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Coagulation-fibrinolysis in twin pregnancies

[ORIGINAL ARTICLE]

Coagulation-fibrinolysis is more enhanced in twin than in singleton pregnancies

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ABSTRACT

Aims: To evaluate that the coagulation-fibrinolysis in late pregnancy in women with twin pregnancies is more pronounced than in women with singleton pregnancies.

Patients and Methods: The plasma levels of D-dimer, fibrinogen/fibrin degradation products (FDP), and fibrinogen, the platelet count, and the antithrombin activity were assessed from 3 weeks before delivery until postpartum day 7 in 48 women (24 singleton and 24 twin pregnancies) without preeclampsia who underwent cesarean sections. The women with singleton or twin pregnancies gave birth at 37.3 ± 1.2 weeks or 35.2 ± 1.4 weeks, respectively.

Results: Compared with the women who had singleton pregnancies, the prenatal D-dimer and FDP levels were consistently and significantly higher and a significantly larger number of women exhibited prenatal levels of D-dimer $> 5.0 \mu\text{g/mL}$ and of FDP $> 10.0 \mu\text{g/mL}$ among the women with twin pregnancies. A significantly larger number of women with twin pregnancies exhibited a prenatal level of fibrinogen $< 420 \text{ mg/mL}$. The prenatal antithrombin activity in the plasma was significantly lower and a significantly larger number of women exhibited a prenatal level of antithrombin activity $< 70\%$ among the women with twin pregnancies.

Conclusions: Coagulation-fibrinolysis is more enhanced in women with twin gestation than in women with singleton gestation.

Key Words: antithrombin activity, D-dimer, coagulation, fibrinolysis, twin

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Over the past two decades, the frequency of multiple births, especially twins, has increased dramatically in many industrialized countries. For instance, the rate of twin pregnancies in the United States increased by 42% between 1980 and 1997 [1]. Twin pregnancy differs from singleton pregnancy in many aspects. The length of gestation is much shorter, and the perinatal mortality rate is much higher for twin pregnancies than for singleton pregnancies [2]. In general, the degree of physiological change in the mother is also greater in women with twin pregnancies than in women with singleton pregnancies. For example, the normal expansion in maternal blood volume is greater in women with twin pregnancies [3]; the average increase in late pregnancy is about 40% to 50% with a single fetus, whereas it is about 50% to 60% with twins [3]. Better understanding of the physiology associated with twin pregnancy may be important for the management of women with twin pregnancies.

The hemostatic balance is physiologically displaced toward hypercoagulability in normal singleton pregnancies [4]. This hypercoagulability is more exaggerated in women with preeclampsia [5,6], in whom the risk of pulmonary thromboembolism is increased [7]. Because women with twin pregnancy are more likely to develop both preeclampsia [8] and pulmonary thromboembolism [7], compared with women with singleton pregnancies, hypercoagulability may further be exaggerated in women with twin pregnancies. However, this issue has not been extensively studied.

We compared perinatal changes in coagulation-fibrinolysis parameters, like the D-dimer, FDP, and fibrinogen levels, the platelet counts, and the antithrombin activity levels, between women with singleton and those with twin pregnancies.

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Patients and Methods

A total of 48 women (24 with singleton pregnancies and 24 with twin pregnancies) who gave birth by cesarean section at our hospital between 2001 and 2004 were studied. All 48 women gave their informed consent to participate in this study, and their D-dimer, FDP, and fibrinogen levels, platelet counts, antithrombin activity, and Ht were determined at 3 weeks, 2 weeks, one week, and one day before delivery, the day after the cesarean section, and on postpartum days 3 and 7. Twenty-four patients with singleton pregnancies underwent cesarean section for various reasons: previous cesarean in 10 patients, breech presentation in 3 patients, dystocia in 3 patients, uterine fibromata in 3 patients, fetal malformations in 3 patients, impaired lung function in one patient, and spinal cord injury in one patient. Thus, none of the patients in the singleton group had preeclampsia. Cesarean section is liberally used for women with twin pregnancies in our hospital. None of the women with twin pregnancies had preeclampsia, but two of them had gestational proteinuria.

