[ORIGINAL ARTICLE]

Title: Pregnancy-induced antithrombin deficiency

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ABSTRACT

OBJECTIVE: Some women exhibit a gradual decline in antithrombin activity during the late stage of pregnancy. This retrospective study was performed to better characterize the laboratory features and water metabolism of such women with pregnancy-induced antithrombin deficiency (PIATD).

METHODS: Among 1493 women who gave birth to a singleton infant at our institution, 114 women who developed PIATD and/or pregnancy-induced hypertension (PIH) were reviewed with respect to perinatal changes in laboratory variables (hematocrit value, fibrinogen, fibrinogen degradation product, D-dimer, uric acid, aspartate aminotransferase, lactate dehydrogenase) and body weight. PIATD was defined as a gradual decline in antithrombin activity to ≤ 65% of normal activity levels. One hundred and fourteen women with neither PIATD nor pregnancy-induced hypertension (PIH) and matched for the cesarean delivery rate were selected as a control group.

RESULTS: Of the 81 women who developed PIH, 19 (23.4%) also developed PIATD. Thirty-three women developed PIATD in the absence of PIH. Coagulation-fibrinolysis was significantly more enhanced and the postpartum reduction in the hematocrit value was significantly larger in women with PIATD, irrespective of the presence or absence of hypertension, than in women without PIATD. The postpartum decrease in body weight was significantly smaller in women with PIATD, irrespective of the presence or absence of hypertension, than in women without PIATD.

CONCLUSIONS: A decrease in antithrombin activity can occur in the absence of hypertension. Even in the absence of hypertension, a decreased plasma volume and enhanced coagulation-fibrinolysis seem to be notable characteristics in women with PIATD. The monitoring of antithrombin activity may be helpful for distinguishing

pregnant women with these insidious risks.

Key words: antithrombin, blood vessel permeability, coagulation-fibrinolysis, dehydration, pregnancy-induced hypertension

INTRODUCTION

Some women develop a gradual decline in antithrombin (AT) activity during the late stage of pregnancy**,** even in the absence of hypertension [9, 16]. This decline in AT activity continues until the day of or one day after delivery, and a prompt normalization of AT activity occurs postpartum in such patients with pregnancy-induced AT deficiency (PIATD) [9]. Because AT is the most important molecule for the anti-coagulation of the circulating blood, delivery delays may be dangerous in women with PIATD. Indeed, the risk of developing pulmonary embolism increases in women with known risk factors for PIATD, such as preeclampsia [6, 17, 18] or multi-fetal pregnancy [2, 6, 10, 16-18]. Further, women with PIATD are at risk of developing acute fatty liver of pregnancy [2, 9]. Indeed, the risk of developing acute fatty liver of pregnancy is reportedly high in women with a known risk factor for PIATD, such as preeclampsia or multi-fetal pregnancy [11]. Because a profoundly decreased AT level is seen in women with acute fatty liver of pregnancy at the time of presentation [2] and because the risk of a perinatal elevation in aspartate aminotransferase increases as the antenatal AT activity decreases [9], the monitoring of AT activity in women who exhibit a gradual decline in AT activity may help to avoid the development of acute fatty liver of pregnancy. These observations suggest that women with PIATD might constitute a high-risk pregnancy group, although the clinical and laboratory features of women with PIATD remain to be studied.

We introduced the measurement of AT activity into clinical practice in 2001 because of its possible usefulness in the management of women with complicated pregnancies. Indeed, AT determination resulted in the appropriate interventions in a patient with PIATD [7]. Our preliminary survey of patients with PIATD suggested a decreased

plasma volume or dehydration, as reported in women with preeclampsia [14, 15] and in a case with acute fatty liver of pregnancy [8]. Enhanced coagulation-fibrinolysis and coagulopathy are other well known laboratory features of preeclampsia [1, 4] and acute fatty liver of pregnancy [2], respectively. Prenatal shortage of the plasma volume or dehydration in the mother may influence postnatal changes in body weight and hematocrit value.

Accordingly, we conducted this retrospective review of the medical records of patients with PIATD, focusing on perinatal changes in coagulation-fibrinolysis and postpartum reductions in hematocrit value and body weight, to better characterize the laboratory features and water metabolism of women with PIATD.

METHODS

The medical records of 114 women diagnosed as having PIH or PIATD as well as 114 women with neither PIH nor PIATD were extracted from those of 1493 women with singleton pregnancies who gave birth at our hospital between January 2002 and December 2006. The 114 women with neither PIH nor PIATD were selected as cesarean section rate-matched control subjects. These 228 medical records were then retrospectively reviewed with respect to perinatal changes in body weight and laboratory data. At our antenatal clinic, all women were checked for blood pressure, body weight and protein in the urine using the dipstick method biweekly after 12 weeks of gestation. Pregnant women who developed hypertension (systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg) after 20 weeks of gestation were diagnosed as having PIH; some of these patients with PIH also developed proteinuria and thus were diagnosed as having preeclampsia. In this study, women with

preeclampsia were included in the PIH group. This study was approved by the institutional review board of our university hospital, and all the women gave their informed consent to participate in this study.

Women with PIH, proteinuria alone (≥ 1+ using the dipstick method), edema alone, excessive weight gain (> 500 g/week), or some other risk factors known to influence obstetrical outcome, such as an advanced age, obesity, and medical complications, were routinely screened for blood abnormalities, including complete blood cell counts, AT activity, serum levels of aspartate aminotransferase (AST), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), and serum levels of creatinine and uric acid (UA). In addition, these laboratory tests were performed routinely one day or immediately before delivery and on postpartum days 1 and 7 for all the patients who underwent cesarean delivery and in some patients with other risk factors. Our institution is a tertiary hospital that admits and manages mainly pregnant women with risk factors who have been referred from an area with approximately 40,000 births each year. Therefore, the cesarean section rate was approximately 45% during the study period and more than 80% of the pregnant women who delivered at our institution were screened at least once for AT activity. Pregnant women who exhibited a gradual perinatal decline in AT activity to ≤ 65% of the normal level were diagnosed as having PIATD. Women who were diagnosed as having PIATD antenatally were monitored closely. The body weights of the women who were admitted to our hospital were checked daily until the day of hospital discharge, which routinely occurred on postpartum day 8.

