The Progression of Serum Prorenin Concentration during Pregnancy

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Abstract

Objective: An association between the renin-angiotensin system and the pathogenesis of pregnancy-induced hypertension has been reported. The prorenin receptor was discovered in 2002, and Wanatabe et al. reported that women with plasma soluble prorenin receptor concentrations above the 75th percentile at delivery had a significantly increased risk of preeclampsia. We evaluated serum prorenin concentrations during pregnancy, and we assessed the incidence of pregnancy-induced hypertension.

Methods: We measured serum prorenin concentrations in 430 pregnant women (565 samples). Regression analysis was performed to determine the associations between the serum prorenin level and maternal/neonatal complications.

Results: The serum prorenin concentration and gestational age had a positive correlation in non-pregnancy-induced hypertension in women with singleton pregnancies (Spearman rank-correlation coefficient, -0.215, p<0.001). The serum prorenin concentration in women with multiple pregnancies was significantly higher than that in women with singleton pregnancies (multiple linear regression analysis, p=0.0001). Low prorenin levels in the third trimester (≤20.1 percentile) were significantly associated with pregnancy-induced hypertension (adjusted odds ratio, 18.16; 95% confidential interval, 1.95-412.41; p=0.0107).

Conclusion: The serum prorenin levels during pregnancy may be adversely correlated with the prorenin receptor, and low prorenin levels in the second trimester were significantly associated with pregnancy-induced hypertension.

Keywords: Prorenin; Preeclampsia; Gestational hypertension; Renin-angiotensin system; Pregnancy-induced hypertension; Prorenin receptor; Risk of preeclampsia; Incidence of pregnancy-induced hypertension; Blood pressure

Abbreviations: PIH: Pregnancy-Induced Hypertension; RAS: Renin-Angiotensin System; BP: Blood Pressure; AT2: Angiotensin 2; (P) RR: Prorenin Receptor; PR: Prorenin; BMI: Body Mass Index; GDM: Gestational Diabetes Mellitus

Introduction

Pregnancy-Induced Hypertension (PIH), which includes preeclampsia and gestational hypertension, occurs in 3-5% of pregnant women, and it can cause maternal death, premature delivery, and fetal growth restrictions [1]. Various studies have identified the etiology and pathology of PIH, and it is clear that anti-angiogenesis factors play an important role.

The Renin Angiotensin System (RAS) also has an important role in hypertension: it maintains the constancy of Blood Pressure (BP) during pregnancy, which increases the cardiac output and circulating plasma volume [2]. Patients with PIH are sensitive to the pressor effects of Angiotensin 2 (AT2) compared to normotensive pregnant women [3,4], and Gant et al. reported that an AT2 infusion test may predict the onset of preeclampsia [2], suggesting that the RAS is associated with the pathogenesis of PIH. The (Pro) Renin Receptor ([P]RR), a new component of the RAS, was discovered by Nguyen ftable in 2002 [5]. Wanatabe et al. reported that pregnant women with Plasma-Soluble (P) RR [s(P)RR] concentrations above the 75th percentile at delivery had a significantly increased risk of preeclampsia [6]. In addition, RAS may have an important role in fetal development [7,8], and tissue RAS may be crucial for placentaion and the pathogenesis of PIH [9]. Since Prorenin (PR) combined with (P) RR activates the tissue RAS, we evaluated the serum PR concentration during pregnancy to determine whether PR is also associated with PIH.

Materials and Methods

This prospective study included 430 pregnant Japanese women who visited the Center of Maternal Fetal and Neonatal Medicine of the Saitama Medical Center at the Saitama Medical University from April to August 2012. Written informed consent was obtained from all patients, and the study protocol was approved by the institution’s ethics committee of the Saitama Medical Center, Saitama Medical University (Saitama, Japan).

