―**Original**―

Clinical Relevance of Grade III Placenta in Assessment of Low Level of Plasma Antithrombin III Activity in Pregnant Women at Term

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Abstract

We previously reported the correlation of placenta grade with low antithrombin III (ATIII) in pregnant women at term. In this report, the clinical relevance of grade III placenta in the assessment of low plasma ATIII was compared with other factors that raise the risk of blood hypercoagulability.

Methods: We investigated the correlation of low ATIII with ultrasonographic placental grade as well as with age, parity, body mass index (BMI), blood pressure, platelet counts and hematocrit in 164 healthy pregnant women at term. We calculated the odds ratio for each variable (clnical factor) to predict low ATIII activity of less than 80% using a multiple logistic regression model.

Results: Low ATIII activity was associated with BMI≧28, systolic blood pressure≧136 mmHg, diastolic blood pressure≧84 mmHg and the presence of grade III placenta. The odds ratio of low ATIII activity was 3.2 for women with BMI≧28 (95% Confidential Interval (CI): 1.1−9.7); 2.7 (95% CI: 0.7−10.3) for women with systolic blood pressure≧136 mmHg; 1.9 (95% CI: 0.3−11.9) for those with diastolic blood pressure≧84 mmHg; and 2.4 (95% CI: 0.8−6.9) for those with placental grade III.

Conclusion: We can assess low placenta ATIII activity by using placental grade with similar odds ratios to BMI and blood pressure in pregnant women at term.
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Key words: grade III placenta, antithrombin III, blood coagulation, pregnancy

Introduction

As pregnancy advances, many coagulation factors are elevated in contrast to the reduction in fibrinolysis activity[1-3]. Therefore, the blood of pregnant women tends to be in a hypercoagulable state and pregnancy is considered a form of acquired thrombophilia[1,4-6]. In fact, it has been reported that the risk of developing thromboembolism in pregnant women is about five times greater than that in nonpregnant women[4].

Anthithrombin III (ATIII) strongly inhibits thrombogenesis in blood vessels, and its plasma concentrations do not markedly fluctuate during pregnancy. Therefore, detection of low plasma concentrations of ATIII in pregnant women may help us to establish an obstetrical strategy to prevent thromboembolism during intrapartal and postpartal periods. In our previous study investigating pregnant women at low risk for thromboeboism, the presence of a high grade placenta assessed by ultrasonography was seen to be correlated with a low level of plasma ATIII

as well as low fibrinolytic activity[7]. However, there are risk factors other than placental grading that raise the risk for thrmoboembolism in pregnant women. Old age and obesity are examples[2,4,7-9]. In women with preeclampsia, intravascular coagulation frequently coexists, and thrombocytopenia or hemoconcentration are frequently associated with low ATIII activity in pathological conditions[9-13]. Therefore, we investigated the clinical relevance of placental grade in the assessment of blood coagulate state together with other factors, including age, obesity, hematocrit (Hct) and hypertensive or thrombocytopenic tendency in pregnant women at term. Analyses were performed using a multiple logistic regression method for the interactive effect of each factor.

Subjects and Methods

1. Subjects

The subjects were 164 pregnant women at term. The gestational age ranged from 37 to 39 weeks, and these women were visiting our clinic during pregnancy. The precise gestational week was determined by fetal CRL (cruwn-rump-length). Healthy pregnant women were selected randomly as subjects, and those with a family or past history of hematological disease or medical complications, such as hepatic or renal dysfunction, were excluded. They all delivered appropriate-for-date (AFD) neonates without congenital anomalies.

Women who suffered from preeclampsia, abnormal glucose tolerance, abruptio placentae, placenta previa and thrombocytopenia or abnormal liver functions like HELLP syndrome during pregnancy were also excluded as subjects. None experienced thromboembolism or disseminated intravascular coagulation (DIC) during or after pregnancy.

Nine subjects underwent caesarean sections due to obstetric indications: four cases due to dystocia, four cases to fetal distress during labor, one to narrow pelvis before onset of labor.

2. Methods

After obtaining informed consent, a venous blood sample was collected from each pregnant woman during an outpatient visit using a blood collection tube containing 0.5 ml sodium citrate (1:9) to measure ATIII activity. Each sample was promptly centrifuged (3000 rpm, 10 min) and the plasma stored frozen at $-80℃$. The level of ATIII activity was measured with a Kabi chromatogenic substrate S-2238 (Mallinkrodt Inc., St. Louis, MO). All measurements were made in our institution's laborator. In addition, the remaining specimens were used to measure complete blood cell counts in an autoanalyzer.

