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Recurrence risk of preeclampsia in a linked population-based cohort: Effects of first pregnancy maximum diastolic blood pressure and gestational age

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A B S T R A C T

Objective: To estimate preeclampsia occurrence and recurrence risk in the 2nd pregnancy and analyze associated risk factors such as 1st pregnancy maximum diastolic blood pressure (maxDBP) and gestational age at delivery (GA).
Study design: Linked cohort of 1st and 2nd pregnancies of 272,551 women from the Dutch Perinatal Registry collected between 2000 and 2007. We defined preeclampsia as hypertension (maxDBP ≥90 mmHg or documented hypertension) plus proteinuria (≥300 mg/24 h) and analyzed its 2nd pregnancy occurrence with logistic regression. Early and late onset preeclampsia were defined by delivery before and after the 34th week, respectively.
Results: Preeclampsia prevalences in the 1st and 2nd pregnancies were 2.5% and 0.9%, respectively. Women with prior preeclampsia had a 10.5% risk of recurrence. For women with term 1st pregnancies and maxDBP < 80 mmHg, the 2nd pregnancy preeclampsia rate was 0.2% (95% CI 0.17%–0.23%), while for those whom presented maxDBP ≥110 mmHg it was 4.2% (95% CI 3.6%–4.8%). First pregnancy late onset preeclampsia was associated with increased preeclampsia recurrence risk proportional to 1st pregnancy maxDBP: in women with a maxDBP between 100 and 109 mmHg the recurrence risk was 8.3%, while for women with a maxDBP ≥110 mmHg this risk was 11% (difference 2.7%; 95% CI 1.0%–4.4%). In 1st pregnancy early onset preeclampsia corresponding rates were 14.8% and 19.3% (difference 4.5%; 95% CI −1.3%–9.7%).
Conclusion: Preeclampsia recurrence risk is 10%. Preeclampsia risk in the 2nd pregnancy increases proportionally to 1st pregnancy maxDBP. Earlier onsets of 1st pregnancy preeclampsia further increase recurrence risk.

1. Introduction

Preeclampsia is a major contributor to maternal and fetal morbidity that affects approximately 3% of all pregnancies [1]. Although its incidence is highest in the first pregnancy, recurrence is still an important problem with estimates ranging from 12% to 38% [2–6]. A wide variety of factors such as previous early onset preeclampsia, preterm delivery, preeclampsia with severe features and maternal preexisting disease have been proposed as risk factors for preeclampsia which may help explain the wide range in recurrence rates [1,3,4,7,8]. In any case, once preeclampsia occurs, appropriate counseling targeted at patient reassurance and need for information about future pregnancies becomes paramount, as well as a better assessment of pertinent risk factors for the individual patient is required.

Considerable effort has recently been put forth in studying the effects of increasingly higher blood pressure levels during pregnancy on maternal and neonatal outcomes. In the CHIPS trial, severe hypertension was associated with poorer outcomes for newborns in both tight and less-tight blood pressure control groups as well as with poorer maternal outcomes in the less-tight group, such as increased risk of acute stroke during and post pregnancy, but follow-up into the next pregnancy was not performed [9–11]. On the other hand, the effects of different hypertension levels on subsequent pregnancies have so far been left unexplored in the literature.

Therefore, in this study we analyzed preeclampsia recurrence and 2nd pregnancy preeclampsia occurrence risks in a large cohort of the Dutch population using the longitudinal Netherlands Perinatal Registry (Perined) records. This population cohort allowed us to evaluate the influence of several factors previously suggested in the literature as well as that of gradually higher levels of pregnancy maximum diastolic blood pressure (maxDBP), which we hypothesized to be useful in further distinguishing patients in low or high risk of preeclampsia in a subsequent pregnancy.

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2. Methods

This study is based on a nationwide prospective cohort dataset extracted from Perined, the result of a validated linkage of three different registries: the midwifery registry (LVR1), the obstetrics registry (LVR2), and the neonatology registry (LNR). It consists of population-based data that covers approximately 96% of all deliveries in the Netherlands and contains information on pregnancies, deliveries and admissions until 28 days after birth.

Perined data is recorded at the child's level and there is no unique maternal identifier to correlate siblings and follow up on subsequent pregnancies. Because of this, we submitted the data on all available 509,559 s deliveries from 2000 to 2007 to a linkage procedure based on the variables birth date of mother, birth date of previous child, and postal code of mother. The final linked cohort contained data on the first and second deliveries of 272,551 women. Further information on the linkage procedure can be found elsewhere [12].