The patient characteristics are shown in Table 1. The mean age and number of nulliparous women did not differ between the two groups. Three of the 24 women (12.5%) with singleton pregnancies gave birth before 37 weeks of gestation: one at 35 weeks because of breech presentation and premature membrane rupture, one at 36 weeks because of a huge uterine fibromata, and one at 36 weeks because of impaired lung function. Seventeen women (70.8%) with twin pregnancies gave birth before 37 weeks because of increased uterine activity.

The estimated blood loss, including amniotic fluid, during the cesarean section was significantly larger among the women with twin pregnancies than among the women with singleton pregnancies. Neither the body mass index [body weight /

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(height)²] at the time of cesarean section nor the birth weight differed between the two groups. None of the infants in either group had an Apgar score of less than 8 at 5 minutes.

Plasma levels of D-dimer and fibrinogen/fibrin degradation products (FDP) were measured using the latex agglutination assay (Mitsubishi Kagaku Iatron Inc., Tokyo, Japan). Plasma fibrinogen level was measured using a thrombin clotting time method (Sysmex Co., Kobe, Japan). Antithrombin activity was measured using the chromogenic substrate assay (Daiichi Pure Chemicals Co., Tokyo, Japan). Platelet counts and Ht were determined using an electronic particle counting system (Beckman Coulter Int., Fullerton, CA, USA).

The data are presented as the means or medians. Paired Wilcoxon and Mann-Whitney U tests were used to analyze the results. A χ^2 test was used to compare frequencies. $P < 0.05$ was considered statistically significant.

Results

Changes in the mean and median values are shown in Figure. 1 and Table 2, respectively. The plasma D-dimer levels gradually increased during the period before delivery and peaked on postpartum day 1 in both groups. The prenatal D-dimer level was consistently and significantly higher in women with twin pregnancies than in women with singleton pregnancies. Similar patterns in perinatal plasma FDP levels were also observed. The prenatal FDP level was also consistently and significantly higher in women with twin pregnancies than in women with singleton pregnancies. In contrast, the plasma fibrinogen level appeared to be lower in women twin than pregnancies than in women with singleton pregnancies, and a nadir value was observed on postpartum day 1 in both groups (Figure. 1). The median value of plasma fibrinogen

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was significantly lower at one week before delivery and on postpartum day 3 in the twin group than in the singleton group (Table 2). The prenatal Ht value (two and one weeks prior to delivery) was significantly lower in women with twin pregnancies than in women with singleton pregnancies. The platelet count gradually decreased during the period before delivery and increased promptly after delivery in both groups. No significant difference in platelet count was observed between the two groups. Antithrombin activity gradually decreased during the period before delivery, and a nadir value was observed on postpartum day 1; the antithrombin activity had normalized by one week after delivery in both groups. The prenatal antithrombin activity level was significantly lower, except at 2 weeks before delivery, in women with twin pregnancies than in those with singleton pregnancies. Mean prenatal values of these parameters according to gestational age was shown in Figure. 2. Difference between the two groups was more pronounced.

Compared with women with singleton pregnancies, a significantly larger number of women with twin pregnancies exhibited high prenatal levels of D-dimer $> 5.0 \mu\text{g/mL}$ and FDP $> 10.0 \mu\text{g/mL}$ (Table 3). Furthermore, a significantly larger number of women with twin pregnancies exhibited prenatal fibrinogen levels of $< 420 \text{ mg/dL}$ and antithrombin activity levels of $< 70\%$.

Discussion

The progressive increase in prenatal D-dimer levels during late gestation and the marked elevation soon after delivery seen in women with singleton pregnancies in this study were consistent with the results of earlier studies in singleton pregnancies

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[9-14]. Our longitudinal study demonstrated that the prenatal plasma levels of D-dimer and FDP were consistently higher in women with twin pregnancies than in women with singleton pregnancies, although the deliveries took place approximately 2 weeks earlier in the twin group than in the singleton group. Because the plasma D-dimer level increases as gestation advances [9-13], as confirmed in this study, the difference in the number of gestational weeks at the time of delivery between the two groups further supports our conclusion which was also demonstrated in the comparison of variables plotted against gestational weeks, although there were several missing data in this analysis (Figure. 2). To our best knowledge, only one other report has dealt with this issue: the authors compared the plasma D-dimer levels in women with singleton and twin pregnancies at 30 weeks of and found a significantly higher plasma D-dimer level among the women with twin pregnancies [15].