The plasma levels of D-dimer and the fibrinogen/fibrin degradation products (FDP) were measured using the latex agglutination assay (Mitsubishi Kagaku Iatron Inc., Tokyo, Japan). The plasma fibrinogen levels were measured using the thrombin clotting

time method (Sysmex Co., Kobe, Japan). The AT activity was measured using the chromogenic substrate assay (Daiichi Pure Chemicals Co., Tokyo, Japan). The platelet counts and hematocrit values were determined using an electronic particle counting system (Beckman Coulter Int., Fullerton, CA, USA). The UA level was determined using the uricase-peroxidase (colorimetric) coupled reaction (Serotec Int., Sapporo, Japan). The AST level was determined using the Japan Society of Clinical Chemistry (JSCC) transferable method (Serotec Int., Sapporo, Japan).

All data were presented as the mean or median values. Unpaired *t*-tests, Kruskal-Wallis tests, Mann-Whitney U tests, Wilcoxon tests and ANOVAs were used to analyze the results. χ^2 tests and Fisher exact tests were used to compare frequencies. A value of $p < 0.05$ was considered statistically significant. The statistical software package StatView 5.0 for Macintosh (SAS Institute Inc. Cary, NC, USA) was used for all data analyses.

RESULTS

Among the 114 women diagnosed as having PIH and/or PIATD, 62 women (54.4%) had PIH alone (PIH group, 28 of whom were preeclamptic), 33 women (28.9%) had PIATD alone (PIATD group), and 19 women (16.7%) had both PIH and PIATD (PIH+PIATD group, 12 of whom were preeclamptic) (Table 1). Thus, the frequency of preeclampsia did not differ significantly between the PIH group and the PIH+PIATD group (45.2% [28/62] vs. 63.2% [12/19], p=0.198). The frequency of PIATD also did not differ significantly between women with gestational hypertension and those with preeclampsia (17.1% [7/41] vs. 30.0% [12/40], p=0.198). The cesarean delivery rate in the control group was matched with the rates in the study groups to enable the

comparison of various parameters, therefore, the cesarean delivery rate did not differ significantly among the four groups. The length of gestation, the rate of preterm birth, the birth weight, the rate of intrauterine growth restriction (IUGR), and the rate of abruptio placentae differed significantly among the groups.

As expected, the clinical outcomes were significantly worst in the PIH+PIATD group. The PIH group had a significantly shorter duration of gestation, a higher frequency of preterm birth, a smaller infant weight, and a higher frequency of IUGR than the control group. However, these parameters did not differ significantly between the control and PIATD groups, except for the duration of gestation. The frequency of a reduced platelet count $< 150 \times 10^9$/L and the frequency of an elevated AST level > 40 IU/L were significantly higher in the groups with PIH and/or PIATD than in the control group. The frequency of an elevated LDH level > 400 IU/L was significantly higher in the PIH+PIATD group than in the other three groups.

AT activity decreased significantly with advancing gestation in all the groups (Table 2). AT activity that was already depressed two weeks prior to delivery decreased perinatally to ≤ 65% of normal in the PIATD and PIH+PIATD groups. The nadir of AT activity seen on postpartum day 1 returned to normal on postpartum day 7 in all the groups.

The FDP level immediately before delivery was significantly higher in the groups with PIATD than in the control group (Figure 1) and was significantly higher in the PIH+PIATD group than in the PIH group. The D-dimer level immediately before delivery was also significantly higher in the groups with PIATD than in the groups without PIATD. The D-dimer level on postpartum day 1 was significantly higher in the PIATD group than in the control group. The fibrinogen level decreased after delivery

in all the groups. The magnitude of the decrease (the difference between the values on -1/0 day and +1 day relative to delivery) was significantly larger in the groups with PIATD (53.2 ± 77.2 mg for PIH+PIATD group, 51.7 ± 83.8 mg for PIATD group) than in the groups without PIATD (20.8 ± 74.9 mg for PIH group, 21.7 ± 57.9 mg for control group), suggesting the peripartum hyperconsumption of fibrinogen in women with PIATD.

The serum urate level seemed to be elevated in patients with PIH and/or PIATD; throughout the study period, it was significantly higher in the PIH+PIATD group than in the PIH, PIATD, or control groups and in the PIH group than in the control group (Figure 2).

The hematocrit value continued to decrease until 7 days after delivery in the groups with PIATD, but not in the groups without PIATD (Figure 3a). The magnitude of the decreases on postpartum days 1 and 7 were significantly larger in the groups with PIATD than in the groups without PIATD (Figure 3b), suggesting prenatal hemoconcentration as a result of enhanced blood vessel permeability in women with PIATD.

Although the maternal body weight at delivery differed significantly among the four groups, the weight gain during pregnancy did not differ among the groups (Table 3). The total weight expulsed during labor (including the infant), the estimated blood loss, and the placenta were significantly larger in the control and PIATD groups than in the groups with PIH, reflecting the larger infants and placentas in the groups with PIATD. However, the postpartum decrease in body weight was significantly smaller in the groups with PIATD than in the control group on postpartum day 3 and was significantly larger in the PIH group than in the control group on postpartum day 7

(Figure 4).