Preeclampsia was defined by the combined presence of hypertension (either maximum diastolic blood pressure ≥90 mmHg or documented hypertension by the care provider) and proteinuria (≥300 mg in 24 h). Chronic hypertension was defined by hypertension diagnosed before pregnancy or new onset hypertension before 20 weeks of pregnancy following the Dutch guidelines for hypertension in pregnancy (blood pressure ≥140/90 mmHg) and documented by the care provider, either a midwife or obstetrician. We also included obstetrician documented records of preeclampsia and eclampsia in the Perined database, as well as women with chronic hypertension that presented proteinuria (≥300 mg in 24 h). In the Dutch perinatal system, blood pressure measurements are performed at every outpatient visit to the care provider and multiple times peripartum. While individual measurements are not recorded in the dataset, the maximum diastolic pressure available in the dataset is based on these measurements. The gestational age at which the highest blood pressure occurred is not recorded. Early onset preeclampsia was characterized by delivery before 34 weeks in cases with preeclampsia. Late onset preeclampsia was defined as preeclampsia cases delivered from the 34th week on.

We compared women who developed preeclampsia in their first pregnancy to those who did not according to their respective baseline demographic, clinical and obstetric characteristics. The analyzed characteristics were: maximum diastolic blood pressure (mmHg), maternal age (years), Caucasian maternal ethnicity (native Dutch and other white women or different ethnic groups such as African/Surinamese, South Asian, Moroccan and Turkish), low socioeconomic status (postal code area with lowest quartile score based on income level, paid job percentage, and education level), chronic hypertension (yes or no), diabetes (yes or no), interpregnancy interval (years), GA at delivery (weeks) and multiple pregnancy (yes or no). The choice of covariates in this study was based on pre-test clinical relevance and model parsimony.

To investigate the effects of GA at delivery in the 1st pregnancy to the preeclampsia risk in the 2nd pregnancy, we further divided the two groups in three categories: extreme preterm (22^{+0}–29^{+6} weeks gestation), early preterm (30^{+0}–33^{+6} weeks gestation) and late preterm (34^{+0}–36^{+6} weeks gestation). In the same manner, we also divided the two groups in categories according to their maxDBP in the 1st pregnancy: < 80 mmHg, 80–89 mmHg, 90–99 mmHg, 100–109 mmHg and ≥110 mmHg. The variable for maximum diastolic blood pressure had 27.8% of missing values and no other covariates evaluated in the logistic regressions had missing values. To avoid potential bias introduced by listwise deletion of these cases in the logistic regressions, we performed a multiple imputation procedure with the aim of producing unbiased estimates as we assumed no systematic error in the registry. We generated five imputed sets using predictive mean matching and the following 1st and 2nd pregnancy variables: preeclampsia (yes or no), hypertension during pregnancy (yes or no), GA (weeks), gestational diabetes (yes or no), multiple pregnancy (yes or no), maternal age (years), birthweight (grams), maxDBP (mmHg), 5th percentile small for GA (yes or no), spontaneous birth (yes or no). In addition, we used the following demographic and clinical variables: low socioeconomic status (yes or no), ethnicity (Caucasian or not), chronic hypertension (yes or no) and diabetes (yes or no).

Student's t or Mann-Whitney U tests were used in the statistical analyzes of continuous data. Categorical data were analyzed with chi-squared tests, and confidence intervals for proportions were found using the Wilson score interval [13]. To assess preeclampsia risk, we used logistic regression to adjust the odds ratios to differences in baseline characteristics and study the influence of maxDBPs and different GAs at delivery. We assessed potential interaction effects between preeclampsia occurrence and maximum diastolic blood pressure. Evidence of interaction effects was first evaluated by product terms. To obtain the relevant point estimates and generate appropriate confidence intervals for interaction effects, we followed the alternative coding scheme initially proposed by Rothman and further developed by Hosmer & Lemeshow [14]. In this approach, interaction between two risk factors (A and B) is evaluated through a single four level variable (−A−B, +A−B, −A+B, +A+B), with no loss of degrees of freedom. Point estimates for each combination and associated confidence intervals are then readily available in the output of most statistics software. Univariate models were run for each of the studied variables and compared to the fully adjusted model. Odds ratios obtained from the five multiple imputation sets were pooled following Rubin's rules [15]. The linkage procedure was performed using the R statistical software environment (version 2.13.1; R Foundation for Statistical Computing, Vienna, Austria). The multiple imputation procedure was performed, and the data were analyzed with IBM SPSS Statistics software (version 20.0.0; IBM Corporation).