Because D-dimer results from the digestion of cross-linked fibrin by plasmin, its plasma level provides information on the degree of fibrin formation and secondary fibrinolysis activated by the enhanced fibrin formation, thereby partially reflecting the coagulation activity. In contrast, because FDP includes the split products of both fibrinogen and fibrin, an enhanced level of FDP does not necessarily reflect the degree of fibrin formation [16]. However, the elevations in both the D-dimer and the FDP levels indicate both enhanced coagulation activity and enhanced fibrinolytic activity. Thus, our results suggest that the enhanced coagulation-fibrinolysis activity that normally occurs during late gestation was more exaggerated in women with twin pregnancies than in women with singleton pregnancies.

The mean plasma fibrinogen level appeared to be lower in women with twin pregnancies than in women with singleton pregnancies in this study, although the

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difference did not reach a significant level possibly because of the relatively small number of study subjects. The lower level of fibrinogen in the twin group may be partly explained by the larger degree of hemodilution in the twin group than in the singleton group [3], as suggested by the changes in the Ht value. However, based on the changes in the D-dimer and FDP levels, the lower plasma fibrinogen level may partially reflect hyperconsumption of fibrinogen in women with twin pregnancies, compared with women with singleton pregnancies. This postulation is also supported by the fact that the nadir value of fibrinogen was seen on postpartum day 1, the day on which the D-dimer and FDP levels peaked in both the singleton and twin groups.

Thrombin generation, as monitored by the level of thrombin-antithrombin complex, is enhanced during the late stage of normal pregnancies [17, 18]. Antithrombin is the most important inhibitor of coagulation and is used to inactivate activated coagulation factors like Xa and thrombin. Therefore, antithrombin activity is reduced in the presence of enhanced thrombin generation in patients with disseminated intravascular coagulation [19]. An enhancement in thrombin generation and a reduction in antithrombin activity has also been reported in women with preeclampsia [18,20]. Prenatal antithrombin activity gradually decreased and was significantly lower in the twin group than in the singleton group in this study, consistent with an earlier report by Tsunoda et al. [21] in which they demonstrated that an antithrombin activity of 111% at 28.6 weeks of gestation decreased to 91% at 35.2 weeks of gestation in women with twin pregnancies, while the decrease was much smaller (from 111% to 106%) in women with singleton pregnancies. These results may also strengthen the concept that coagulation is exaggerated in women with twin pregnancies, compared with women with singleton pregnancies. The larger degree of decrease in antithrombin activity may

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have reflected more pronounced thrombin generation in the twin group. Because thrombin converts fibrinogen into fibrin, plasma level of fibrinogen may be decreased in such a condition, as suggested in this study.

In conclusion, during the advanced stage of gestation, the plasma levels of D-dimer and FDP were higher and the plasma level of antithrombin activity was lower in women with twin pregnancies than in women with singleton pregnancies. All our results indicated that the enhanced coagulation-fibrinolysis activity that normally occurs during late gestation was more exaggerated in women twin pregnancies than in women with singleton pregnancies. This may partially explain why women with multifetal pregnancies are at a 3- to 4-fold increased risk of pulmonary embolism during the third trimester and peripartum compared with women with singleton pregnancies [7].

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Figure Legends

Figure 1. Perinatal changes in the plasma levels of D-dimer, FDP (fibrinogen/fibrin degradation products), and fibrinogen, and in the hematocrit value, platelet count, and antithrombin activity of peripheral blood from 24 women with singleton (○) and 24 women with twin (●) pregnancies

Data are presented as the mean.

*, $p < 0.05$ and **, $p < 0.01$ for singleton pregnancies vs. twin pregnancies.

Figure 2. Prenatal values of the plasma levels of D-dimer, FDP (fibrinogen/fibrin degradation products), and fibrinogen, and in the hematocrit value, platelet count, and antithrombin activity of peripheral blood

Number of missing data was 2, 2, 2, and 2 for women with singleton pregnancies (○) at 33 weeks, 34 weeks, 35 weeks, and 36 weeks, respectively. Corresponding number of missing data for women with twin (●) pregnancies was 1, 4, 7, and 12, respectively.

Data are presented as the mean.

*, $p < 0.05$ and **, $p < 0.01$ for singleton pregnancies vs. twin pregnancies.

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Table Legends

Table 1. Patient characteristics of 24 women with singleton pregnancies and 24 women with twin pregnancies

Data are presented as the mean $\pm$ SD and the ranges.

