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[ORIGINAL ARTICLE]

Association of antithrombin activity with plasma aldosterone concentration and plasma renin activity in pregnant women

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Abstract

OBJECTIVE: To test the hypothesis that the blood antithrombin (AT) activity is correlated with the plasma aldosterone concentration (PAC), the plasma renin activity (PRA), and/or the PAC-to-PRA ratio during the late stage of pregnancy.

METHODS: The AT activity, PAC, and PRA were determined within 7 days prior to delivery in 47 women, consisting of 30 normotensive and 6 hypertensive women with singleton pregnancies and 11 normotensive women with twin pregnancies.

RESULTS: The median values of the 47 women were 86% of the normal activity level for the AT activity, 442 pg/ml for the PAC, 3.7 ng/ml/h for the PRA, and 108 pg/ml per ng/ml/h for the PAC-to-PRA ratio. Women with an AT activity ≤ 86% had a significantly lower PRA and a higher PAC-to-PRA ratio than women with an AT activity > 86% (3.5 ± 3.0 vs. 6.6 ± 4.7 ng/ml/h for PRA, *P*=0.008; 156 ± 109 vs. 97 ± 46 pg/ml per ng/h for PAC-to-PRA ratio, *P*= 0.021). The AT activity was significantly correlated positively with the PRA and negatively with the PAC-to-PRA ratio.

CONCLUSIONS: The existence of a common pathophysiological background between a reduced AT activity and a reduced PRA during the late stage of pregnancy was suggested.

(**Key words:** aldosterone, antithrombin activity, blood vessel permeability, hypertension, preeclampsia, renin activity)

Introduction

Women with hypertension are likely to show a decreased AT activity [1-3]. Some pregnant women without hypertension, however, also develop a gradual decline in AT activity (normal reference range, 80% - 120%) during the late stage of pregnancy, even in the absence of hypertension [4,5], and the 10^{th}, 3^{rd}, and 1^{st} percentile values of AT activity are 74%, 69%, and 66% of the normal activity level, respectively, in otherwise healthy women immediately before undergoing vaginal delivery [6]. Pregnant women with a decreased AT activity are thought to suffer from antenatal hemoconcentration, or in other words, a shortage in the circulating plasma volume [7, 8].

Both the plasma aldosterone concentration (PAC) and the plasma renin activity (PRA) are markedly elevated during pregnancy, and the enhanced renin-angiotensin-aldosterone system (RAS) is thought to play a vitally important role in salt balance and maintaining an adequate and increased circulating plasma volume during pregnancy [9]. The circulating plasma volume is decreased in preeclampsia [10], and preeclampsia is thought to occur as a result of a derangement in the delicate RAS [9], although the precise mechanisms leading to the development of preeclampsia remain unknown. Reductions in the PAC and PRA occur temporally close to the clinical manifestation of preeclampsia in women with this condition [11-13], and an increase in the PAC-to-PRA ratio also occurs in women with preeclampsia because of the relatively smaller decrease in the PAC than in the PRA in women with this disease condition [12].

Thus, both the AT activity and the RAS may be associated with the volume status during pregnancy. Accordingly, we conducted this study to determine whether the AT activity was correlated with the PAC, PRA, and/or PAC-to-PRA ratio determined within 7 days prior to delivery.

Methods

This study was conducted prospectively after being approved by the institutional review board of Hokkaido University Hospital. A total of 47 women, consisting of 36 women with singleton pregnancies and 11 women with twin pregnancies, provided their written informed consent to participate in this study and gave birth during the 20-month period between October 2009 and May 2011 at Hokkaido University Hospital (Table 1). All the participants donated 10 mL of blood within 7 days prior to delivery to determine the PAC, PRA, and AT activity levels. All 36 women with singleton pregnancies were normotensive (systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg) before 20 weeks of gestation, but 6 women became hypertensive during pregnancy. These 6 women were classified as hypertensive women with singleton pregnancies. The remaining 30 women were normotensive throughout pregnancy and the postpartum period. Of the 11 women with twin pregnancies, none developed hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) or proteinuria (≥ 0.3 g/day) while pregnant, but 2 of them transiently developed hypertension during the postpartum period.