3. Results

A total of 509,559 s deliveries were available for analyses. From this total we matched 272,551 (53%) to the corresponding first delivery. Of these, a total of 6679 (2.4%) women developed preeclampsia in the 1st pregnancy, versus 2548 (0.9%) in the 2nd pregnancy. There were 702 women who presented preeclampsia in both pregnancies, a recurrence rate of 10.5% (95% CI 9.8%–11.2%). Conversely, de novo preeclampsia in the 2nd pregnancy occurred in 1846 (72.4%) of the women. Of this group, 60% had presented gestational or chronic hypertension but not preeclampsia in the 1st pregnancy. Only 28% of the women that developed preeclampsia in the 2nd pregnancy presented no form of hypertension in the 1st pregnancy.

We present baseline characteristics of the two comparison groups in Table 1. Maternal ages were comparable, as well as the number of Caucasians and women with low socioeconomic status in each group. Women that did not present preeclampsia were less likely to have diabetes (0.9% *vs* 2.1%; p-value < 0.0001), chronic hypertension (0.9% *vs* 6.7%; p-value < 0.0001), and to have a multiple pregnancy (0.8% *vs* 2.6%; p-value < 0.0001). Women who presented preeclampsia had slightly higher interpregnancy intervals (2.5 years ± 1.2 *vs* 2.7 ± 1.3; p-value < 0.0001). Mean GAs were lower in women with preeclampsia (39.2 ± 2.2 *vs* 37.1 ± 3.0; p-value < 0.0001).

In the 1st pregnancy, 3357 (50.3%) preeclampsia occurrences were identified because of proteinuria and documented hypertension (yes or no), 1112 (16.6%) because of proteinuria and maximum diastolic blood pressure higher or equal to 90 mmHg, and 2204 (33,0%) were identified through the obstetrician records in the Perined database. Of the 2728 women with documented chronic hypertension, 454 (16,6%) presented proteinuria, and 6 of these did not fill any of the other criteria for preeclampsia. In the 2nd pregnancy preeclampsia occurrences were identified in the same way and the respective numbers are as follows: 873 (34,2%), 1010 (39,6%) and 662 (25,9%). Superimposed preeclampsia in the 2nd pregnancy occurred in 222 (8.1%) women. Three did not fill the other criteria and were identified through documented proteinuria and chronic hypertension.

Fig. 1 presents the risk of preeclampsia in the 2nd pregnancy in relation to different levels of maxDBP in the 1st pregnancy, GA at delivery and

Table 1
Baseline maternal characteristics at 1st pregnancy delivery.

	No preeclampsia (n = 265872)	Preeclampsia (n = 6679)	p value
Maternal age, years[†]	28.6 ± 4.2	28.5 ± 4.4	0.362
Interpregnancy interval, years[†]	2.5 ± 1.2	2.7 ± 1.2	< 0.0001
GA at delivery, weeks[†]	39.2 ± 2.2	37.1 ± 3.0	< 0.0001
Caucasian, n (%)	232,101 (87.3)	5872 (87.9)	0.133
Low socioeconomic status, n (%)	71,258 (26.8)	1753 (26.2)	0.548
Chronic Hypertension, n (%)	2274 (0.9)	454 (6.8)	< 0.0001
Diabetes, n (%)	2561 (1.0)	142 (2.1)	< 0.0001
Multiple pregnancy, n (%)	2018 (0.8)	172 (2.6)	< 0.0001

[†] Given as mean ± SD.

