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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)