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Original Article

Risk assessment of hypertensive disorders in pregnancy with maternal characteristics in early gestation: A single-center cohort study

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ABSTRACT

Objective: Hypertensive disorders in pregnancy are major causes of maternal mortality and morbidity. Although the combined risk assessments of maternal history, blood pressure, uterine artery Doppler, and maternal serum marker seem to be highly predictive of the development of hypertensive disorders, this method is a little complicated to be performed on many low-risk pregnant women. The aim of this study is to evaluate the use of maternal characteristics, and physical findings early in the second trimester, as predictive factors of hypertensive disorders.

Materials and Methods: This is a retrospective cohort study undertaken in a single tertiary care center in Japan. Singleton pregnant women without underlying disease and evaluated before 14 weeks of gestation were included. We conducted multivariate logistic regression analysis and decision tree analysis to elucidate the potential risk factors of hypertensive disorders, including gestational hypertension and preeclampsia.

Results: In total, 1986 women were evaluated, of whom 863 were nulliparous and 1123 were multiparous, and 166 (8.3%) were diagnosed with hypertensive disorders. In multivariate analysis, maternal age $\geq$ 40 years, prepregnancy BMI $\geq$ 30 kg/m^2, *in vitro* fertilization and embryo transfer (IVF-ET), family history of hypertension, and blood pressure $\geq$ 130/85 mmHg at first visit were independent risk factors for the nulliparous women. Maternal age $\geq$ 40 years, a history of previous hypertensive disorders, and blood pressure $\geq$ 130/85 mmHg at first visit were independent risk factors for the multiparous women. According to the decision tree analysis, high-risk populations were as follows: women $\geq$ 40 years old who conceived thorough IVF-ET and women with prepregnancy BMI $\geq$ 30 kg/m^2 who conceived spontaneously in nulliparous women; women with a history of hypertensive disorders and women with blood pressure $\geq$ 130/85 mmHg in the absence of the previous history.

Conclusion: The combination of maternal background and physical findings is useful to identify the population with a high risk of hypertensive disorders.

Introduction

Hypertensive disorders complicate approximately 6–8% of all pregnancies [1]. These pathological conditions consist of gestational hypertension (GH) and preeclampsia (PE), both of which are major causes of maternal mortality and morbidity. They constitute 14% of the overall incidence of maternal death [2] and an estimated 50,000–60,000 PE cases are related to maternal deaths per year worldwide [3]. Hypertensive disorders in pregnancy can cause severe maternal complication such as HELLP (hemolysis, elevated liver enzyme levels, and low platelet count) syndrome, neurological and cerebral manifestations, and renal changes [4], which sometimes need early termination of pregnancy. GH is also related to adverse pregnancy outcomes [5], and GH in some women possibly progresses to PE [6]. Thus, pregnant women considered to be at high risk of hypertensive disorders may need to be managed more carefully for maternal and fetal conditions. In addition, the possibility of low-dose aspirin (LDA) administration before 16 weeks of

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gestation for the prevention of PE for high-risk women has been shown [7–9]. Thus, identifying high-risk women during the early period of pregnancy will be valuable for the prevention and certain management of the aforementioned pregnancy complications.

Recent studies have demonstrated the value of risk assessment, with the combination of obtaining information on maternal history, blood pressure, uterine artery Doppler, and maternal serum marker to determine the individual risk of hypertensive disorders in early gestation [10–12]. Although these combinational assessments seem to be highly predictive of the development of hypertensive disorders, this method is a little complicated to be performed on many low-risk pregnant women. With respect to the risk assessment of hypertensive disorders with maternal baseline characteristics, previous history of maternal hypertensive disease is a highly predictive factor but is based on meta-analysis including nulliparous women [13].

The aim of this study is to evaluate the use of maternal characteristics, and physical findings early in the second trimester, as predictive factors of hypertensive disorders. We elucidate the individual risk of hypertensive disorders without using uterine artery Doppler flow and maternal serum markers in each group of nulliparous and multiparous, healthy, singleton pregnant women in a single cohort.