All the women were allowed an unrestrained sodium diet. Venous blood was drawn into ethylenediamine tetraacetic acid (EDTA) Vacutainer tubes while the participants were in a seated position after they had been ambulatory. The plasma samples were processed at room temperature to avoid the cryoactivation of prorenin, and the samples were stored at -40°C until assayed. PRA was measured using a well-established radioimmunoassay kit (PRA [SRL]; Special Reference Laboratory Co., Tokyo, Japan) according to the manufacturer's instructions. The PAC was measured using a

radioimmunoassay kit (Spac–S aldosterone; Dai-ichi Radioimmunoassay Laboratory Co., Tokyo, Japan) according to the manufacturer's instructions. The intra- and inter-assay coefficient variations were less than 11.0% for the PRA and less than 7.0% for the PAC. The AT activity was measured using a chromogenic substrate assay (Daiichi Pure Chemicals Co., Tokyo, Japan) in our laboratory.

The statistical analyses were performed using the JMP8 statistical software package (SAS, Cary, NC). Differences in the means were tested using the Tukey-Kramer HSD (honestly significant difference) test between each group, and categorical variables were compared using the $\chi 2$ test. A P value of less than 0.05 was considered to indicate statistical significance.

Results

The median values determined in the 47 women were 86% of the normal activity level for the AT activity, 442 pg/ml for the PAC, 3.7 ng/ml/h for the PRA, and 108 pg/ml per ng/ml/h for the PAC-to-PRA ratio (Table 2). Hypertensive women with singleton pregnancies were more likely to exhibit PAC and PRA values below the median values, compared with normotensive women with singleton pregnancies (Table 2). Neither systolic nor diastolic blood pressure differed between two groups divided by the median value of AT activity (Table 3). Women with an AT activity ≤ 86% were significantly more likely to exhibit a lower PRA level and a higher PAC-to-PRA ratio than women with an AT activity > 86% (Table 3).

The correlations between the AT activity and the systolic blood pressure, diastolic blood pressure, PAC, PRA, and PAC-to-PRA ratio were analyzed. Although the AT activity was not significantly correlated with the systolic blood pressure, diastolic blood

pressure, or PAC, the AT activity was significantly correlated positively with the PRA and negatively with the PAC-to-PRA ratio (Figures 1 and 2).

Discussion

This study demonstrated that AT activity was significantly correlated positively with the PRA and negatively with the PAC-to-PRA ratio, but not with the blood pressure in pregnant women who were within 7 days of delivery. These results suggested the existence of a common pathophysiological background between a reduction in AT activity and a reduction in the PRA.

In normal pregnancy, an increase in almost all the components of RAS occurs [9]. A suggested sequence of events is as follows: initial vasodilation and a subsequent lower blood pressure, followed by increases in PRA release and angiotensin II generation for the maintenance of blood pressure within the normal range [14]. The suppression of RAS, as evidenced by a reduced PRA and PAC, occurs in women with pregnancy-induced hypertension [11-13, 15], as was also confirmed in the present study. However, the decrease in the PRA precedes the development of hypertension [11, 15, 16]: women with twin pregnancies exhibit a decrease in the PRA during the third trimester in the absence of hypertension and subsequently develop hypertension postpartum [15]; a low PRA of < 4.0 ng/mL/hour at 20 weeks of gestation can predict the development of superimposed preeclampsia among women with chronic hypertension [16]. Thus, hypertension is not responsible for the decrease in the PRA and suppression of the RAS. Although direct effecter(s) leading to the suppression of the PRA and the contribution of the placental RAS to the suppression of the PRA [9] remain to be studied, changes in the plasma volume may be involved in the suppression of the

PRA [14, 17].

