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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: $p<0.0001$). 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 during late pregnancy 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 Millitus

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 placentation 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 0 days gestation: 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 assays 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 patients. There was a negative correlation between them (Spearman rack 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 patients, there was a negative correlation between gestational age and PR concentration (Spearman rank correlation coefficient, -0.2606: $p=0.0346$) (Figure 2).

Baseline characteristics	
Age, year (median [range])	35 (16–47)
BMI before pregnancy (median [range])	21.4 (14.4–43.3)
Gestational age at delivery (median [range])	38 weeks 2 days (16 weeks 0 day–41 weeks 3 days)
Number of fetuses	
Singleton	370 (86)
Twin	59 (13.7)
Triplet	1 (0.2)
Parity	
Primipara	238 (55.3)
Multipara	192 (44.7)
Complicating disease	
Hypertension	23 (5.3)
Diabetes mellitus/Gestational diabetes mellitus	18 (4.2)
Thyroid disease	18 (4.2)
Psychological disorder	16 (3.7)
Kidney disease	11 (2.6)
Collagen disease	7 (1.6)
Gestational complications	
Pregnancy-induced hypertension	36 (8.4)
Early onset	2/36 (5.5)
Late onset	31/36 (86.1)
Postpartum	3/36 (8.3)
Intrauterine fetal death	7 (1.62)
Small for gestational age*	
Singleton	25 (6.8)
Multiple pregnancy (both)	5 (8.3)
Multiple pregnancy (one of the pair)	12 (20)
Placenta previa	3 (0.8)

*Defined as an infant whose birth weight is <−1.5 standard deviations
All values are number (percentage), except where indicated

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

Table 2: Multivariate analysis of the serum PR level during pregnancy.

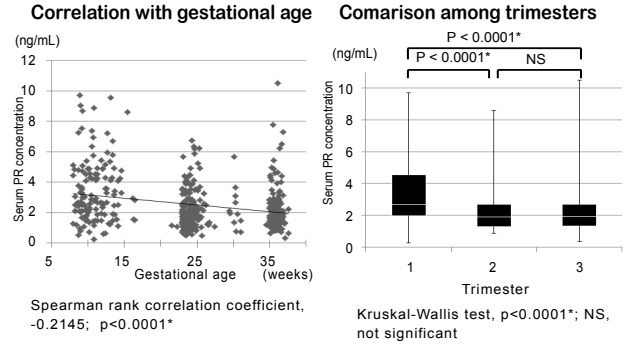


Figure 1: The correlation between serum Prorenin (PR) concentration and gestational age (non-pregnancy-induced hypertensive, singleton pregnancy patients).

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

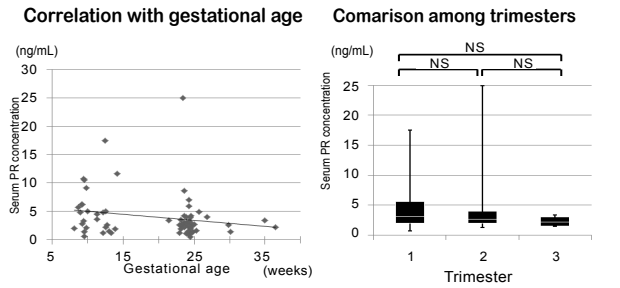


Figure 2: The correlation between serum prorenin (PR) concentration and gestational age (non-pregnancy-induced hypertensive, multiple pregnancy patients).

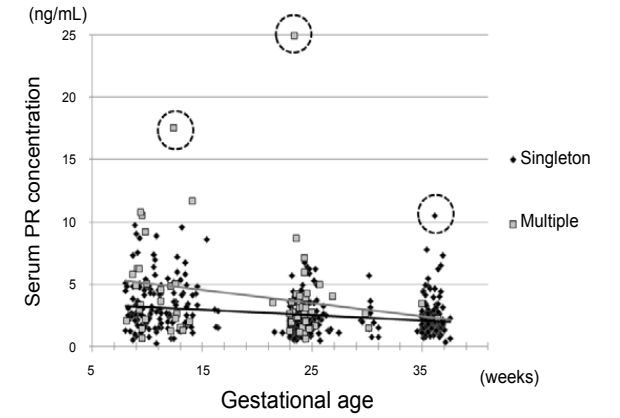


Figure 3: Serum Prorenin (PR) concentration and gestational age (singleton pregnancy versus multiple pregnancies).

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 (0.597–1.121)	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 3a: Multivariate logistic regression analysis of the association between serum prorenin concentration and pregnancy-induced hypertension (PIH).

the predictors of PIH is shown in Figure 4. The area under the ROC curve for the PR concentration was the second largest after BMI before pregnancy. The cutoff serum PR concentration was 1.279 ng/mL (20.1 percentile), as determined from this ROC curve. The adjusted odds ratio for PIH was 18.16 when the serum PR concentration was ≤ 1.279 ng/mL during the third trimester. The sensitivity, specificity, positive predictive value, and negative predictive value are also shown in Table 3b.

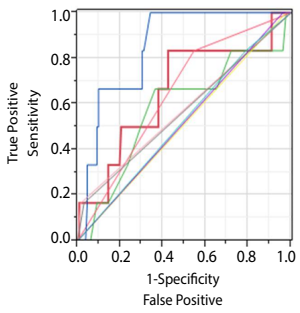
Discussion

The present study demonstrated the association between PR levels and pregnancy: First, the serum PR concentration showed a significant negative correlation with gestational weeks, and serum PR levels in patients with multiple pregnancies were significantly higher than in those in patients with singleton pregnancies, especially during early pregnancy. Second, there was no significant correlation between serum PR concentration and BP. Third, low serum PR levels during the third trimester were significantly associated with PIH.

Compared to the decreased s(P)RR levels during pregnancy, as reported by Watanabe et al. [4], the serum PR levels during pregnancy showed contrasting results, that is, increased. Plasma s(P)RR levels increased gradually from early pregnancy to delivery and were higher in twin pregnancies at delivery. There was a significant association between high plasma s(P)RR levels at delivery and PIH. However, there was a difference in its association with BP. High plasma s(P) RR levels during early pregnancy can predict elevated BP later in pregnancy: however, we were not able to detect a significant association between the serum PR levels and BP. We thought that the serum PR concentration may have less influence on BP regulation. It was assumed that the decrease in peripheral vascular resistance decreased BP after the second trimester due to a physiological change from pregnancy, because the vascular sensitivity to the pressor effects of AT2 decreases during pregnancy [2]. Our findings on the association between serum PR levels and BP may be related to these issues.

In Figures 2 and 3 there are a few outliers (shown in Figure 3 as the circle of the dotted line). They had a common point that repeat caesarean section but PR level of the patients of repeat caesarean section did not show clear trend, then we thought that probably the abnormal high PR concentration was the error that occurred in processes such as the specimen processing and it is more likely to be a simple coincidence.

From the present study findings, we thought that serum PR



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)

BMI, body mass index; ART, assisted reproductive technology; DM, diabetes mellitus; GDM, gestatinal diabetes mellitus

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

	Adjusted OR (95% CI)	P-value
PR ≤1.279 ng/mL during the third trimester	18.16 (1.95-412.41)	0.0107

OR: Odds Ratio; CI: Confidence Interval

	PIH	Non-PIH	n = 140 (No data available = 2)
≤Cutoff	5	8	Positive predictive value, 38.5%
>Cutoff	1	124	Negative predictive value, 99.2%
	Sensitivity, 83.3%	Specificity, 93.9%	

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 deciduas 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 1 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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