Materials and methods

This is a retrospective cohort study performed from January 2011 to December 2013 in the Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi, Japan. Singleton pregnant women who visited our clinic before 14 weeks of gestation and delivered after 20 weeks of gestation were included. We excluded patients with chronic diseases such as chronic hypertension, diabetes mellitus, autoimmune disease, and chronic nephritis.

All of the patients were asked to complete a questionnaire on maternal age, racial origin, methods of conception, obstetric history, cigarette smoking during pregnancy, medical history, and second-degree family history, including hypertension at their first visit. The questionnaire was reviewed by midwives and then checked by obstetricians. Body mass index (BMI) was calculated by dividing weight by the square of height. Urinary examination was checked by using a dipstick. Blood pressure was measured in the sitting position, using either arm, using an automated sphygmomanometer. Gestational age was confirmed by the measurement of the fetal crown–rump length (CRL) on ultrasonography within the period when the CRL ranges from 14 mm to 41 mm. Until 34 weeks of gestation, the patients visited fortnightly, and after 35 weeks of gestation, they visited weekly for a prenatal checkup. If the patient's blood pressure was $\geq$ 140/90 mm Hg, self-monitoring of blood pressure was prescribed. When hypertensive disorder was suspected, admission for intensive maternal and fetal monitoring was offered. During the hospital stay, the patients underwent blood tests and measurement of 24-hour proteinuria accumulation to confirm the diagnosis and to rule out secondary hypertension.

Hypertensive disorders in pregnancy, including GH and PE, were diagnosed according to the diagnostic criteria of the National High Blood Pressure Education Program Working Group [1]. PE was defined by the development of new-onset hypertension with proteinuria after 20 weeks of gestation, and GH was defined as the development of new-onset hypertension without proteinuria after 20 weeks of gestation and the normalization of blood pressure levels by 12 weeks postpartum. The diagnostic threshold for hypertension was a systolic blood pressure $\geq$ 140 mm Hg or a diastolic blood pressure $\geq$ 90 mm Hg on two occasions at least 6 hours apart. Proteinuria was defined as a protein excretion of 300 mg/d from 24-hour urine collection. If there was only a dipstick available, repeated semiquantitative test results of 1+ were considered as positive.

The primary outcome was the development of hypertensive disorders, including PE and GH. We reviewed maternal age ($\geq$ 40 years), BMI before pregnancy ($\geq$ 30 kg/m^2), *in vitro* fertilization and embryo transfer (IVF-ET), smoking during pregnancy, family history of hypertension, and systolic blood pressure $\geq$ 130 mm Hg or diastolic blood pressure $\geq$ 85 mm Hg at first visit as potential maternal risk factors. In multiparous women, a history of previous hypertensive disorder in pregnancy was also reviewed. The prevalence of each risk factor was compared between the women with and without hypertensive disorders during pregnancy. Nulliparous and multiparous women were evaluated individually in order to determine the value of data regarding the history of a previous hypertensive disorder.

For statistical analysis, the Chi-square test was used for nominal data, and the Mann–Whitney *U* test was used for continuous data. A p value < 0.05 was considered statistically significant. Multivariate logistic regression analysis with a step-up procedure was conducted to calculate the adjusted odds ratio (aOR) of risk factors with a p value < 0.2 in the univariate analysis. In addition, we calculated sensitivity, specificity, positive predictive value and negative predictive value of each independent risk factor. Significant risk factors in the multivariate logistic regression analysis were assessed using the decision tree analysis to find the high-risk combination of the extracted factors. Each factor was weighted due to the likelihood ratio of developing hypertensive disorders by using the Chi-square test, and optimized stratification was automatically performed according to the descending order of likelihood ratio. All the statistical analyses were performed using the statistical software package JMP 10 (SAS Institute Inc., Cary, NC, USA).

All the pregnant women provided written informed consent for the provision of their information.

Results

In our hospital, 4489 women with singleton pregnancy delivered, of whom 2143 met the inclusion criteria. One hundred and fifty-seven women had chronic diseases, including 32 with chronic hypertension, 53 with autoimmune disease, nine with nephritis, 68 with prepregnancy diabetes mellitus, and five with overlapping diseases. Finally, 1986 women were evaluated in the study, of whom 863 were nulliparous and 1123 were multiparous.