A previous report stated that “One of the most striking features of normal pregnancy, apparent both by physical examination and by hemodynamic and hormonal measurement, is early and marked vasodilation” [17], resulting in an increase in the circulating plasma volume [18]. However, the circulating blood volume is markedly reduced in women with preeclampsia [10] and is lowest among women progressing to eclampsia [19]. Although the precise mechanisms leading to the contraction of the circulating plasma volume are not well understood, an increased blood vessel permeability in response to vascular endothelial cell dysfunction allowing the leakage of the plasma into the extravascular space may be one of the possible explanations [20]. Although difference did not reach a significant level mainly due to a small number of study subjects with hypertension in this study, a reduced AT activity is one of the laboratory characteristics seen in women with preeclampsia, eclampsia, and HELLP syndrome [1-4, 19]. Six out of 11 women with eclampsia exhibited a reduced AT activity of less than 65% of the normal activity level before or soon after an eclamptic fit [21]. As women with pregnancy-induced AT deficiency, defined as a gradual decline in the AT activity to less than 65% of the normal activity level, show a larger decrease in the hematocrit value postpartum in the absence of hypertension, compared with women without pregnancy-induced AT deficiency [7], women with a reduced AT activity are suggested to suffer from antenatal hemoconcentration, or in other words, a contraction of the circulating plasma volume even in the absence of hypertension [7,8].

Thus, as both reduced PRA and a reduced AT activity may be associated with an inadequate volume status that should be maintained adequately during normal pregnancy, the existence of a significant correlation between AT activity and PRA was

expected. The present study confirmed that this expectation was true. As the determination of AT activity is part of the routine work-up for patients who are admitted to the intensive care unit [22], the determination of AT activity may be easier to perform than the determination of the PRA in most clinical laboratories. The AT molecule moves from the blood into extravascular spaces in the presence of an increased blood vessel permeability, implying that the AT activity in the blood reflects the degree of blood vessel permeability [20]. A modest decrease in the plasma volume is usually difficult to anticipate in clinical practice in the absence of hypertension. This study, as well as the results of previous studies [7, 20], suggests that the AT activity reflects the degree of the plasma volume contraction during pregnancy.

In conclusion, our hypothesis was supported in this study. The existence of a positive correlation between the AT activity and the PRA suggested a common pathophysiological background between a reduced AT activity and a reduced PRA during the late stage of pregnancy.

References

1. Weiner CP, Brandt J. Plasma antithrombin III activity: an aid in the diagnosis of preeclampsia-eclampsia. AJOG 1982; 142: 275-81.

2. Weenink GH, Borm JJJ, ten Cate JW, Treffers PE. Antithrombin III levels in normotensive and hypertensive pregnancy. Gynecol Obstet Invest 1983; 16: 230-42.

3. Winer CP, Kwaan HC, Xu C, Paul M, Burmeister L, Hauck W. Antithrombin III activity in women with hypertension during pregnancy. Obstet Gynecol 1985; 65:301-6.

4. Minakami H, Watanabe T, Izumi A, Matsubara S, Koike T, Sayama M, Moriyama I, Sato I. Association of a decrease in antithrombin III activity with a perinatal elevation in aspartate aminotransferase in women with twin pregnancies: relevance to the HELLP syndrome. J Hepatol. 1999; 30: 603-11.

5. Tsunoda T, Ohkuchi A, Izumi A, Watanabe T, Matsubara S, Sato I, Minakami H: Antithrombin III activity and platelet count are more likely to decrease in twin pregnancies than in singleton pregnancies. Acta Obstet Gynecol Scand 2002; 81: 840-5

6. Morikawa M, Yamada T, Yamada T, Koyama T, Akaishi R, Ishikawa S, Takeda M, Nishida R, Araki N, Minakami H. Antithrombin activity, platelet count, hemoglobin concentration and hematocrit value determined immediately before vaginal delivery among healthy women. Hokkaido J Med Sci, in press

7. Morikawa M, Yamada T, Yamada T, Shimada S, Koyama T, Cho K, Minakami H. Pregnancy-induced antithrombin deficiency. J Perinat Med 2010; 38: 379-85.

8. Minakami H, Morikawa M, Yamada T, Yamada T. Candidates for the determination of antithrombin activity in pregnant women. J Perinat Med 2011; 39: 369-74.