Eighty-one women with PIH were divided into two groups, 41 with gestational hypertension and 40 with preeclampsia, and a subanalysis of the postpartum changes in hematocrit value and body weight was performed (Figures 5 and 6). Although the magnitude of the decreases in the hematocrit value on postpartum days 1 and 7 was significantly larger in women with preeclampsia than in women with gestational hypertension and normal controls (Figure 5), the postpartum decrease in body weight did not differ significantly among the three groups (Figure 6).

DISCUSSION

In this study, the degree of coagulation-fibrinolysis was consistently more exaggerated in women with PIATD than in women without PIATD. The larger peripartum decrease in fibrinogen supports the enhancement of coagulation-fibrinolysis in these women with PIATD. Exaggerated coagulation-fibrinolysis is a well-known abnormality in patients with PIH [1, 4]. In this study, women with PIH were divided into a PIH+PIATD group and a PIH group according to the presence or absence of PIATD. The former group exhibited a more exaggerated degree of coagulation-fibrinolysis than the latter group. In addition, women with PIATD alone showed a more exaggerated degree of coagulation-fibrinolysis than the women with PIH alone or the control women in this study. Thus, the presence of PIH alone did not have a large effect on coagulation-fibrinolysis in the absence of PIATD. Reduced AT activity in women with PIH is another well-known phenomenon [6, 17, 18], and our study also demonstrated that as many as 19 (23.5%) of 81 women with PIH also had PIATD. These results support the enhanced coagulation-fibrinolysis seen in women

with PIH described in earlier reports [4] and reflect the presence of coagulation-fibrinolysis in women with PIATD who are inevitably included amongst women with PIH.

This study demonstrated that women with PIATD exhibit a larger decrease in their hematocrit values and a smaller decrease in their body weights postnatally than women without PIATD. An increase in water retention is a normal physiological alteration during pregnancy. Clearly demonstrable pitting edema of the ankles and legs is seen in most pregnant women, especially during the late stages of pregnancy [3]. Edema resulting from the retention of excess water in the interstitial space can be massive in women with PIH, mainly because of the increased blood vessel permeability [5, 12], and usually results in hemoconcetration and a decrease in the circulating plasma volume in patients with PIH [14, 15]. The process involved in the retention of water is reversed by parturition, and excess water in the interstitial space returns into the intravascular space, resulting in a fall in the hematocrit value, and then is excreted as urine. The extent of the postpartum decrease in the hematocrit value may therefore reflect the degree of antenatal hemoconcentration and the decrease in the circulating plasma volume. In this study, women with PIATD, irrespective of the presence or absence of hypertension, showed a larger and sustained decrease in the hematocrit value after delivery, suggesting a more severe antenatal hemoconcentration and decrease in the plasma volume in women with PIATD than in women without PIATD. Although women with PIH showed a relatively high absolute hematocrit value compared with women without PIH antenatally, the changes in the postnatal hematocrit value differed according to the presence or absence of PIATD. Women with PIH alone showed a pattern of change in the hematocrit value similar to that observed in the control women.

These results may suggest that the decrease in the plasma volume described in women with PIH in earlier reports [14, 15] may have reflected the plasma volume in women with PIATD who have been included in the group with PIH.

The postpartum decrease in body weight is expected to be relatively small in women who have suffered from antenatal dehydration and a decrease in the plasma volume. Indeed, the postpartum decrease in body weight was consistently smaller in women with PIATD irrespective of the presence or absence of hypertension than in women without PIATD, supporting the above-mentioned "severe antenatal hemoconcentration and decrease in plasma volume in women with PIATD". Women with PIH alone showed the largest decrease in body weight. The reason for this finding may be explained as follows. Because the pattern of change in the hematocrit value in women with PIH alone was similar to that observed in the control women, the women with PIH alone may not have experienced a decrease in the circulating plasma volume but may have had excess water in the interstitial space as a result of increased blood vessel permeability. The intake of water may have had compensated for the leakage of plasma into the extravascular space in these women with PIH alone. This excess water may have returned to the intravascular space after delivery and may have then been excreted promptly as urine (since a shortage in the circulating plasma volume did not exist), resulting in the relatively large postpartum decrease in body weight observed in the women with PIH alone. In contrast, an insufficient intake of water or an inappropriate urine output may have caused a decrease in the total body water in women with PIATD.

The magnitude of the postpartum decrease in the hematocrit value was significantly larger in the 40 women with preeclampsia than in the 41 women with gestational

hypertension, but the postpartum decrease in body weight did not differ significantly between the two groups. However, the postpartum decrease in body weight differed in the two hypertensive women groups divided by the presence or absence of PIATD (Figure 4). These results suggested that women with preeclampsia may have a larger plasma volume reduction, consistent with the results of an earlier study [14], and further that these women may have had a larger increase in interstitial fluid, compared with women with gestational hypertension. The presence of PIATD, rather than the presence of proteinuria, might be a better predictor of a decrease in interstitial fluid as well as a decrease in circulating plasma in hypertensive pregnant women.

In this study, the incidence of PIATD was 23.5% (19/81) in women with PIH (17.1% [7/41] for women with gestational hypertension and 30.0% [12/40] for women with preeclampsia). Although all the women without hypertension were not screened for AT activity, PIATD was detected in 33 (2.3%) out of 1412 women without hypertension. This incidence among women without hypertension might not be representative of the incidence among women with uncomplicated pregnancies, since a considerable number of the women in our study population had risk factors other than hypertension and because the results of our preliminary study (unpublished data) suggested that the incidence of PIATD was 1.0% among women with uncomplicated singleton pregnancies.

In conclusion, some women exhibit a gradual perinatal decline in AT activity to ≤ 65% of normal, even in the absence of hypertension. Such women with a gradual decline in AT activity to ≤ 65% of normal suffer from exaggerated coagulation-fibrinolysis and may also suffer from a decreased interstitial fluid and circulating plasma volume. The monitoring of AT activity may be helpful in

293 distinguishing women with these insidious risks.