The maternal demographic characteristics are shown in Table 1. Maternal age, BMI before pregnancy, and the first blood pressure measurement of women with hypertensive disorders were significantly higher than those of the women without disorders in both nulliparous and multiparous women. Multipara women with hypertensive disorders had a more frequent history of hypertensive disorders. Blood pressure data was lacking in 38 cases. In these cases, the patient's data was included in the analysis, excluding the blood pressure.

One hundred and sixty-six women (8.3%) were diagnosed with hypertensive disorders during pregnancy, including 116 with GH (5.8%) and 50 with PE (2.6%). The incidence of all hypertensive disorders, GH and PE were 10.2% (88), 6.1% (53), and 4.1% (35), respectively, among the nulliparous women, and 6.9% (78), 5.6% (63), and 1.3% (15) among the multiparous women. Among the nulliparous women, maternal age $\geq$ 40 years [$p = 0.04$, aOR 1.891, 95% confidence interval (CI) 1.028–3.476], BMI before pregnancy $\geq$ 30 kg/m^2 ($p < 0.01$, aOR 3.869, 95% CI 1.546–9.686), IVF-ET ($p < 0.01$, aOR 2.370, 95% CI 1.353–4.150), family history of hypertension ($p = 0.036$, aOR 1.666, 95% CI 1.033–2.686), and blood pressure at first visit ($p = 0.016$, aOR 2.571, 95% CI 1.194–5.534)

Table 1
Maternal characteristics at first visit ($n = 1986$).

	Hypertensive disorders		p
	Yes 88 (10.2)	No 775 (89.8)	
Nulliparous women (n=863)			
Maternal age (y)	36.0 (18–44)	32.0 (15–50)	<0.01*
>40 y	20 (22.7)	79 (10.2)	<0.01*
BMI before pregnancy	23.1 (16.6–35.5)	20.6 (14.5–42.9)	<0.01*
BMI >30	8 (9.1)	21 (2.7)	<0.01*
Smoking during pregnancy	2 (2.3)	37 (4.8)	0.407
Gestational wk at 1st BP measurement	11 (5–14)	10 (5–14)	0.219
Systolic BP	118.0 (90–148)	112.0 (71–145)	<0.01*
Diastolic BP	72.0 (54–94)	66.0 (29–96)	<0.01*
BP>130/85mmHg at 1st BP measurement	10 (11.4)	21 (2.7)	<0.01*
	Hypertensive disorders		p
	Yes 78(6.9)	No 1045(93.1)	
Multiparous women ($n = 1123$)			
Maternal age (y)	36.0 (25–44)	34.0 (17–47)	<0.01*
>40 y	17 (21.7)	89 (8.5)	<0.01*
BMI before pregnancy	22.3 (16.8–39.8)	20.8 (15.3–47.8)	<0.01*
BMI >30	6 (7.7)	26 (2.5)	<0.01*
Smoking during pregnancy	5 (6.4)	68 (6.5)	0.973
Gestational wk at 1st BP measurement	10 (6–14)	10 (4–14)	0.212
Systolic BP	119.0 (96–139)	112.0 (78–156)	<0.01*
Diastolic BP	74.0 (48–92)	65.0 (33–95)	<0.01*
BP >130/85mmHg at 1st BP measurement	12 (15.4)	26 (2.5)	<0.01*
History of hypertensive disorder	18 (23.1)	38 (3.6)	<0.01*

Data are shown as median (range) or n (%).
* $p < 0.05$, χ^2 test and Mann–Whitney U test.
BMI = body mass index; BP = blood pressure.

were independent risk factors of the development of hypertensive disorders in multivariate analysis (Table 2). Among the multiparous women, the history of hypertensive disorders ($p < 0.01$, aOR 6.599, 95% CI 3.379–12.733), blood pressure $\geq$ 130/85 mm Hg at first booking ($p < 0.01$, aOR 5.796, 95% CI 2.812–11.945), and maternal age $\geq$ 40 years ($p = 0.012$, aOR 2.273, 95% CI 1.200–4.308) were independently associated with the development of hypertensive disorders (Table 3). Sensitivity, specificity, positive predictive value, and negative predictive value of independent risk factors are shown in Table 4.