On the same day, abdominal ultrasonography (Mochida SONOVISTA, MEU-1584 EUB, Japan) was performed to assess placental grading for each pregnant woman. Placental grading from grades 0 to III was determined according to Granum's critera[14]. A summary of the criteria is as follows; Grade 0 placenta: the chorionic plate appears as a smooth, straight, and well-defined dense line. The substance and basal layer of the placenta appear as homogeneous and no densities, respectively. Grade I placenta: Subtle undulations in the chorionic plate and few scattered echogenicity in placental substance are observed, resulting in a loss of homogenicity. Grade II placenta: A more marked indentation is observed in the chorionic plate, which extends into the placenta substrate but not to the basal layer. The placental substance appears to be incompletely divided by the appearance of linear or comma-like echogenic densities. The basal layer becomes punctuated with linear echoes. Grade III placenta: In the chorionic plate, a more marked indentation develops and communicates with the basal layer. In the center of the placental substance, circular densities with echo-spared areas appear with large and irregular densities. In the basal layer, large and somewhat confluent basal echogenic areas develop. The echogenic calcificated areas in both the placental substance and the basal layer can create acoustic shadows.

Three trained ultrasonographers, assessing photocopies of the placental images a few days later, did the determination. Placental grading assessed by the three authors matched in 96.0% of the cases. When the placental assessment did not agree, the highest grade was used for the subsequent analyses.

Since ATIII activities less than 80% are

Table 1   Comparison of plasma AT Ⅲ activities related to clinical factors

Variable	AT Ⅲ < 80% (n = 45)	AT Ⅲ ≧ 80% (n = 119)	Significance
Age	30.7 ± 4.4	29.7 ± 4.4	ns
Parity	0.4 ± 0.7	0.4 ± 0.6	ns
Gestational weeks at measurement	38.7 ± 1.4	38.3 ± 1.8	ns
Body weight （Kg）	67.3 ± 6.6	63.1 ± 9.1	p < 0.01
Height （cm）	158.8 ± 5.7	159.0 ± 4.8	ns
BMI	24.9 ± 3.5	26.4 ± 2.3	p < 0.01
BMI ≧ 28	12 (26.7%)	19 (16.0%)	ns
Systolic BP （mmHg）	119.6 ± 13.7	114.3 ± 14.0	p < 0.05
Systolic BP ≧ 136mmHg	7 (15.6%)	8 (6.7%)	p < 0.05
Diastolic BP （mmHg）	71.7 ± 10.2	69.3 ± 10.6	ns
Diastolic BP ≧ 84mmHg	6 (13.3%)	9 (7.5%)	ns
AT Ⅲ activity （%）	73.4 ± 2.9	96.4 ± 10.4	p < 0.001
Hct （%）	35.8 ± 3.3	34.6 ± 2.7	p < 0.05
Hct ≧ 38%	6 (13.3%)	9 (7.5%)	ns
Platelet counts （×10,000/μl）	23.3 ± 5.4	25.3 ± 7.0	ns
Platelet counts < 18,000/μl	4 (8.9%)	11 (9.2%)	ns
Grade Ⅰ placenta	5 (11.1%)	31 (26.1%)	p < 0.05
Grade Ⅱ placenta	17 (37.8%)	50 (42.0%)	ns
Grade Ⅲ placenta	23 (51.5%)	38 (31.9%)	p < 0.02
Gestational weeks at delivery	38.7 ± 1.0	38.3 ± 1.8	ns
Birth weight （gr）	3,141 ± 315	3,258 ± 404	ns

AT Ⅲ activity: Antithrombin Ⅲ activity, BMI: Body mass index, BP: Blood pressure, Hct: Hematocrit, ns: Not significant. Data are expressed as mean±standard deviation or n（%）. n: Number of pregnant women.

considered abnormal in our institute, ATIII activities less than 80% were defined las ow ATIII activity. We investigated the relationship between low ATIII activities and age, parity and the presence of low platelet counts, high Hematocrit （Hct）, high blood pressure, high body mass index （BMI） and grade III placenta. Since our healthy subjects did not have abnormal findings in complete blood cell count or blood pressure, the 90 and 10 percentile of the values were defined as the upper and lower limits in the present study, respectively.