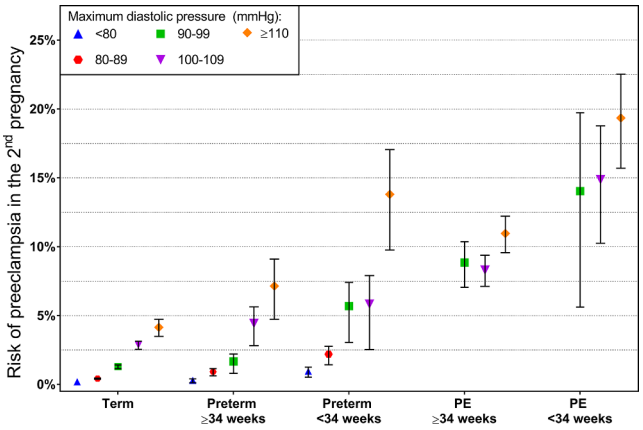

Fig. 1. Rate of 2nd pregnancy PE by 1st pregnancy maxDBP, GA at delivery and PE occurrence. Rate of 2nd pregnancy preeclampsia and 95% confidence interval by 1st pregnancy gestational age at delivery (weeks), preeclampsia occurrence and maximum diastolic blood pressure (mmHg). *Abbreviations*: PE: preeclampsia; maxDBP: maximum diastolic blood pressure; GA: gestational age.

history of preeclampsia. The presence of severe hypertension (maxDBP ≥110 mmHg) in late onset 1st pregnancy preeclampsia was associated with a 11% rate of recurrence, significantly higher than the 8.3% rate found for preeclamptic women whose maximum DPB levels were between 100 and 109 mmHg. A similar tendency was observed in women with early onset preeclampsia, although the smaller incidence resulted in overlapping confidence intervals. While the recurrence rate of those with maxDBP equal or above 110 mmHg after early onset preeclampsia was 19.3%, the rates of those within the 90–99 and 100–109 mmHg categories were 14% and 14.8%, respectively.

As expected, women with term 1st pregnancies and low levels of maxDBP (< 80 mmHg) had a very low risk of preeclampsia in the 2nd pregnancy: 0.20% (95% CI 0.17%–0.23%). Increased but still normal levels of maxDBP of 80–89 mmHg more than doubled this risk to 0.42% (95% CI 0.39%–0.46%). Severe hypertension and no preeclampsia in these pregnancies raised 2nd pregnancy preeclampsia risk to 4.1% (95% CI 3.6%–4.8%).

Table 2 presents the results of the logistic regressions with preeclampsia in the 2nd pregnancy as the outcome. Increasing levels of maxDBP in the 1st pregnancy were associated with increased risks of preeclampsia in the 2nd pregnancy for women without prior history of preeclampsia. Slightly elevated but not hypertensive levels of maxDBP were already associated with increased risks: women with levels between 80 and 89 mmHg had an adjusted odds ratio (aOR) of 2.3 (95% CI 1.9–2.7) for the occurrence of preeclampsia in the following pregnancy. Levels equal or above 110 mmHg were associated with higher risks, with an aOR of 20.7 (95% CI: 16.7–25.6).

Preeclampsia history was identified as the main risk factor for recurrence. The aOR associated with severe hypertensive cases (≥110 mmHg) was 43.1 (95% CI 35.5–52.5). This risk is compounded by earlier preterm deliveries as these were also associated with increasing rates of 2nd pregnancy preeclampsia. The group of women whose 1st pregnancy ended before 30 weeks had an aOR of 3.9 (95% CI 3.2–4.8), and the risk gradually decreased with increasing GA.

Women with chronic hypertension were at increased risk of superimposed preeclampsia in the 2nd pregnancy with an aOR of 2.3 (95% CI: 2.0–2.7). History of preeclampsia in women with chronic hypertension resulted in a 21.4% chance of recurrence on the 2nd pregnancy, as opposed to 5.5% for those with only chronic hypertension (difference 15.9%; 95% CI 12.2%–19.9%). Women with diabetes were also at increased risk as their aOR was 1.8 (95% CI: 1.4–2.3). Prior preeclampsia and diabetes resulted in a 2nd pregnancy preeclampsia risk of 15.5%, while for isolated diabetes the risk to 1.8% (difference 13.7%; 95% CI 8.6%–20.5%).

In the univariate regression, a multiple 1st pregnancy was associated with increased preeclampsia risk in the 2nd pregnancy with an OR of 1.5 (95% CI 1.2–1.8). However, in the multivariate model there was an apparent protective effect as the aOR was 0.6 (0.4–0.9). Stepwise adjustment of the univariate regression to additionally account for the effects of 1st pregnancy GA at delivery is enough to reverse the effect of a multiple 1st pregnancy from increased to lower risk of preeclampsia in the 2nd pregnancy (aOR 0.6; 95% CI 0.5–0.7). On the other hand, if the 2nd pregnancy was a multiple pregnancy, risk of preeclampsia was higher (aOR: 3.8; 95% CI 3.2–4.5). Supplemental Tables S1 and S2 show the results of the regression analyses without use of imputed data and with Perined identified preeclampsia cases only, respectively.

