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Original Article

Clinical risk factors for gestational hypertensive disorders in pregnant women at high risk for developing preeclampsia

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ABSTRACT

Objectives: To evaluate clinical risk factors for the development of gestational hypertensive disorders in a group of pregnant women at high risk for developing preeclampsia. Secondly we evaluated the incidence and recurrence rate of preeclampsia and pregnancy-induced hypertension.
Study design: A prospective analysis of data obtained from a cohort study was performed. Pregnant women were included who had at least one of the following risk factors for preeclampsia: previous history of preeclampsia, previous history of HELLP syndrome, chronic hypertension, diabetes mellitus, multiple pregnancy, obesity, or autoimmune disease. Univariate and multivariate logistic regression analyses were used to evaluate the role of clinical characteristics and risk factors in the development of hypertensive disorders.
Main outcome measures: Development of gestational hypertensive disorders.
Results: Thirty-five percent (36/103) developed a hypertensive disorder. The univariate analysis identified preeclampsia in a previous pregnancy (OR 2.94, 95% CI: 1.25–6.91, $p = 0.013$) as a significant risk factor. Multivariate logistic regression revealed that a previous history of preeclampsia was the only significant independent risk factor for gestational hypertensive disorders (OR 2.89, 95% CI: 1.17–7.08, $p = 0.021$). Women with a previous history of PE had the highest incidence rate of 51.4% for hypertensive disorders compared to the incidence rates of other risk factors (20.8%–38.5%).
Conclusion: A previous history of preeclampsia proves to be a strong independent clinical risk factor for gestational hypertensive disorders in high-risk pregnant women, even in our relatively small cohort study.

Introduction

Preeclampsia (PE) is a hypertensive disorder, complicating 2–8% of all pregnancies in the developed world [1]. It is one of the leading causes of maternal mortality and severe maternal morbidity [1]. The etiology is still unknown, but the understanding of the pathophysiology is growing. It is generally agreed that the placenta plays a critical role in the pathophysiology of PE [2]. Redman et al. [2]

Abbreviations: BMI, Body Mass Index; CI, confidence interval; HELLP, Hemolysis, Elevated Liver enzymes, Low Platelets; N/A, not applicable; OR, odds ratio; *p*-value, probability value; PE, preeclampsia; PIH, pregnancy-induced hypertension; SLE, systemic lupus erythematosus.

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described a two stage model explaining the pathophysiology: in the first stage, which takes place in the first half of the pregnancy, placental development is disturbed. Remodeling of the maternal spiral arteries is impaired leading to a decreased maternal blood supply to the placenta. This is called poor placentation. As pregnancy proceeds, the placenta will need increased blood supply to sustain the growing demand. An underdeveloped placenta will ultimately get oxidatively stressed. This is called the second stage. The placenta then releases factors into the maternal circulation that creates the clinical features of PE, which appears to arise from a generalized systemic inflammatory response, of which endothelial dysfunction is a prominent component [2].

Early recognition of PE is crucial for better obstetric care of pregnant women at risk and their unborn children. Some of the factors released from the placenta are being studied as biochemical markers to predict PE [3]. But these markers cannot be used in the first trimester because differences in these markers are only seen a few weeks before PE develops [3]. Recently, a prediction model was developed based on maternal characteristics, biophysical and biochemical markers (placental growth factor and pregnancy-associated plasma protein A) at 11–13 weeks gestation [4]. But this model still needs further implementation. Other biochemical markers lack a simple screening test or are not specific for PE alone [3].

On the other hand, clinical risk factors are easier to access in the first trimester of pregnancy. Different studies have described several clinical risk factors for PE [5–8]. Some are similar to those for atherosclerosis [5], which can be explained by the endovascular background of PE [1,2,5]. These risk factors include: hypertension, obesity, diabetes mellitus, advanced age, hypercholesterolemia, dyslipidemia, microalbuminuria, antiphospholipid syndrome, vasculitis and thrombophilia [5]. Other clinical risk factors are a previous history of PE, multiple pregnancy, family history of PE and nulliparity [6–8]. Many of the above mentioned clinical risk factors for PE were indeed identified by North et al. [9] in a multicenter cohort study. These authors identified, among others, maternal age, mean arterial pressure and Body Mass Index (BMI) as risk factors for PE.