9. Irani RA and Xia Y. The functional role of the renin-angiotensin system in pregnancy and preeclampsia. Placenta 2008; 29: 763-71.

10. Silver HM, Seebeck MA, Carlson R: Comparison of total blood volume in normal, preeclamptic, and nonproteinuric gestational hypertensive pregnancy by simultaneous measurement of red blood cell and plasma volumes. Am J Obstet Gynecol 1998; 179: 87-93.

11. August P, Lenz T, Ales KL, Druzin ML. Edersheim TG, Hutson JM, et al. Longitudinal study of the renin-angiotensin-aldosterone system in hypertensive pregnant women: deviations related to the development of superimposed preeclampsia. Am J Obstet Gynecol 1990; 163: 1612-21.

12. Brown MA, Wang J, Whitworth JA. The renin-angiotensin-aldosterone system in pre-eclampsia. Clin Exp Hypertens 1997; 19; 713-26.

13. Langer B, Grima M, Coquard C, Bader A-M, Schlaeder G, Imbs J-L. Plasma active renin, angiotensin I, and angiotensin II during pregnancy and in preeclampsia. Obstet Gynecol 1998; 91: 196-202.

14. August P, Mueller FB, Sealey JE, Edersheim TG. Role of renin-angiotensin system in blood pressure regulation in pregnancy. Lancet 1995; 345: 896-7.

15. Koyama T, Yamada T, Furuta I, Morikawa M, Yamada T, Minakami H. Plsama aldosterone concentration and plasma renin activity decrease during the third trimester in women with twin pregnancy. Hypertens Preg, in press

16. August P, Helseth G, Cook EF, Sison C. A prediction model for superimposed preeclampsia in women with chronic hypertension during pregnancy. Am J Obstet Gynecol 2004; 191: 1666-72.

17. Lindheimer MD, August P. Alsosterone, maternal volume status, and healthy pregnancies: a cycle of differing views. Nephrol Dial Transplant 2009; 24: 1712-4.

18. Pritchard JA. Changes in blood volume during pregnancy. Anesthesiology 1965;

26:393-9.

19. Zeeman GG, Cunningham FG, Pritchard JA. The magnitude of the hemoconcentration in preeclampsia. Hypertens Preg 2009; 28: 127-37.

20. Morikawa M, Yamada T, Yamada T, Koyama T, Akaishi R, Takeda M, Araki N, Cho K, Minakami H. Evidence of the escape of antithrombin form the blood into the interstitial space in pregnant women. J Perinat Med. 2010; 38: 613-5.

21. Yamada T, Kuwata T, Matsuda H, Deguchi K, Morikawa M, Yamada T, Furuya K, Matsubara S, Minakami H. Risk factors of eclampsia other than hypertension: pregnancy-induced antithrombin deficiency and extraordinary weight gain. Hypertens Preg 2011 Dec 9. [Epub ahead of print] PMID: 22149018

22. Sakr Y, Reinhart K, Hagel S, Kientopf M, Brunkhorst F. Antithrombin levels, morbidity, and mortality in a surgical intensive care unit. Anesth Analg 2007: 105: 715-723.

Figure legends

Figure 1: Correlation between antithrombin activity in the blood and plasma renin activity. The antithrombin activity and the plasma renin activity were determined within 7 days prior to delivery in 47 women, consisting of 30 normotensive (●) and 6 hypertensive （×） singleton pregnancies and 11 normotensive women with twin pregnancies (△). The antithrombin activity was significantly and positively correlated with the plasma renin activity.

Figure 2: Correlation between antithrombin activity in the blood and plasma aldosterone concentration-to-plasma renin activity ratio. The antithrombin activity and the plasma renin activity were determined within 7 days prior to delivery in 47 women, consisting of 30 normotensive (●) and 6 hypertensive （×） singleton pregnancies and 11 normotensive women with twin pregnancies (△). The antithrombin activity was significantly and negatively correlated with the ratio of the plasma aldosterone concentration to the plasma renin activity.