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FIGURE LEGENDS

Figure 1: Perinatal changes in FDP, D-dimer, and fibrinogen. ○, Control group (n=114); Δ, PIH group (n=62); ●, PIATD group (n=33); ▲; PIH+PIATD group (n=19). Significant differences were seen as follows: Control vs. PIATD, PIH+PIATD for FDP immediately before delivery; PIH vs. PIH+PIATD for FDP immediately before delivery; PIH vs. PIATD, PIH+PIATD for D-dimer immediately before delivery; Control vs. PIATD, PIH+PIATD for D-dimer immediately before delivery; Control vs. PIATD for D-dimer on postpartum day 1.

Figure 2: Perinatal change in serum urate. ○, Control group (n=114); Δ, PIH group (n=62); ●, PIATD group (n=33); ▲; PIH+PIATD group (n=19). Significant differences were seen as follows: PIH+PIATD vs. PIH, PIATD, Control at any point; PIH vs. Control at any point; Control vs. PIATD immediately before delivery.

Figure 3: Perinatal change in hematocrit value (a) and its net decreases on postpartum days 1 and 7 (b). ○, Control group (n=114); Δ, PIH group (n=62); ●, PIATD group (n=33); ▲; PIH+PIATD group (n=19); *, $p < 0.05$ between groups; **, $p < 0.01$ between groups. Significant differences were seen as follows (for Fig. 4a): Control vs. PIH at 2 weeks before delivery; Control vs. PIH+PIATD immediately before delivery; PIATD vs. PIH, PIH+PIATD immediately before delivery; PIATD vs. Control, PIH on postpartum day 1; Control vs. PIH on postpartum day 1; PIATD vs. Control, PIH on postpartum day 7; PIH vs. PIH+PIATD on postpartum day 7.

Figure 4: Postpartum decease in maternal body weight (a) and net decreases on

postpartum days 3 and 7 (b). ○, Control group (n=114); Δ, PIH group (n=62); ●, PIATD group (n=33); ▲; PIH+PIATD group (n=19); *, $p < 0.05$ between groups. The patterns of maternal body weight reduction (a) differed significantly among the four groups, as shown using an ANOVA.

Figure 5: Perinatal changes in hematocrit values (a) and net decreases on postpartum days 1 and 7 (b). ○, Control group (n=114); ●, Gestational hypertension group (n=41); ▲; Preeclampsia group (n=40); *, $p < 0.05$ between groups; **, $p < 0.01$ between groups. Significant differences were seen (for Fig. 5a) between the control vs. gestational hypertension group and between the control vs. preeclampsia group before delivery.

Figure 6: Postpartum deceases in maternal body weight and net decreases on postpartum days 3 and 7 (b). ○, Control group (n=114); ●, Gestational hypertension group (n=41); ▲; Preeclampsia group (n=40). No significant differences were seen among the three groups.

Figure
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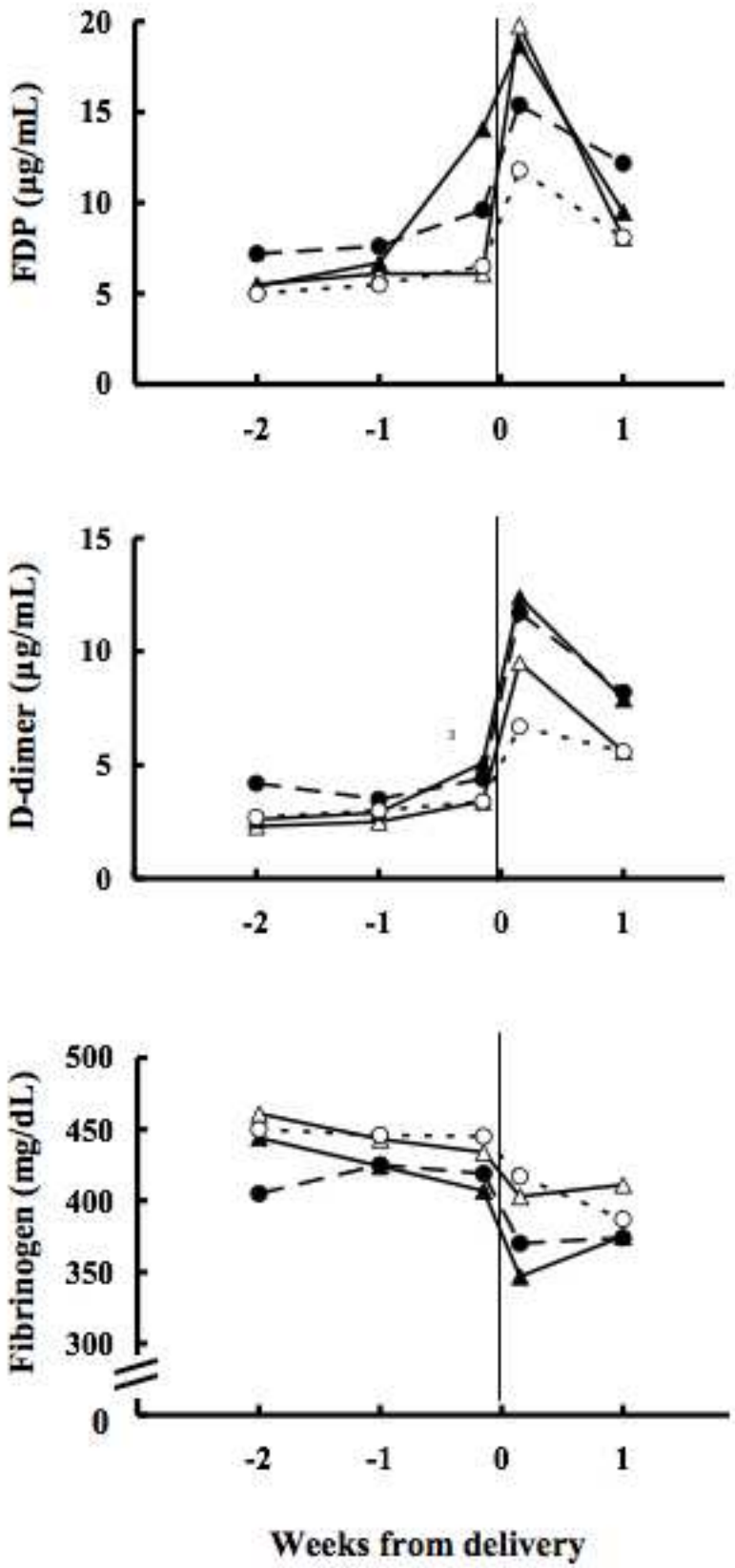
Figure 1 Morikawa M, *et.al.*