However, little is known about which factors are the most important factors contributing to (the recurrence rate of) PE. Our first aim was to perform a prospective cohort study to evaluate clinical risk factors for women who were at "high risk" for PE based on their obstetric history or presence of other clinical risk factors. Our second aim was to evaluate the incidence or recurrence rate of PE and/or pregnancy-induced hypertension (PIH) for each risk factor.

Materials and methods

Before the start of the study, the study protocol was approved by the Medical Ethics Committee of the University Medical Centre of Groningen in February 2009. The study procedures were in accordance with the Helsinki Declaration (1975, revised 1983, World Medical Association Declaration of Helsinki). Data were prospectively collected between March 2009 and March 2012. We included pregnant women who were in their first trimester of pregnancy, who visited our outpatient clinic, and who were at high risk for developing PE. The inclusion criteria were previous history of PE, previous history of Hemolysis, Elevated Liver enzymes and Low Platelets syndrome (HELLP syndrome), chronic hypertension, diabetes mellitus, multiple pregnancy, obesity and autoimmune diseases.

Chronic hypertension during pregnancy was defined according to the International Society for the Study of Hypertension in Pregnancy [10]: hypertension before pregnancy or before 20 weeks of gestation of >140/90 mmHg and/or taking antihypertensive medication prior to pregnancy or at recruitment. The diagnosis of pregestational diabetes type 1 and 2 was accepted when patients were treated with insulin therapy before conception or in the first trimester of the pregnancy. Autoimmune diseases included diseases with a high risk for developing vascular thrombosis, like systemic lupus erythematosus (SLE), antiphospholipid syndrome and vasculitis. Obesity was defined as a BMI of at least 30 kg/m^2 at the beginning of the pregnancy.

The medical data of the subjects were entered in a database. The primary endpoint was gestational hypertensive disorders (PE or PIH). We subdivided PE into early-onset (<34 + 0 weeks of gestation) versus late-onset (≥34 + 0 weeks of gestation) and mild versus severe PE [11]. Mild PE was defined as a diastolic blood pressure (Korotkoff V) of at least 90 mmHg and/or a systolic blood pressure of at least 140 mmHg (measured on two occasions each more than four hours apart) with proteinuria of more than 0.3 gram/24 h [10,12]. Severe PE was defined as mild PE with one or more of the following additional 'adverse features': systolic blood pressure of at least 160 mmHg and/or diastolic blood pressure of at least 110 mmHg (measured on two occasions at least four hours apart), proteinuria of at least 5 gram/24 h, and/or when HELLP syndrome was present. The HELLP syndrome was defined as lactate dehydrogenase >600 IU/L, aspartate aminotransferase or alanine aminotransferase >70 IU/L, and platelet count $<100 * 10^9$ cells/L [13]. HELLP syndrome without hypertension and/or proteinuria will be solely defined as HELLP syndrome and not as PE.

Thus, we have defined four subtypes of PE: early-onset mild, early-onset severe, late-onset mild, and late-onset severe PE. PIH was defined as a blood pressure >140/90 mmHg after 20 weeks of gestation without proteinuria.

Eligible women of 18 years or older with the above mentioned inclusion criteria were asked to participate in the study. After the women were given sufficient information, written informed consent was obtained.

We evaluated whether the occurrence of our primary endpoint could be predicted based on the risk factors (PE in history, HELLP syndrome in history, chronic hypertension, diabetes mellitus, multiple pregnancy, obesity, and autoimmune diseases) and clinical characteristics (parity, maternal age, gestational age at delivery, smoking, BMI, ethnicity, systolic and diastolic blood pressure at booking, and medication). Women who developed PE or PIH were compared to women who did not develop PE or PIH.