4. Discussion

We investigated the recurrence risk of preeclampsia and additional risk factors for its occurrence in 2nd pregnancies. Our main findings are that the maxDBP in the 1st pregnancy is directly proportional to preeclampsia risk in the 2nd pregnancy for women with no history of preeclampsia, and that GA at delivery is inversely proportional to this risk. We were also able to confirm that preeclampsia history is a major risk factor although there is no clear evidence that the degree of hypertension presented by itself further increases preeclampsia risk in the 2nd pregnancy.

Based on a retrospective cohort of 211 subsequent deliveries it was previously reported that increasing levels of hypertension in an early onset preeclamptic 1st pregnancy increased early onset 2nd pregnancy preeclampsia risk [16]. Our results do not support this claim as risk confidence intervals found over different levels of hypertension overlapped considerably for women with history of preeclampsia. Additionally, three previous studies identified preterm birth as a risk factor for preeclampsia in the 2nd pregnancy. Two of them were based on large cohorts and our results are consistent with them, although only one of the three reported on increased risks beyond very early preterm delivery as we did [3,7]. Reporting conflicting results, van Rijn et al. found recurrence rates for preeclampsia not related to delivery before 28 weeks of gestation in 120 hospital-based subsequent pregnancies [2].

Although chronic hypertension is generally identified as a risk factor for preeclampsia, the literature presents conflicting results regarding its

Table 2
Risk factors for preeclampsia in the second pregnancy.

First pregnancy	n	N	%	Odds ratio (95% CI)		Adjusted Odds ratio (95% CI)[†]	
Maximum diastolic pressure							
No preeclampsia	265,871	1846	0.7				
< 80 mmHg	103,794	232	0.2	Reference		Reference	
80–89 mmHg	113,196	537	0.5	2.1	(1.8–2.5)	2.3	(1.9–2.7)
90–99 mmHg	30,630	422	1.4	6.2	(5.2–7.4)	6.7	(5.6–8.0)
100–109 mmHg	13,404	405	3.0	13.8	(11.5–16.7)	13.9	(11.5–16.8)
≥ 110 mmHg	4847	250	5.2	24.2	(19.7–29.8)	20.7	(16.7–25.6)
Preeclampsia	6680	702	10.5				
< 90 mmHg	224	21	9.4	40.7	(24.4–68.0)	35.1	(21.3–57.7)
90–99 mmHg	1234	115	9.2	45.2	(35.6–57.5)	40.7	(31.9–51.9)
100–109 mmHg	2570	231	9.0	43.8	(36.1–53.2)	36.8	(30.2–44.9)
≥ 110 mmHg	2652	335	12.6	64.0	(53.2–77.0)	43.1	(35.5–52.5)
GA							
Term	250,471	1921	0.8	Reference		Reference	
34–$36^{6/7}$ weeks	15,404	314	2.0	2.7	(2.4–3.0)	1.6	(1.4–1.9)
30–$33^{6/7}$ weeks	4335	189	4.4	5.9	(5.5–6.4)	2.6	(2.2–3.1)
< 30 weeks	2341	124	5.3	7.2	(6.6–8.0)	3.9	(3.2–4.8)
Chronic Hypertension	2728	222	8.1	10.2	(9.5–11.0)	2.3	(2.0–2.7)
Diabetes	2703	68	2.5	2.8	(2.5–3.2)	1.8	(1.4–2.3)
Multiple pregnancy	2190	30	1.4	1.5	(1.2–1.8)	0.6	(0.4–0.9)
Multiple pregnancy (2nd pregn.)	5403	162	3.0	3.4	(3.2–3.7)	3.8	(3.2–4.5)

CI: confidence interval; n: total within category; N: 2nd pregnancy preeclampsia within category. All risk factors present in the 1st pregnancy unless otherwise indicated.

[†] Fully adjusted model that also includes maternal ethnicity, socioeconomic status and maternal ages in both pregnancies.

effect on recurrence risk. Sibai et al. studied 369 women with chronic hypertension and concluded that a history of preeclampsia did not increase rates of superimposed preeclampsia [17]. On the other hand, Langenveld et al. and van Rijn et al. reported higher recurrence risk in women with chronic hypertension [2,16]. Our results concur with the latter.