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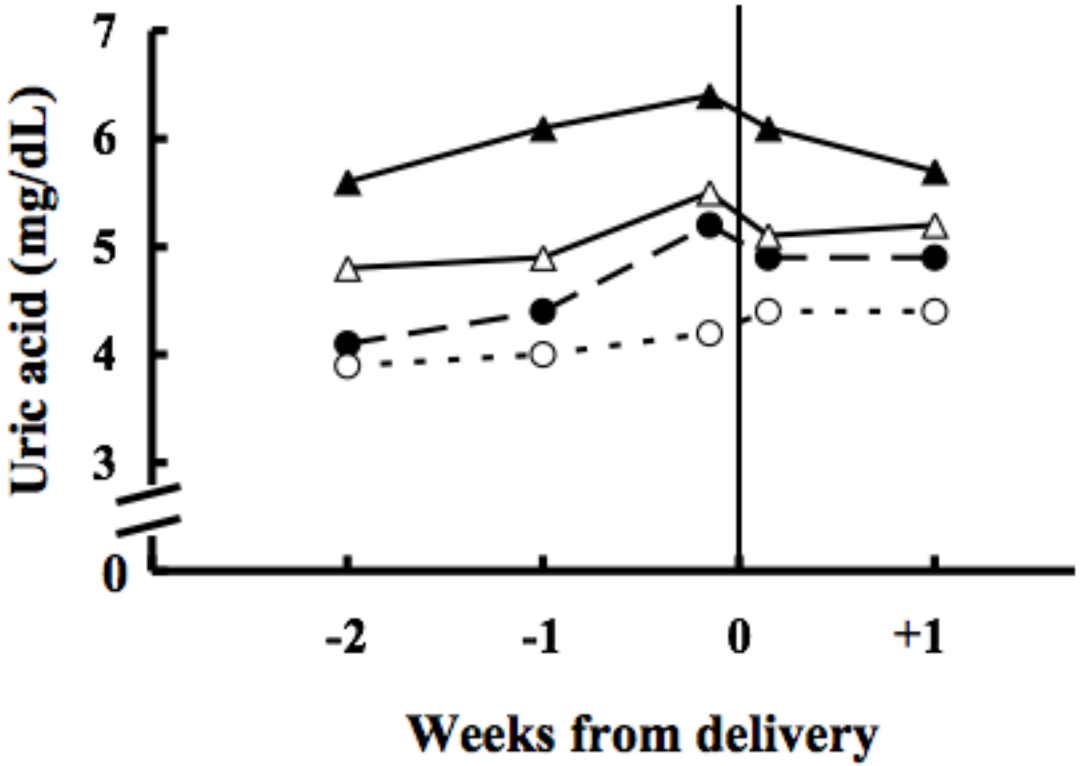

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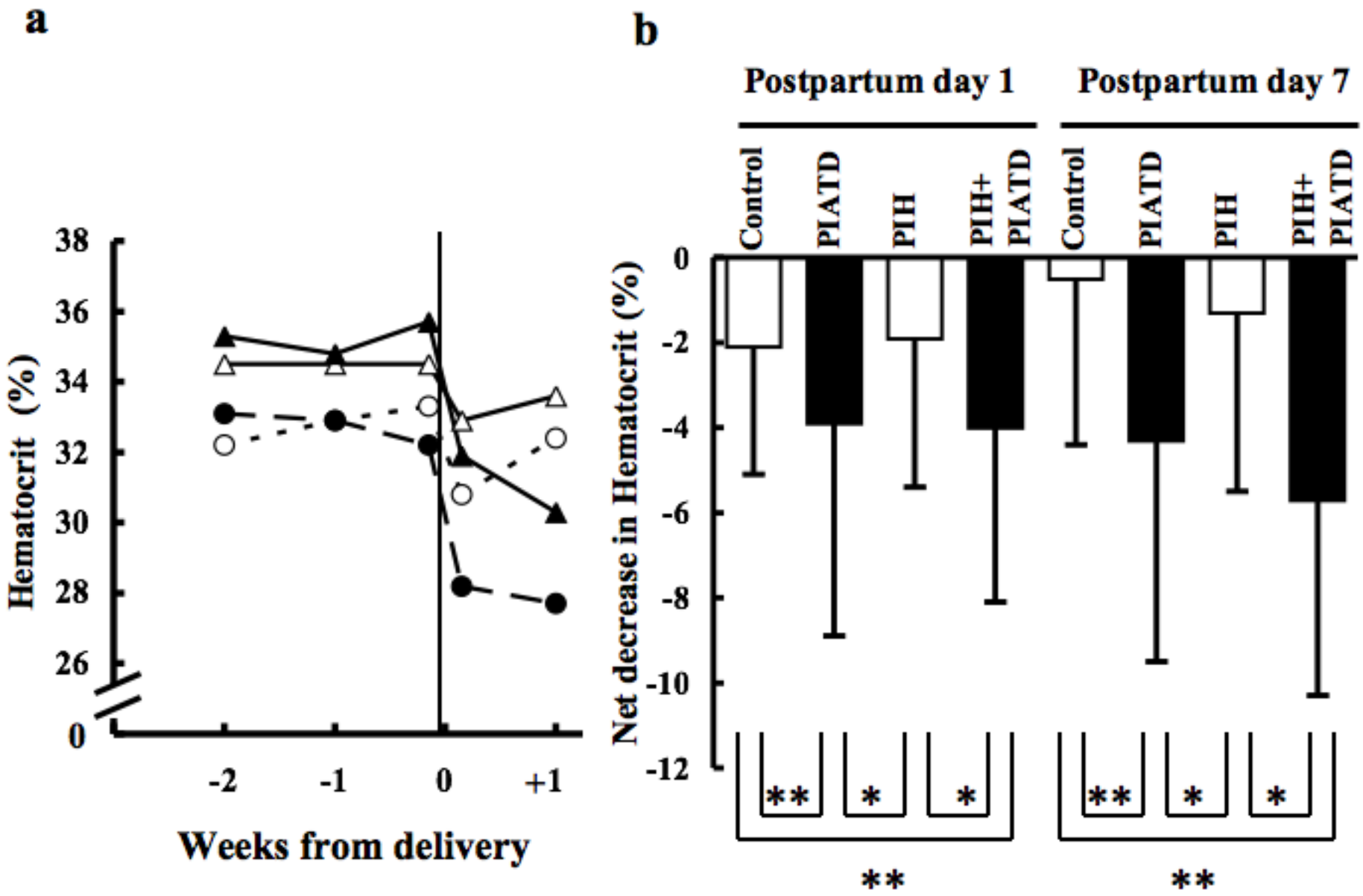