According to the decision tree analysis, IVF-ET was the primary factor to stratify nulliparous women. Women older than 40 years in the IVF-ET group and women with a prepregnancy BMI higher than 30 kg/m^2 in the non-IVF-ET group tended to develop the disorders frequently (36% and 24%, respectively). The multiparous women were primarily stratified according to the history of hypertensive disorders. About one-third of the women with a history of hypertensive disorders repeatedly developed the disorders during their current pregnancies. In the absence of a previous history, the incidence of the disorders among the women with blood pressure $\geq$ 130/85 mm Hg was relatively high (24%; Figure 1).

Discussion

In this study, we revealed the incidence of new-onset hypertensive disorders among healthy singleton pregnant women who consistently received prenatal care in a single center and demonstrated the independent risk factors assessable in the first trimester. Our results indicate that for nulliparous women, the extracted risk factors were older maternal age, high blood pressure at first visit, IVF, and family history of hypertension. Meanwhile, regarding the multiparous women, older maternal age, high blood pressure, and history of hypertensive disorders were recognized as independent risk factors.

Although most of the previous studies discussed methods of predicting PE [10–13], we primarily intended to predict hypertensive disorders, including both PE and GH, because PE and GH both cause severe maternal complications [14] and adverse pregnancy outcomes such as preterm birth, small for gestational age, and neonatal hospital stay [5]. Hauth et al [14] showed that pregnant women with GH developed elevated levels of liver enzymes and renal dysfunction more frequently than women without GH. According to another study described by Villar et al [5], the aORs of

Table 2
Risk factors of hypertensive disorders during pregnancy in nulliparous women ($n = 863$).

Values	cOR (95% CI)	p	aOR (95% CI)	p
Maternal age $\geq$ 40 years	2.591 (1.495–4.492)	<0.01*	1.893 (1.030–3.486)	0.040*
BMI before pregnancy $\geq$ 30 kg/m^2	3.590 (1.540–8.369)	<0.01*	3.583 (1.451–8.846)	<0.01*
IVF-ET	3.059 (1.831–5.110)	<0.01*	2.374 (1.356–4.156)	<0.01*
BP $\geq$ 130/85 mm Hg	3.871 (1.906–7.861)	<0.01*	2.606 (1.213–5.598)	0.014*
Smoking during pregnancy	0.463 (0.109–1.958)	0.219	NA	NA
Family history of HT	1.599 (1.012–2.254)	0.043*	1.671 (1.036–2.694)	0.035*

* $p < 0.05$. Univariate analysis and multivariate logistic regression analysis.
aOR = adjusted odds ratio; BMI = body mass index; BP = blood pressure; cOR = crude odds ratio; HT = hypertension; IVF-ET = in vitro fertilization and embryo transfer; NA = not assessed.

Table 3
Risk factors of hypertensive disorders during pregnancy in multiparous women (n = 1123).

Values	cOR (95% CI)	p	aOR (95% CI)	p
Maternal age ≥ 40 y	2.994 (1.676–5.345)	<0.01*	2.273 (1.200–4.308)	0.012*
BMI before pregnancy ≥ 30 kg/m^2	3.266 (1.302–8.190)	<0.01*	2.808 (0.944–7.237)	0.062
IVF-ET	2.654 (1.368–5.150)	<0.01*	1.940 (0.864–4.026)	0.10
BP ≥130/85 mm Hg	6.896 (3.502–13.580)	<0.01*	5.796 (2.812–11.945)	<0.01*
Smoking during pregnancy	0.984 (0.384–2.516)	0.973	NA	NA
Family history of HT	1.591 (0.982–2.579)	0.057	1.212 (0.693–2.057)	0.49
History of hypertensive disorder	7.950 (4.284–14.754)	<0.01*	6.599 (3.379–12.733)	<0.01*

* $p < 0.05$. Univariate analysis and multivariate logistic regression analysis
aOR = adjusted odds ratio; BMI = body mass index; BP = blood pressure; cOR = crude odds ratio; HT = hypertension; IVF-ET = *in vitro* fertilization and embryo transfer; NA = not assessed.