Blood samples were obtained at a routine blood testing during prenatal checkup, and 565 samples were obtained. We divided the samples by gestational age. The first trimester was before 14 weeks and the second trimester was between 14 weeks 0 days and 27 weeks 6 days: and the third trimester was 28 weeks 0 days or later. The serum PR concentration was examined using the direct enzyme-linked immunosorbent assay (Innovative Research Inc., Novi, MI, USA) in our center. We performed two tests for 1 sample and calculated the mean.

BPs was measured using an automated sphygmomanometer at every routine prenatal checkup. After resting, patients were made to sit with their right arm at their heart level.

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PIH was defined using the definition and classification proposed by the Japan Society for the Study of Hypertension in Pregnancy [10] (i.e., a BP of ≥140/90 mmHg with or without proteinuria (≥300 mg of protein in a 24-hr urine specimen) after 20 weeks gestation in a patient with neither hypertension nor proteinuria prior to pregnancy). Early-onset PIH was defined as the presentation of hypertension before 32 weeks of gestation.

Regression analysis was used to determine the association between serum PR level and maternal complications. Statistical analysis was performed by JMP 10 (SAS Institute, Inc., Cary, NC), and a p<0.05 was considered statistically significant.

Results

The clinical characteristics and gestational complications of the study participants are shown in Table 1. Thirty-six patients presented with PIH. Multivariate analyses of the serum PR levels are shown in Table 2. The significant effective factors for the PR concentration were gestational age at blood sampling, singleton pregnancy, and kidney disease, and PIH had a stronger influence on the PR level.

Figure 1 shows the correlation between PR concentration and gestational age at blood sampling in non-PIH, singleton pregnancy, and kidney disease, and PIH had a stronger influence on the PR level.

Table 1: Baseline and gestational characteristics of the study participants.

| Factor                        | Coefficient estimate | 95% CI          | t ratio | p-value |
|-------------------------------|----------------------|-----------------|---------|---------|
| Gestational age at blood sampling | -0.049              | -0.067 to -0.031 | -5.31   | <0.0001 |
| Single pregnancy              | -0.570              | -0.822 to -0.319 | -4.45   | <0.0001 |
| Kidney disease                | 0.597               | 0.05 to 1.14     | 2.16    | 0.031   |
| PIH                           | -0.339              | -0.671 to -0.007 | -2.01   | 0.0455  |
| ART                           | -0.204              | -0.433 to 0.319  | -1.74   | 0.0823  |
| Hypertension                  | -0.321              | -0.714 to 0.071  | -1.61   | 0.1085  |
| Maternal age                  | 0.008               | -0.029 to 0.046  | 0.42    | 0.6718  |
| Primipara                     | 0.012               | -0.163 to 0.189  | 0.14    | 0.89    |
| BMI before pregnancy          | -0.002              | -0.038 to 0.034  | -0.10   | 0.9204  |
| (G)DM                         | -0.005              | -0.461 to 0.451  | -0.02   | 0.9831  |

CI: Confidence Interval; PIH: Pregnancy-induced Hypertension; ART: Assisted Reproductive Technology; BMI: Body Mass Index; DM: Diabetes Mellitus; (G)DM: Gestational Diabetes Mellitus. The factors of statistical significance are in bold-faced type.

Figure 1: The correlation between serum Prorenin (PR) concentration and gestational age (non-pregnancy-induced hypertensive, singleton pregnancy patients).

The serum PR concentrations were significantly higher in patients with multiple pregnancies than in patients with singleton pregnancies (covariance analysis, p<0.0001), especially in the second trimester for the non-PIH patients (Figure 3).

Univariate analyses showed a significant association between low serum PR concentrations in the first trimester and elevated systolic and diastolic BPs at 32 weeks of gestational age (p=0.002 and p=0.015, respectively) and systolic BP at 36 weeks of gestational age (p=0.029). However, in the multivariate analysis adjusted for age, Body Mass Index (BMI) before pregnancy, comorbidities (i.e., hypertension, Gestational Diabetes Mellitus (GDM), and kidney disease), parity, and multiple pregnancies showed no significant correlation between the serum PR concentration and BP.