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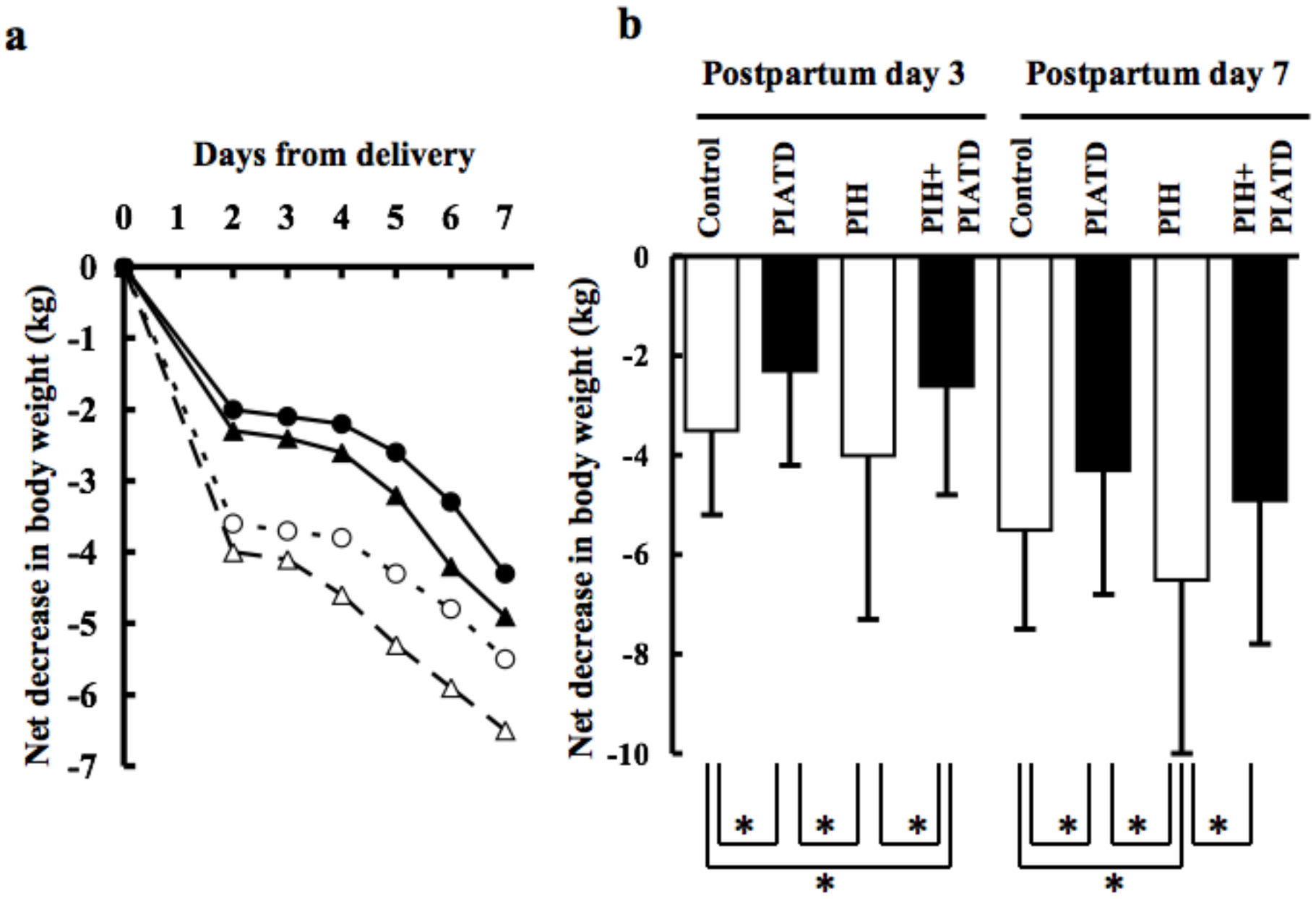