BMI for each pregnant woman was calculated from body weight and height. Among pregnant Japanese women, those with a BMI≧28 are defined as obese [15]. Thus a BMI≧28 was used as the upper limit of BMI in the present study.

Statistical Analysis

A chi-square test with Yate's correction was used to compare incidence （number of pregnant women） between the two groups, and a Student t-test to compare average values between the two groups. P values of less than 0.05 were considered significant.

The Odds ratio, which indicates the relationship between low ATIII activity and other variables （clinical factors）, was calculated after analyzing those variables by SPSS using a multiple logistic regression model. We also determined by odds ratios the level of the relationship between each clinical factor and AT III activity<80%.

Results

1) Clinical profile and plasma ATIII activity （Table 1）

The pregnant women in the present study were divided into two groups: ATIII activity≧80% （normal ATIII activity group） and AT III activity <80% （low AT III activity group）. The pregnant women in the low AT III activity group accounted for 45 of the 164 subjects （27.4%）. Table 1 shows the clinical profiles of these two groups.

1 a）Age, parity, and gestational weeks at measurement

There were no significant differences between the two groups in age, parity, gestational weeks at measurement, gestational weeks at delivery and neonatal weight.

1 b） Body weight, height and BMI

The body weight for the low ATIII activity group was significantly higher than that for the normal ATIII activity group （p＜0.01）, although there was no significant difference in height between these groups. Consequently, the BMI for the low ATIII activity group was significantly greater than that for the normal ATIII activity group （p＜0.01）. A total of 26.7% of the pregnant women in the low ATIII activity group were overweight （BMI≧28）, while only 16.0% of the pregnant women in the normal ATIII activity group were BMI≧28. However, the difference in incidence was not significant between the groups.

1 c） Blood pressure, hematocrit （Hct）, and platelet counts

The upper limit for Hct and systolic and diastolic blood pressures was defined as 38%, 136 mmHg and 84 mmHg, respectively, which corresponded to the 90 th percentiles of the present subjects. The lower limit for platelet counts was defined as $180,000/\mu l$, which corresponded to the value at the 10 th percentile. The upper and lower limits were used for subsequent analysis.

①Blood pressure

The systolic blood pressure in the low ATIII activity group was significantly higher than that in the normal ATIII group （p＜0.05）. There was a significant difference between these two groups in the number of women with systolic blood pressure≧ 136 mmHg （p＜0.05）.

No significant difference was observed in diastolic blood pressure between the two groups. Furthermore, there was no significant difference between the two groups with respect to the number of women with blood pressure≧84 mmHg.

②Hematocrit

The average Hct for the low ATIII activity group was significantly higher than that for the normal AT

III activity group （p＜0.05）. However, no significant difference was observed in the number of women with Hct≧38% between the two groups.

③Platelet counts

Although platelet counts for the low ATIII activity group tended to be lower than those in the normal ATIII activity group, no significant difference was observed between the two groups. There was no significant difference in the number of women with platelet counts of less than $180,000/\mu l$ between the two groups.

④RBC, WBC and Hemoglobin

There were no significant differences between the two groups in RBC, WBC, or hemoglobin.

⑤Ultrasonographic placental grading

None of the women in the present study had a grade 0 placenta, and thus only placental grades of I through III were observed. Of the 164 women, 36 （22%）had a grade I placenta, 67（40.9%）had a grade II placenta, and 61 （37.2%） had a grade III placenta. The prevalence of grade I placentas was significantly higher in the normal ATIII activity group （26.1%） than in the low ATIII activity group（11.1%） （p＜0.05）. For grade II placentas, no significant difference was observed between the two groups. The prevalence of grade III placentas was significantly higher in the low ATIII activity group （51.1%） than in the normal ATIII activity group （31.9%） （p＜0.02）.

2） Comparison of variables between different placental grading （Table 2）

Compared pregnant women with grade I placentas, the average ATIII activity in those with grade III placentas were significantly lower （p＜0.05） and the prevalence of pregnant women with low ATIII activity was higher （p＜0.05）.