Multivariate logistic regression analysis was performed to examine the association between serum PR concentrations and PIH for each trimester. Multivariate models were adjusted for age, parity, BMI before pregnancy, comorbidities (i.e., kidney disease, hypertension, and GDM), assisted reproductive technology, and multiple pregnancies. This analysis showed that low PR levels during the third trimester were significantly associated with PIH (Table 3a).

The receiver operating characteristic (ROC) curve analysis for patients, there was a negative correlation between gestational age and PR concentration (Spearman rank correlation coefficient, -0.2145; p<0.0001*). Among the trimesters, PR levels were significantly higher in the first trimester than in the later trimesters. Additionally, in the non-PIH multiple pregnancy
Table 3a: Multivariate logistic regression analysis of the association between serum prorenin concentration and pregnancy-induced hypertension (PIH).

| Gestational period | Total, n | PIH, n (%) | Adjusted OR* (95% CI) | p-value |
|--------------------|----------|------------|-----------------------|---------|
| First trimester    | 169      | 21 (12.4)  | 0.757 (0.517–1.01)    | 0.0605  |
| Second trimester   | 256      | 15 (5.9)   | 0.893 (0.597–1.212)   | 0.4142  |
| Third trimester    | 140      | 6 (4.3)    | 0.274 (0.054–0.937)   | 0.0377  |

OR: Odds Ratio; CI: Confidence Interval
*Odds ratio, in which PIH develops when the plasma PR concentration increases by 1 ng/mL.

Table 3b: Multivariate logistic regression analysis for prorenin (PR) and pregnancy-induced hypertension (PIH).

| Predictor | Area under the curve |
|-----------|----------------------|
| BMI before pregnancy | 0.8491 |
| Prorenin at 3rd trimester | 0.6559 |
| Parity | 0.6439 |
| Maternal age | 0.5808 |
| Kidney disease | 0.5758 |
| Multiple pregnancy | 0.5682 |
| ART | 0.5227 |
| DM/GDM | 0.5189 |
| Hypertension | 0.5114 |

The cutoff concentration of plasma PR was 1.279 ng/mL (20.1 percentile).

The receiver operating characteristic curve analysis for the predictors of pregnancy-induced hypertension.

Figure 4: The receiver operating characteristic curve analysis for the predictors of pregnancy-induced hypertension.

| PIH | Non-PIH | n = 140 (No data available = 2) |
|-----|---------|---------------------------------|
| ≤Cutoff | 5 | 8 | Positive predictive value, 36.5% |
| >Cutoff | 1 | 124 | Negative predictive value, 99.2% |

Odds ratio in which the PIH is present when the plasma prorenin concentration is under the cut-off level

Table 3b: Multivariate logistic regression analysis for prorenin (PR) and pregnancy-induced hypertension (PIH).
might play a role as an angiogenesis factor (placental development) in pregnancy rather than as a BP modulator. The recent "two-stage disorder" theory explains the pathogenesis of PIH. Early in normal pregnancy, extra villous cytotrophoblasts invade the uterine spiral arteries in the decidua and myometrium, and these invasive cytotrophoblasts replace the endothelial layer of the maternal spiral arteries (i.e., spiral artery remodeling). This remodeling develops wide-caliber low-resistance vessels, which provide a sufficient placental bed. The aforementioned theory explains that PIH results from poor placental development in which correct remodeling has failed [8,11]. PR, (P)RR, and angiotensin I regulate the placental angiogenesis through the vascular endothelial growth factor expression [12,13]. Low serum PR levels during the third trimester in association with PIH may be related to incomplete placental angiogenesis.

In fact, low serum PR levels may be a result rather than a cause of PIH. Serum PR levels might decrease compensatorily as a result of PIH. The pathogenesis and etiology between early-onset and late-onset PIH may be different; however, the number of PIH cases was not enough for statistical analysis. We plan to conduct a further study that measures serum s(P)RR and PR from the maternal and cord blood sample.

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