Table 4
Predictive value of independent risk factors of hypertensive disorders during pregnancy.

	Sensitivity	Specificity	PPV	NPV
Nulliparous women				
Maternal age ≥ 40 y	22.7	89.8	20.2	91.1
BMI before pregnancy ≥ 30 kg/m^2	9.1	97.3	27.6	90.4
IVF-ET	28.4	88.5	21.9	91.6
BP ≥ 130/85 mm Hg	11.8	97.2	32.3	90.8
Family history of HT	38.6	71.7	13.4	91.1
Multiparous women				
Maternal age ≥ 40 y	21.8	91.5	16.0	94.0
BP ≥ 130/85 mm Hg	15.6	97.5	31.6	93.9
History of hypertensive disorder	23.1	96.4	32.1	94.4

Data are shown as %.
BMI = body mass index; BP = blood pressure; HT = hypertension; IVF-ET = in vitro fertilization and embryo transfer, NPV = negative predictive value; PPV = positive predictive value.

fetal death and preterm delivery were 2.5 and 3.8, respectively, in the PE group, and 1.6 and 1.2, respectively, in the GH group. They concluded that both PE and GH significantly increased the incidence of adverse pregnancy outcomes. Therefore, the prediction and risk assessment of both PE and GH are clinically meaningful for perinatal management.

The antenatal care trial research of the World Health Organization conducted in some countries of South America and Asia showed that the incidence of PE was 2.2% and that of gestational hypertension was 7.0% among pregnant women, including those with chronic complications [5]. The present study demonstrated that the incidence rates of PE and GH were 2.6% and 5.8%, respectively. This might be because women with chronic disease, who were regarded as high risk for hypertensive disorders, were excluded in our population. Among the nulliparous women, the incidence of PE was 4.1%, which was similar to the incidence of 5.3% in a prospective observational study of only nulliparous women without any chronic complications [15]. Among the multiparous women, Baschat et al [11] showed an incidence of PE of 3.1%. This higher incidence could also be explained by the different study participants, including any women with complications.

We evaluated the usefulness of maternal history and blood pressure at booking as the simplest biophysical marker for the prediction of hypertensive disease in pregnancy. The independent risk factors found in our study were similar to those reported in previous studies. The risk factors of PE at antenatal booking were reviewed by Duckitt and Harrington D [13] in a systematic review. They identified a previous history of PE [risk ratio (RR) 7.19], nulliparity (RR 2.91), family history of PE (RR 2.90), increased BMI before pregnancy (RR 2.47), maternal age (RR 1.96), and increased diastolic blood pressure ≥ 80 mm Hg at booking (RR 1.38) as the affecting factors of PE. The presence of hypertensive disorders in previous pregnancy was the most remarkable factor, as also shown in our study. However, the estimated aOR of the previous PE in the population included nulliparous women. It is certain that only multiparous women have a history of hypertensive disorders in pregnancy, so assessment of multiparous women only would be adequate. Therefore, we evaluated the predictive value of a previous history of hypertensive disorders in a population restricted to multiparous women. Meanwhile, nulliparous women may have unrecognized risk factors such as any chronic diseases that cause adverse pregnancy outcomes if they do not undergo medical assessment. In addition, nulliparous women have been thought as potentially at high risk because of immunological factors such as first exposure to paternal antigens [16]. Therefore, it might be appropriate to separately estimate the risk of hypertensive disorders among nulliparous and multiparous women. In our study, the associated factors of the disorders among the multiparous women were previous hypertensive disorders, blood pressure at first booking, and maternal age, while prepregnancy BMI data was not collected. In the nulliparous women, prepregnancy BMI, blood pressure at first visit, IVF, maternal age, and family history of hypertension were independent risk factors. Our study revealed the difference in risk factors between nulliparous and multiparous