Fig. 1

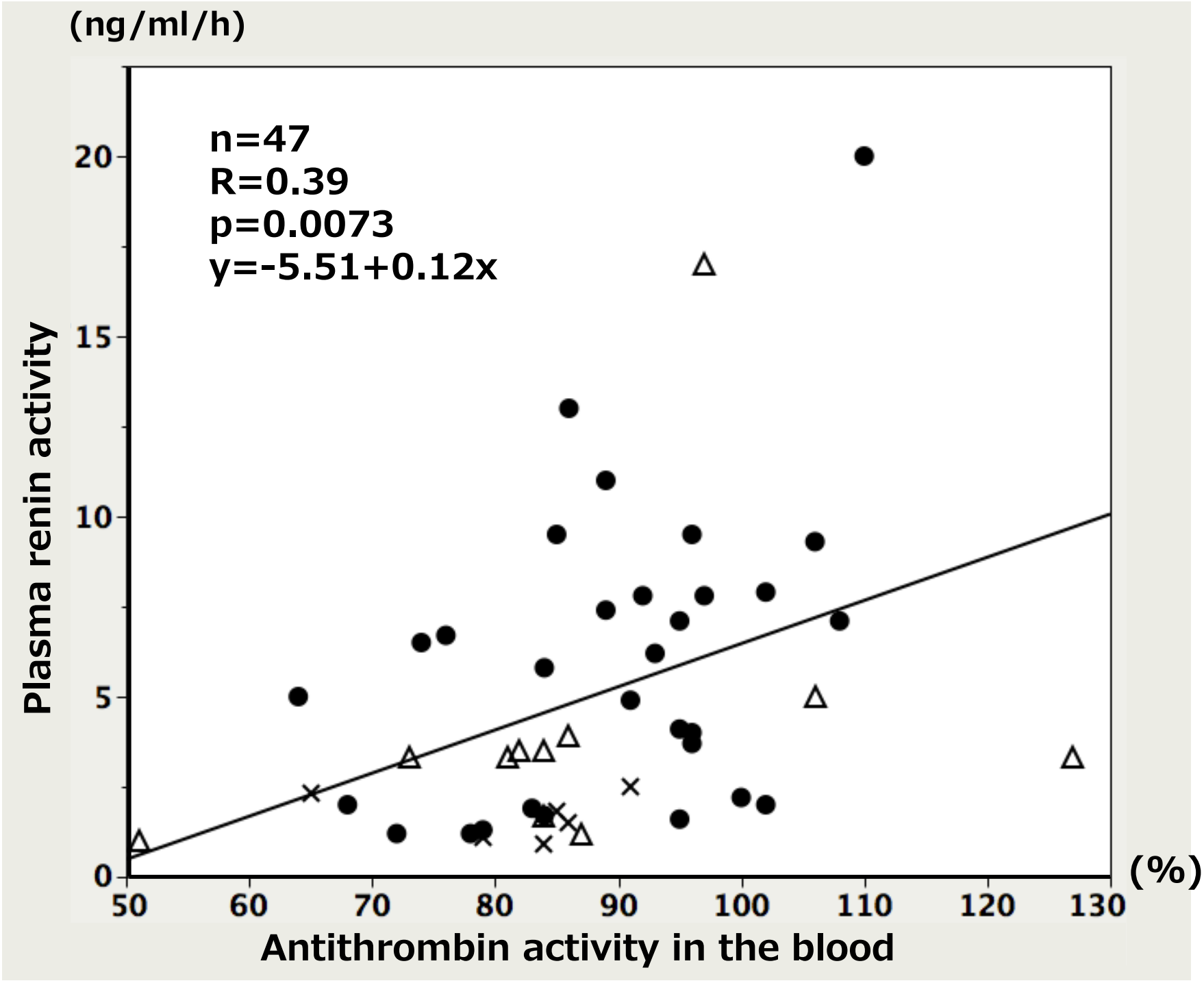

(ng/ml/h)
n=47
R=0.39
p=0.0073
y=-5.51+0.12x
Plasma renin activity
0
5
10
15
20
50
60
70
80
90
100
110
120
130
(%)
Antithrombin activity in the blood

