for recurrent preeclampsia based on patient-reported preconceptional characteristics has moderate performance. Therefore, early risk stratification of subsequent pregnancies that allows for customization of antenatal care and personalized prevention strategies, is not yet possible. Future research should determine whether subtypes of preeclampsia can be more accurately predicted prior to a subsequent pregnancy.

Author contributions

MPHK designed this study. ANB collected the data. Analysis and interpretation of the data was performed by RCB, JMJC, IFZ and MPHK. RCB and IFZ wrote the first draft of the manuscript. Critical feedback was provided by JMJC, ANB, AF, EZT and MPHK. All authors contributed to reviewing and editing the manuscript.

Data statement

Data that support the findings of this study are available upon reasonable request from the corresponding author.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2022.02.003.

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