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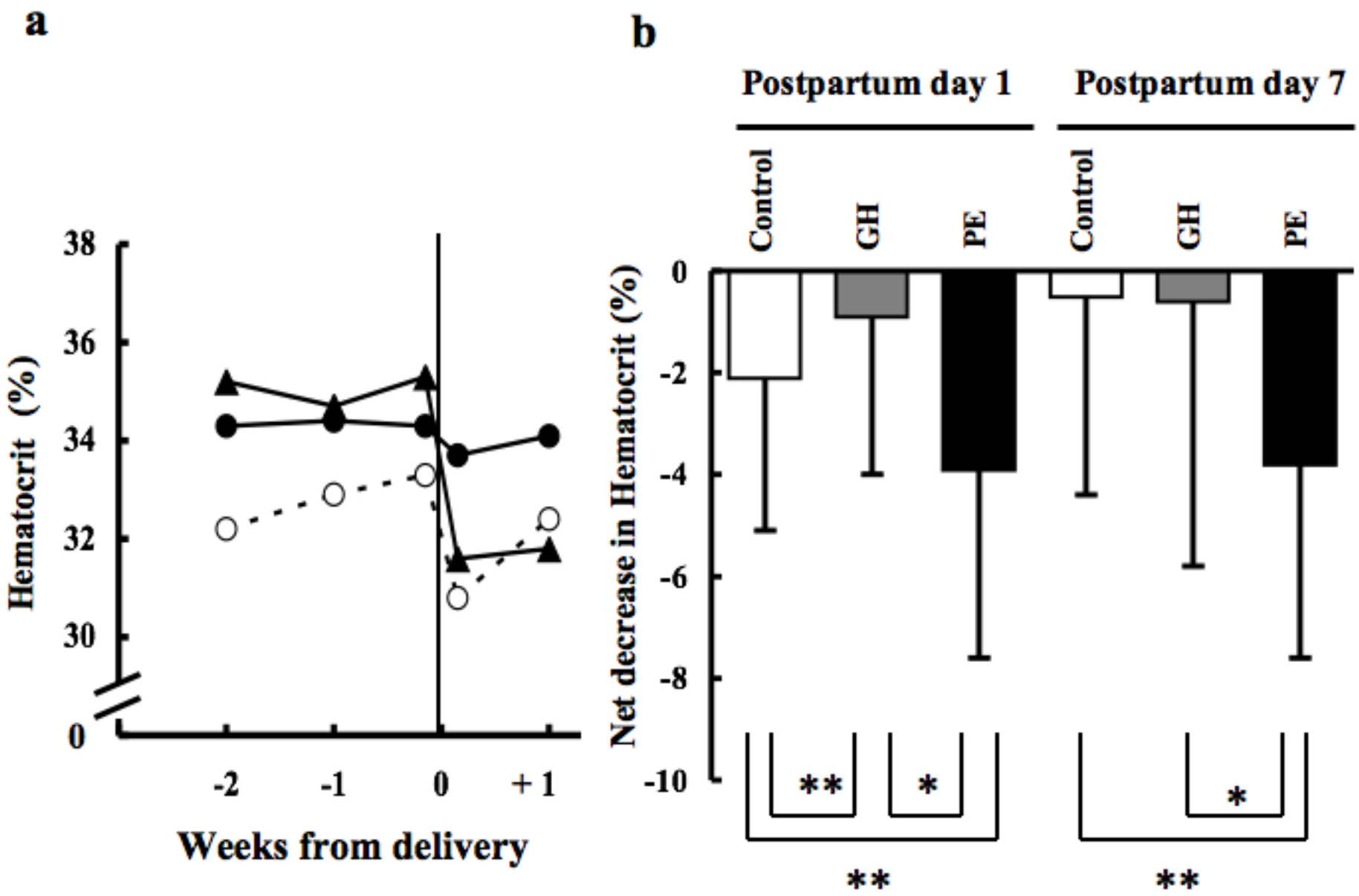

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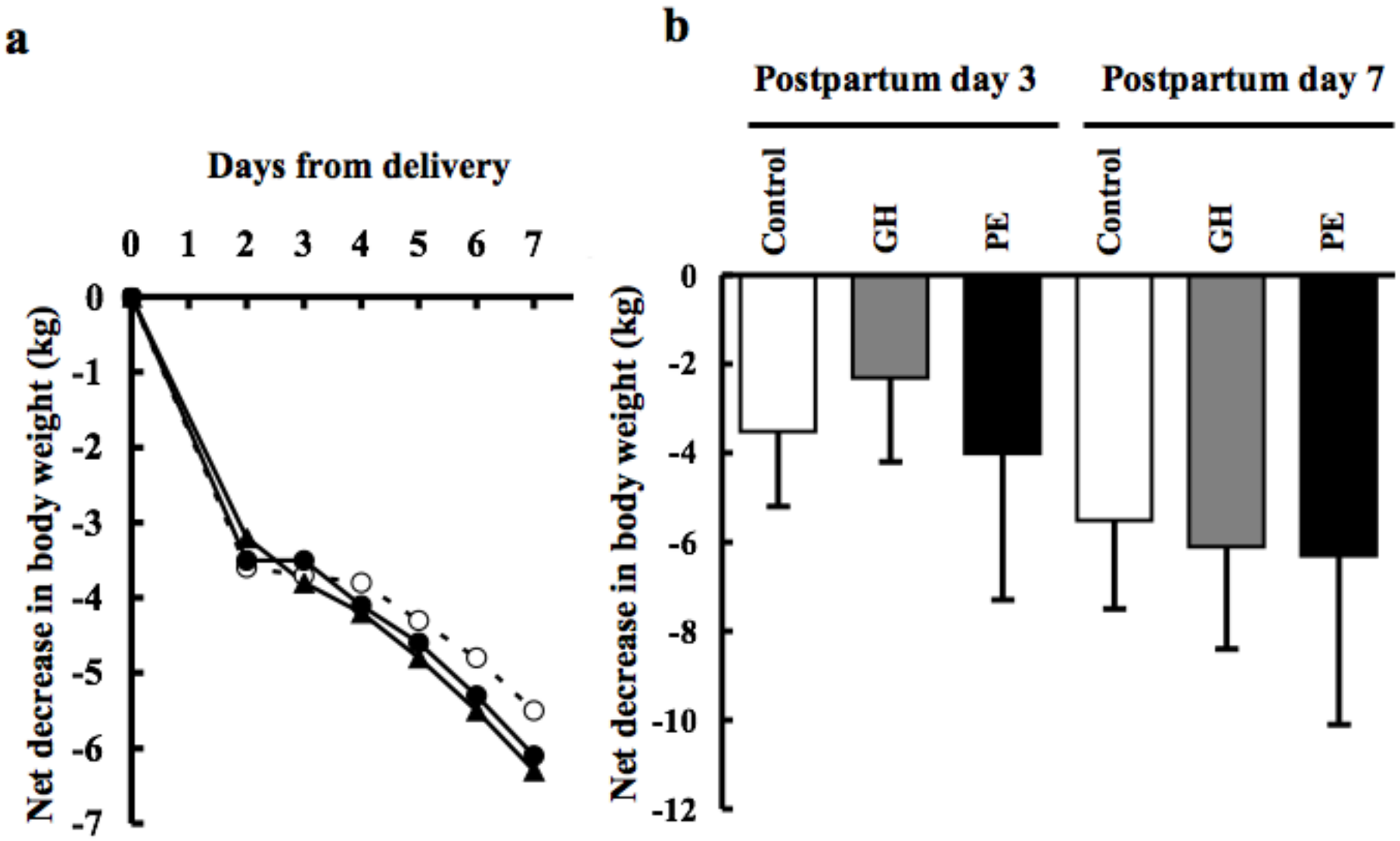