Fig. 2

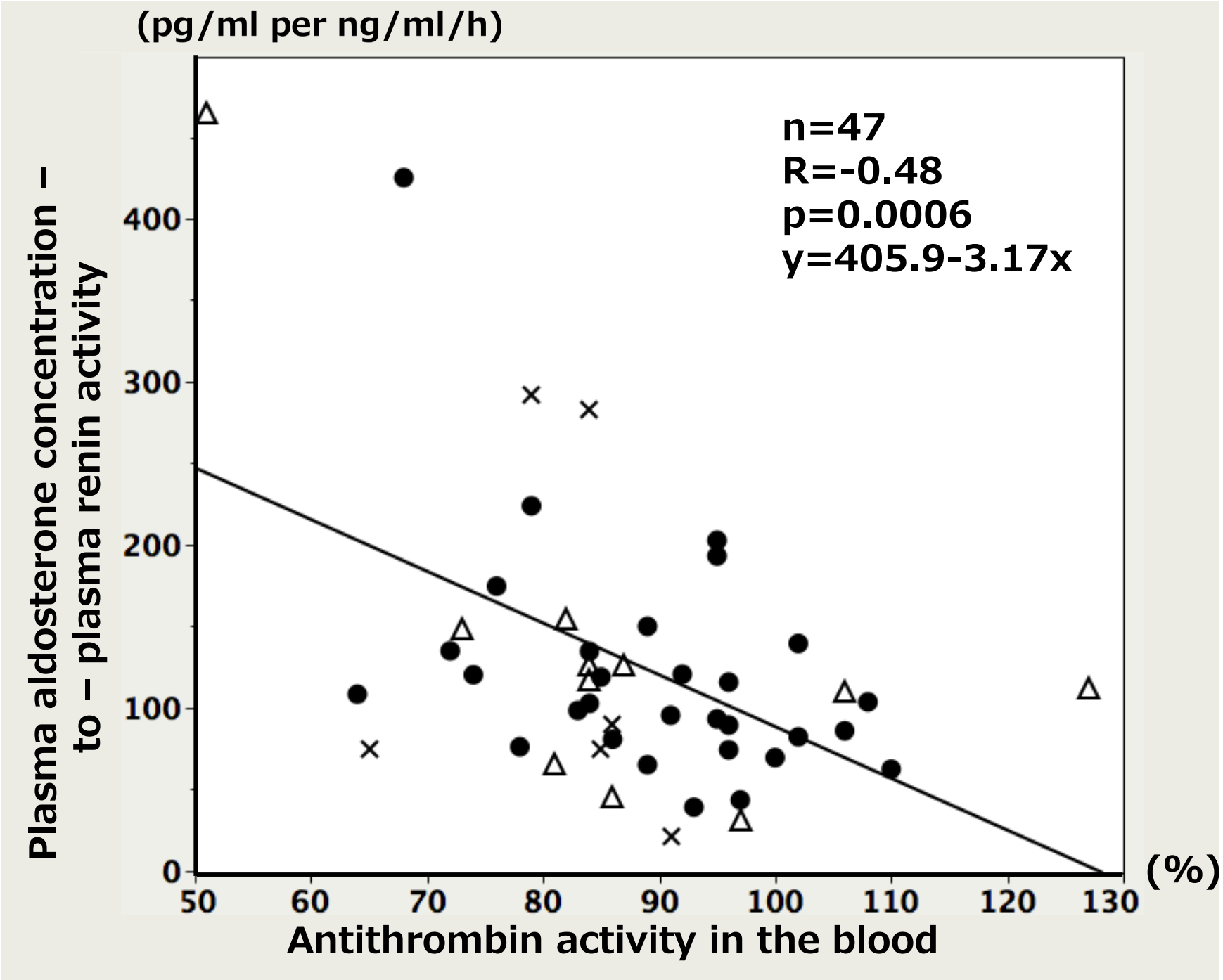

(pg/ml per ng/ml/h)
Plasma aldosterone concentration – to – plasma renin activity
n=47
R=-0.48
p=0.0006
y=405.9-3.17x
400
300
200
100
0
50
60
70
80
90
100
110
120
130
(%)
Antithrombin activity in the blood