We performed our study on data from Perined. The registry covers approximately 96% of all pregnancy and birth characteristics of the country. No a priori power calculation was performed due to the large sample size available. We were unfortunately unable to adjust for certain factors such as BMI, smoking, medication use (such as aspirin and anti-hypertensive drugs), pre-existing vascular and kidney disease, history of thrombophilia, paternal influence and family history of preeclampsia as these are either not contained in Perined or severely underreported. Furthermore, there is likely underreporting of diabetes mellitus and chronic hypertension [18,19]. These results are based on a population-based cohort and consequently women in all BMI ranges, smokers or not, with or without family history of preeclampsia and other known preeclampsia risk factors were included. This makes it unlikely that non-inclusion of these compromises the significance of our results because of the large effect sizes found.

Of these, BMI is the most relevant as, although the effect size associated with obesity is usually lower than that of chronic hypertension, it is widely more prevalent. Obesity rates in women of reproductive age in most developed countries range from 14 to 20%, reaching up to 60% in some countries. These account worldwide for about 30% of the preeclampsia cases [20–24]. As modifiable risk factors, effects on preeclampsia risks in a subsequent pregnancy imposed by high pre-pregnancy BMI as well as gestational weight gain in the index gestation are of interest. Whether these effects are causal or representative of a system prone both to metabolic syndrome and preeclampsia, and whether BMI reduction in the interpregnancy interval would be enough to lessen the associated risk are so far subject only to speculation.

As we were interested in the preeclampsia risk in a subsequent pregnancy, a probabilistic linkage procedure was performed to identify siblings and the characteristics of their pregnancies and deliveries. Failure to match was because of missing values on the linkage variables or a first delivery prior to 1999. Changes in the home address also resulted in non-linkage as “postal code of mother” was one of the linkage variables. The linked dataset was comparable to the Dutch national data on both demographic characteristics and obstetric outcomes [25]. The prevalence of preeclampsia in the 1st pregnancy in our database is most likely underestimated as women that only had one child are not part of the longitudinal database. A large Swedish cohort reported an overall preeclampsia rate of 4.1% that dropped to 3.9% if these women were excluded [7].

Systolic blood pressure is not available in the dataset. This restricted our definition of preeclampsia which may have further lowered preeclampsia prevalence in our study. Perined’s independent recording of preeclampsia and eclampsia occurrences, which we made use of, in association with the inclusion of cases of documented hypertension and proteinuria mitigate this issue as women with preeclampsia limited to systolic blood pressure hypertension were counted in. Our sensitivity analysis showed consistent results when the model was restricted to these cases only. Similarly, the inclusion of proteinuria as a criterion in the preeclampsia definition was standard practice over the years of data collection [26].

The recent increase in the use of aspirin during pregnancy has benefited women at high risk for preeclampsia [27]. The US Preventive Task Force defines this high risk group as women who present with a history of preeclampsia, multifetal gestation, chronic hypertension, diabetes, renal or autoimmune disease [28]. Our results indicate that women with elevated maxDBP in their 1st pregnancy have a preeclampsia risk at least in the same order of magnitude as women in this high-risk group, whether they developed preeclampsia or not. As there is evidence that the intervention causes little harm to those without contraindications, and that the potential benefit is substantial, it is worth considering high diastolic blood pressure in a previous pregnancy as a risk factor for which the recommendation to use of aspirin from the 12th week of gestation may be advisable.

5. Conclusion

We found that the degree of severity of hypertension in the 1st pregnancy has direct relation to preeclampsia rates in the 2nd pregnancy in women with no preeclampsia history. Previous preeclampsia remains the biggest risk factor for preeclampsia in a subsequent pregnancy. Furthermore, low 1st pregnancy GAs at delivery further increase preeclampsia risk in the 2nd pregnancy. These findings improve the awareness of individual risks of occurrence and recurrence of preeclampsia allowing better management of subsequent pregnancies.

Disclosure statement

The authors report no conflict of interest.

Presentation

These findings were orally presented at the 20th World Congress of the International Society for the Study of Hypertension in Pregnancy (ISSHP), October 24th, 2016.

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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.2018.10.010.

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