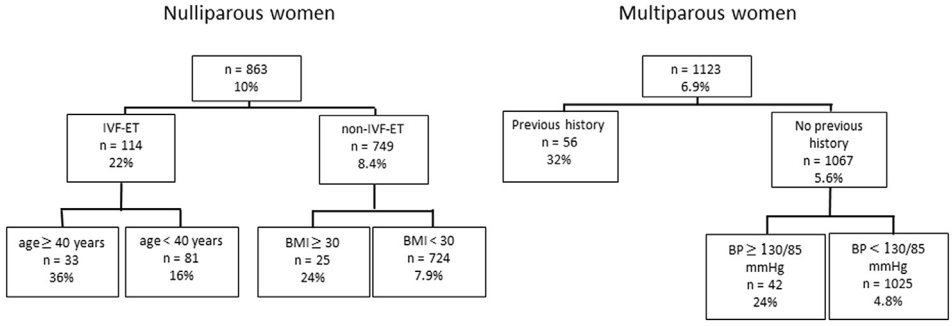

Figure 1. Decision tree analysis for the prediction of the hypertensive disorders. Decision tree analysis for prediction of hypertensive disorders shows the valuable combination of risk factors for prediction in each nulliparous and multiparous woman. BMI, body mass index; BP, blood pressure; IVF-ET, in vitro fertilization and embryo transfer.

women, and provides more accurate information to manage healthy singleton pregnancies. In respect of predictive value, the risk factors we have shown tend to have relatively high specificity and negative predictive value, along with low sensitivity and positive predictive value, which means they might be helpful to recognize patients with a lower risk of hypertensive disorders. These findings were similar to the predictive values of algorithm which comprise maternal characteristics, serum marker and uterine artery Doppler in the previous report of North et al [17].

For blood pressure assessment, we focused on blood pressures ≥ 130/85 mm Hg, which is referred to as "high–normal blood pressure" [18]. A previous study by Ohkuchi et al [19] on the prevalence of PE and GH according to categorized BMI and blood pressure in the second trimester demonstrated a higher incidence in women with high–normal blood pressure or hypertension than in women with normal blood pressure, after adjustment for BMI. Some guidelines have already noted various ranges of blood pressure at a stage prior to hypertension; for example, the clinical guidelines of the Society of Obstetricians and Gynaecologists of Canada recommend systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 80 mmHg at booking as a risk marker of PE [20]. By contrast, Cnossen et al [21] assessed the prediction ability of systolic, diastolic, mean arterial pressure, and their combination at the first and second trimesters for PE, and concluded that mean arterial pressure in the low-risk group and diastolic BP in the high-risk group at second trimester were the most valuable. Although recent large-scale prospective studies have discussed the association between mean blood pressure and the onset of diseases [10,11], mean blood pressure seems inappropriate to use because it needs to be calculated and may not be simple to apply to a large population. Therefore, we considered high–normal blood pressure at first booking as the optimum option.

Recently, the significance of first-trimester screening of PE using the combination of maternal background, blood pressure, and maternal serum markers, and assessment of uterine artery Doppler flow has been demonstrated [10–12]. As indicated in our study, a clear prediction, especially in nulliparous women may, be difficult. Therefore, the aforementioned additional information is needed for a more accurate prediction. However, maternal serum makers such as pregnancy-associated plasma protein-A level are not measured in routine prenatal care in some countries [22], as they are in our institution. Moreover, uterine artery Doppler may be difficult to perform as a screening test for all pregnant women. It may be said that screening with only maternal history and blood pressure at first visit is simple to apply for primary hospitals that are required to examine many low-risk pregnant women. Introducing additional risk assessments and careful follow-up for populations found to be at high risk in the simple assessment might be efficient.

The strength of our study is that it evaluated a large cohort of healthy singleton pregnant women who were managed uniformly in a single center from early in the second trimester. In addition, we separately calculated aOR for nulliparous and multiparous, and revealed the difference between nulliparous and multiparous women, thereby providing a more accurate risk estimation. In addition, we carefully collected most of the data from individual medical records to ensure data accuracy. One limitation of this study is the missing data due to its retrospective design. The blood pressure data of 38 women was missing, however, this number is not large enough to affect the results. Another limitation was that the use of LDA was unscreened in this cohort. However, because we did not prophylactically administer LDA even to the high-risk population in this period, the number of women using LDA seems small. LDA is now considered as a way of preventing PE [3]. In the future, we should include the number and characteristics of patients using LDA and evaluate its effectiveness.