Table 1. Demographic characteristics of the 47 study subject

Age (years old)	32.1±4.7
Nulliparous	22 (46.8%)
Singleton pregnancy	36 (76.6%)
Twin pregnancy	11 (23.4%)
Hypertension†	6 (12.8%)
Preeclampsia	4 (8.5%)
Cesarean delivery	33 (70.2%)
Gestational week at delivery (weeks)	36.2 ± 4.4
Preterm birth < 37 weeks	9 (19.1%)
Preterm birth < 33 weeks	7 (14.9%)

Data are presented as the mean ± SD or the number of women (percentage of the 47 women). †, including women with gestational hypertension and preeclampsia.

Table 2. Levels of blood pressures and blood variables in the three patient groups

	Singleton pregnancy		Twin pregnancy
	Normotensive (n=30)	Hypertensive (n=6)	(n=11)
Gestational week at delivery	38.0±2.3	31.0±7.5†	34.5±1.1†
Systolic blood pressure (mmHg)*	110 ±10	164 ±21 #	113 ±13
Diastolic blood pressure (mmHg)*	65 ±8	87 ±16 #	61 ±11
AT activity (%)	90 ±12	82 ±9	87 ±19
> 86%	18 (60.0%)	1 (16.7%)	4 (36.4%)
PAC (pg/ml)	610 ±357	178 ±96†	376 ±159
≥ 442 pg/ml	18 (60.0%)	0 (0.0%)†	6 (54.5%)
PRA (ng/ml/h)	6.0 ±4.2	1.7 ±0.6	4.2 ±4.4
≥ 3.7ng/ml/h	21 (70.0%)	0 (0.0%) †	3 (27.3%)
PAC/PRA (pg/ml per ng/ml/h)	121 ±73	139 ±117	137 ±116
≥ 108 pg/ml per ng/ml/h	14 (46.7%)	2 (33.3%)	8 (72.7%)

Data are presented as the mean ± SD or the number of women (percentage of each patient group). *, The highest blood pressure recorded prenatally; AT, antithrombin; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PAC/PRA, ratio of PAC to PRA; †, $P<0.05$ and #, $P<0.0001$ versus women with normotensive singleton pregnancies, respectively.

An AT activity of 86%, a PAC of 442 pg/ml, a PRA of 3.7 ng/ml/h, and a PAC/PRA of 108 pg/ml per ng/ml/h were the median values for the 47 women.

Table 3. Levels of blood pressures and blood variables in two groups divided according to antithrombin activity

	Antithrombin activity (%)		
	≤86% (n=24)	> 86% (n=23)	*P*-value
Systolic blood pressure (mmHg)*	122 ± 26	113 ± 15	0.104
≥ 118 mmHg	12 (50.0%)	12 (52.2%)	0.882
Diastolic blood pressure (mmHg)*	69 ± 15	65 ± 9	0.319
≥ 64 mmHg	11 (45.8%)	12 (52.2%)	0.664
PAC (pg/mL)	443 ± 331	560 ± 335	0.235
≥ 442 pg/mL	11 (45.8%)	13 (56.5%)	0.464
PRA (ng/mL/h)	3.5 ± 3.0	6.6 ± 4.7	0.008
≥ 3.7 ng/mL/h	7 (29.2%)	17 (73.9%)	0.002
PAC/PRA (pg/mL per ng/mL/h)	156 ± 109	97 ± 46	0.021
≥ 108 pg/mL per ng/mL/h	15 (62.5%)	9 (39.1%)	0.109

Data are presented as the mean ± SD or the number of women (percentage of each patient group).

*, The highest blood pressure recorded prenatally; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PAC/PRA, ratio of PAC to PRA. A systolic blood pressure of 118 mmHg, a diastolic blood pressure of 64 mmHg, an antithrombin activity of 86%, a PAC of 442 pg/mL, a PRA of 3.7 ng/mL/h, and a PAC/PRA of 108 pg/mL per ng/mL/h were the median values for the 47 women.