The prevalence of pregnant women with blood pressure≧136 mmHg, Hct≧38%, platelet counts＜ $180,000/\mu l$ and BMI≧28 had no correlation with placental grade.

3） Assessment of low ATIII activity based on odds ratios （Table 3）

In order to assess low ATIII activity, we prepared a multiple logistic regression model incorporating age, parity, BMI, placenta grading,

Table 2　Comparison of chlinical factors between different placental grades

Variable	Grade I placenta (n = 36)	Grade II placenta (n = 67)	Grade III placenta (n = 61)
Age	29.7 ± 4.6	30.5 ± 4.4	29.8 ± 4.7
Parity	0.4 ± 0.5	0.4 ± 0.5	0.4 ± 0.7
Gestational weeks at measurement	37.8 ± 1.6	37.9 ± 1.8	38.2 ± 1.9
BMI	25.8 ± 2.9	25.2 ± 3.7	25.3 ± 2.9
BMI ≧ 28	8 (22.2%)	12 (17.9%)	11 (18.0%)
Systolic BP (mmHg)	116.1 ± 11.8	116.8 ± 16.5	115.4 ± 12.1
Systolic BP ≧ 136mmHg	4 (11.1%)	8 (11.9%)	3 (4.9%)
Diastolic BP (mmHg)	69.8 ± 13.4	69.9 ± 11.2	69.6 ± 8.7
Diastolic BP ≧ 84mmHg	3 (8.3%)	7 (10.4%)	5 (8.2%)
AT III activity (%)	95.6 ± 14.1 *	89.9 ± 14.4	85.3 ± 15.0
AT III activity < 80%	5 (13.9%) *	5 (7.5%)	5 (8.2%)
Hct (%)	35.4 ± 2.6	34.7 ± 2.9	35.0 ± 2.7
Hct ≧ 38%	5 (14.5%)	5 (7.5%)	5 (8.2%)
Platelet counts (×10,000/μl)	25.3 ± 7.0	24.2 ± 6.3	25.9 ± 6.4
Platelet counts < 18,000/μl	4 (11.1%)	6 (9.0%)	5 (8.2%)

BMI: Body mass index, BP: Blood pressure, AT III activity: Antithrombin III activity, Hct: Hematocrit.
* Indicates significant differrence (p < 0.05) from data in grade III placenta. Data are expressed as mean ± standard deviation or n (%). n: Number of pregnant women.

Table 3　Odds ratio for low AT III activity

Variable	Odds ratio	95% Confidential interval
Age	1.0	0.9— 1.1
Parity	1.5	0.7— 3.0
Gestational weeks	1.0	0.7— 1.3
Grade I placenta	0.5	0.1— 9.7
Grade III placenta	2.4	0.8— 6.9
BMI ≧ 28	3.2	1.1— 9.7
Systolic BP ≧ 136mmHg	2.7	0.7—10.3
Diastolic BP ≧ 84mmHg	1.9	0.3—11.9
Hct ≧ 38%	0.4	0.1— 1.6

Low AT III activity: Plasma antithombin III activity < 80%, BMI: Body mass index, Hct: Hematocrit, BP: Blood pressure. Odds ratio was obtained by multiple logistic regression method.

Hct, platelet counts and blood pressure (p<0.04). The adjusted odds ratio for each variable was calculated (**Table 3**).

The odds ratio for BMI≧28 was 3.2 (95% confidential interval (CI): 1.1–9.7); for systolic blood pressure≧136 mmHg it was 2.7 (95% CI: 0.7–10.3); for diastolic blood pressure≧84 mmHg it was 1.9 (95% CI: 0.3–11.9); and for grade III placenta it was 2.4 (95% CI: 0.8–6.9). The Odds ratios for a gradeIplacenta and HCT≧38% were below 1.0.

Platelet counts<180,000/μl were not used in the

multiple logistic regression model as index variables, because the statistical significance of the model became p>0.05.

Discussion

We investigated whether the risk of blood hypercoagulability with low ATIII activity could be predicted by the presence of a grade III placenta as well as other clinical factors including age, parity, BMI, Hct, low platelet counts after calculating effects of the intractions of these clinical factors with low AT III activity.