In conclusion, we separately showed the maternal risk factors of hypertensive disorders before the early stage of the second trimester of pregnancy in nulliparous and multiparous women. The combination of background assessment and physical findings might be useful as a simple way to identify the population with a high risk of hypertensive disorders.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

References

[1] Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000;183:s1–22.

[2] Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health 2014;2:e323–33.

[3] American College of Obstetricians and Gynecologists TFoHiPHip. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122–31.

[4] ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Obstet Gynecol 2002;99(33):159–67.

[5] Villar J, Carroli G, Wojdyla D, Abalos E, Giordano D, Ba'aqeel H, et al. Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? Am J Obstet Gynecol 2006;194:921–31.

[6] Barton JR, O'Brien JM, Bergauer NK, Jacques DL, Sibai BM. Mild gestational hypertension remote from term: progression and outcome. Am J Obstet Gynecol 2001;184:979–83.

[7] Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet 2007;369:1791–8.

[8] Villa PM, Kajantie E, Raikkonen K, Pesonen AK, Hamalainen E, Vainio M, et al. Aspirin in the prevention of pre-eclampsia in high-risk women: a randomised placebo-controlled PREDO Trial and a meta-analysis of randomised trials. BJOG 2013;120:64–74.

[9] Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. London: Royal College of Obstetricians and Gynaecologists; 2010. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0033454/.

[10] Poon LC, Nicolaides KH. First-trimester maternal factors and biomarker screening for preeclampsia. Prenat Diagn 2014;34:618–27.

[11] Baschat AA, Magder LS, Doyle LE, Atlas RO, Jenkins CB, Blitzer MG. Prediction of preeclampsia utilizing the first trimester screening examination. Am J Obstet Gynecol 2014;211. 514.e1–7.

[12] Myers JE, Kenny LC, McCowan LM, Chan EH, Dekker GA, Poston L, et al. Angiogenic factors combined with clinical risk factors to predict preterm pre-eclampsia in nulliparous women: a predictive test accuracy study. BJOG 2013;120:1215–23.

[13] Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 2005;330:565.

[14] Hauth JC, Ewell MG, Levine RJ, Esterlitz JR, Sibai B, Curet LB, et al. Pregnancy outcomes in healthy nulliparas who developed hypertension. Calcium for Preeclampsia Prevention Study Group. Obstet Gynecol 2000;95:24–8.

[15] Sibai BM, Gordon T, Thom E, Caritis SN, Klebanoff M, McNellis D, et al. Risk factors for preeclampsia in healthy nulliparous women: a prospective multicenter study. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Am J Obstet Gynecol 1995;172:642–8.

[16] Taylor RN. Review: immunobiology of preeclampsia. Am J Reprod Immunol 1997;37:79–86.

[17] North RA, McCowan LM, Dekker GA, Poston L, Chan EH, Stewart AW, et al. Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. BMJ 2011;342:d1875.

[18] Shimamoto K, Ando K, Fujita T, Hasebe N, Higaki J, Horiuchi M, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). Hypertens Res 2014;37:253–390.

[19] Ohkuchi A, Iwasaki R, Suzuki H, Hirashima C, Takahashi K, Usui R, et al. Normal and high-normal blood pressures, but not body mass index, are risk factors for the subsequent occurrence of both preeclampsia and gestational hypertension: a retrospective cohort study. Hypertens Res 2006;29:161–7.

[20] Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. J Obstet Gynaecol Can 2014;36:575–6.

[21] Cnossen JS, Vollebregt KC, de Vrieze N, ter Riet G, Mol BW, Franx A, et al. Accuracy of mean arterial pressure and blood pressure measurements in predicting pre-eclampsia: systematic review and meta-analysis. BMJ 2008;336:1117–20.

[22] Registry EC. EUROCAT Special Report: Prenatal Screening Policies in Europe 2010. 2010. http://www.eurocat-network.eu/prenatalscreeninganddiagnosis/generalinformation/policiesineuropeancountries.