Table
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Table 1. Clinical backgrounds of four groups

	*Control (n=114) [a]	PIATD (n=33) [b]	PIH (n=62) [c]	PIH+PIATD (n=19) [d]	*p value* <0.05
Maternal age (years)	30.5±5.7	33.5±6.3	33.4±5.0	31.6±6.4	a vs b,c
Nulliparous (%)	57.0	63.6	61.3	84.2	NS
Cesarian delivery (%)	70.2	87.9	69.4	78.9	NS
Gestational week at delivery (GW)	37.3±2.0	36.8±3.1	35.6±3.3	34.2±2.7	a vs b,c,d / b vs d
Preterm delivery (%)	16.7	27.3	45.2	78.9	a vs c,d / b,c vs d
Birth weight (g)	2777±498	2801±788	2249±831	1978±579	a vs c,d / b vs c,d
IUGR (%)	4.4	6.1	27.4	26.3	a vs c,d
Abruptio placenta (%)	0.0	3.0	3.2	15.8	a vs d
Platelet count < $150x10^9$/L (%)	0.0	21.2	12.9	36.8	a vs b,c,d / c vs d
AST > 40 IU/L (%)	6.1	12.1	14.5	12.9	a vs b,c,d
LDH > 400 IU/L (%)	5.2	6.1	9.7	31.6	d vs a,b,c

* , Cesarean section rate - matched control; NS, not significant; GW, gestational week;
IUGR, intrauterine growth restriction; AST, aspartate aminotransferase; LDH,lactate dehydrogenase
Data are presented as the mean ± SD or frequency (%)

Table

Table 2. Change in antithrombin activity (%)

	Dates from delivery					
	-2 weeks [a]	-1 week [b]	-1 day [c]	+1 day [d]	+1 week [e]	*p-value <0.05*
1. Control (n=114)	95.8 ± 9.7	95.8 ± 12.8	93.9 ± 13.2	82.9 ± 13.0	107.2 ± 15.0	*b vs c* *d vs a, b, c, e*
2. PIATD (n=33)	81.3 ± 11.8	83.4 ± 13.5	76.1 ± 13.0	59.5 ± 4.1	93.7 ± 12.8	*b vs c* *d vs a, b, c, e*
3. PIH (n=62)	90.6 ± 11.6	91.0 ± 14.1	89.4 ± 13.3	83.3 ± 11.8	111.8 ± 12.8	*d vs a, b, c, e*
4. PIH+PIATD (n=19)	79.5 ± 7.4	69.8 ± 8.5	67.1 ± 13.1	64.4 ± 13.2	99.2 ± 13.0	*a vs b, c, d* *e vs b, c, d*

Table

Table 3 . Factors influencing postpartum decrease in maternal body weight

	Control [a] (n=114)	PIATD [b] (n=33)	PIH [c] (n=62)	PIH+PIATD [d] (n=19)	*p value <0.05*
Weight gain (kg) [#]	8.97 ± 4.18	8.96 ± 4.36	8.01 ± 5.83	8.40 ± 4.43	*NS*
Weight at delivery (kg)	62.9 ± 10.8	61.6 ± 9.7	71.1 ± 15.2	65.2 ± 11.5	*c vs a, b*
Sum of expulsed weight (kg)	4.20 ± 0.97	4.38 ± 1.13	3.39 ± 1.01	3.32 ± 1.18	*a vs c, d*
					b vs c, d
Infant (kg)	2.78 ± 0.50	2.80 ± 0.79	2.25 ± 0.83	1.98 ± 0.58	*a vs c, d*
					b vs c, d
Blood loss (kg) [*]	0.83 ± 0.64	0.95 ± 0.59	0.62 ± 0.41	0.90 ± 0.90	*NS*
Placenta (kg)	0.59 ± 0.13	0.63 ± 0.13	0.52 ± 0.18	0.44 ± 0.11	*d vs a, b*

#, Weight gain during pregnancy ; * , Estimated blood loss including amniotic fluid ; NS, not significant.
Data are presented as the mean ± SD