The prevalence of BMI≧28 was 31 cases (18.9%) and its odds ratio for ATIII activity<80% was 3.2, which was the greatest among the variables investigated in the present study. It is well known that obese pregnant women are at risk of thromboembolism [4,6,16]. The present results showed that pregnant women with BMI≧28 had three times greater risk of ATIII activity than those without this clinical factor. Low ATIII activity was found in obese subjects [17], although the detailed mechanism of this has not been clarified yet either in pregnant or non-pregnant women. Decreased fibrinolytic activity [18] or elevated free fatty acids may be implicated as a causative agent to reduce ATIII activity [19].

Obesity is frequently accompanied by hypertension, insulin resistance and increased plasma lipid levels both in pregnant and non-pregnant subjects [13,20]. Such metabolic disturbances occur in preeclampsia and might be responsible, at least in part, for endothelial dysfunction [21,22] that could lead to low ATIII activity due to intravascular coagulation. The average systolic blood pressure in the pregnant women with BMI≧28 was high compared with that in those with BMI<28 (p<0.01); 125±10.4 mmHg and 114.4±13.8 mmHg, suggesting that hypertensive tendency depends on high BMI. Thus, obese women in the present study seem to possess somewhat subclinical pathological conditions like preeclampsia, although the present subjects did not suffer from overt preeclampsia.

Systolic blood pressure≧136 mmHg was calculated as the second highest clinical risk factor for ATIII activity<80% in the present study. BMI was greater in the pregnant women with systolic blood pressure≧136 mmHg (27.3±2.9) than in those <136 mmHg (24.9±3.0) (p<0.01). Obese pregnant women tend to develop hypertension compared with non-obese pregnant women [23]. The mechanism of low ATIII activity in pregnant women with hypertensive tendency seems to be similar to that in those with high BMI. A relatively small number of healthy pregnant women, corresponding to the upper 10 percentile, seem likely to have a hemodynamic pathology similar to those with preeclampsia. This may be true for pregnant women with diastolic blood pressure≧84 mmHg. This is explained by the findings that the pregnant women with systolic blood pressure≧136 mmHg had a higher diastolic blood pressure (72.0±15.7 mmHg) than those with a blood pressure<136 mmHg (69.4±9.5 mmHg) (p<0.001).

Pregnancy is associated with blood hypercoagulability, and hypercoagulation is even more pronounced during the third trimester in healthy pregnant women [3]. A previous study showed a relationship between low ATIII activity and the presence of a grade III placenta [7]. A grade III placenta is a morphologically mature placenta because its prevalence, detected by ultrasonography, is high in full term and post-term pregnancies [24].

According to Kara et al [25], the echogenic areas of grade III placentas are histologically equivalent to a fibrinous layer, thus suggesting the presence of intervillous thrombosis. Furthermore, the above study found that calcificated areas represented fibrin deposition indicating hypercoagulation in high grade placentas. Therefore, increased blood coagulation at the tissue level of the placenta may be, at least in part, related to blood coagulation due to advances in placenta grade [7,25].

ATIII activity<70% is generally accepted as the lower pathological limit and indicates chronic disseminated intravascular coagulation. Such a condition is frequently observed in patients with preeclampsia [9]. However, ATIII activity<80% is a subclinical condition because 27% of the healthy pregnant women in the present study possessed low ATIII activity without pathologic symptoms. However, subclinical ATIII<80% should not be ignored. In pregnant women with naturally elevated coagulation activity, coagulation increases to abnormally high levels a few hours after placental separation [26]. This may contribute to a higher prevalence of thromboemobolic disease during the pueraperium as well as in caesarean delivery [1,2,4,5].

Therefore, the postpartal period is identified as a risky period for thromboembolic disease even in healthy women [6]. The present study showed that the presence of a grade III placenta correlated with ATIII activity<80% but did not depend on other clinical factors, as shown in **Table 2.**

The causes of hypercoagulability in healthy pregnant women predisposed to thromboembolic disease must be multifactorial [1,5-8]. In the present study using the multiple logistic regression method, the presence of BMI≧28, systolic blood pressure≧136 mmHg, and a grade III placenta were identified as risk factors for ATIII activity<80%: The presence of each risk factor increased the risk to above 2.4 times greater than the absence of these factors. However, it has not been well established how to treat pregnant women with each risk factor to prevent thromboembolic disease during pueruperium. To establish this, further study is necessary, including an investigation of the relevant roles of other factors in coagulation and fiblynolysis

in thromboembolic disease and their association with ATⅢ.

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