BMI, body mass index [body weight, kg / (height, m)²]

Table 2. Median and range of hemostasis parameters in 24 women with singleton pregnancies and 24 women with twin pregnancies

FDP, fibrinogen/fibrin degradation products

Data are presented as the median and range.

Table 3. Positive rate (%) of hemostasis parameters in 24 women with singleton pregnancies and 24 women with twin pregnancies

FDP, fibrinogen/fibrin degradation products

*, $p < 0.05$ and **, $p < 0.01$ for singleton pregnancies vs. twin pregnancies.

Table 1. Patient characteristics of 24 women with singleton pregnancies and 24 women with twin pregnancies

	Twin pregnancy (n=24)	Singleton pregnancy (n=24)	p value
Age (years)	32.1±5.2 [18-41]	31.1±4.6 [24-41]	NS
Nullipara (%)	70.8	54.2	NS
Gestational week at delivery (weeks)	35.2±1.4 [32-37]	37.3±1.2 [35-41]	NS
Preterm delivery (%)	70.8	12.5	<0.0001
Blood loss at delivery (g)	1354±554 [280-2400]	869±510 [155-1790]	0.006
BMI at delivery	24.6±4.0 [19.9-37.5]	26.2±4.7 [19.2-39.2]	NS
Birth weight (g)	2144±392 [1325-2930]	2771±499 [1925-4125]	NS
Apgar score < 8 (5 min) (%)	0.0	0.0	NS

Data are presented as the mean ± SD and the ranges, BMI: body mass index [body weight, kg / (height, m)²]

Table 2. Median and range of hemostasis parameters in 24 women with singleton pregnancies and 24 women with twin pregnancies

Days from delivery		-3weeks	-2weeks	- 1week	-1day	+1day	+3days	+7days
D-dimer (μ g/mL)	Singleton	2.4** 0.7-4.9	2.5** 0.9-6.3	3.2* 0.8-6.4	3.1* 1.2-7.4	4.5* 1.8-36.3	3.2 1.4-9.7	4.8 1.8-27.4
	Twin	3.8 0.7-12.6	3.7 2.1-12.3	4.5 2.1-12.3	5.1 1.6-10.9	8.4 3.3-40.8	3.5 1.7-37.2	5.7 1.9-29.7
FDP (μ g/mL)	Singleton	4.4** 2.6-14.4	5.0** 2.7-19.6	5.0** 2.6-23.6	5.6** 2.6-17.7	8.2** 2.6-32.7	5.9* 3.1-11.3	6.9 3.4-33.4
	Twin	7.2 4.0-17.7	7.9 4.0-15.4	9.0 4.3-17.9	8.6 4.6-23.3	14.9 6.2-72.0	7.0 3.9-40.2	8.0 3.2-39.0
Fibrinogen (mg/dL)	Singleton	449 287-576	437 362-628	445** 375-599	440 337-562	422 227-550	485* 331-762	403 225-602
	Twin	443 330-564	436 317-560	413 314-496	409 291-517	364 276-528	419 365-560	373 275-554
Platelet Count ($\times 10^9$ /L)	Singleton	239 152-431	234 132-463	236 125-473	213 120-466	216 108-408	231 161-383	325 200-491
	Twin	219 156-382	202 145-343	201 132-304	186 121-312	190 120-343	242 151-524	351 241-756
Antithrombin activity (%)	Singleton	97.0* 77-117	90.0 79-116	87.0* 77-115	85.0* 74-112	79.0* 54-110	91.0 75-110	99.0 82-135
	Twin	89.0 74-120	84.0 68-125	83.0 62-118	80.0 55-112	70.0 48-110	86.0 41-130	102.0 82-141

Data are presented as the median and range, FDP:fibrinogen/fibrin degradation products

*, p<0.05 and **, p<0.01 for singleton pregnancies vs. twin pregnancies.

Table 3. Positive rate (%) of hemostasis parameters in 24 women with singleton pregnancies and 24 women with twin pregnancies

Days from delivery		-3weeks	-2weeks	-1week	-1day	+1day	+3days	+7days
D-dimer > 5.0 μ g/mL	Singleton	0.0**	4.2*	16.7*	20.8*	45.8*	33.3	45.8
	Twin	29.2	29.2	45.8	50.0	83.3	20.8	54.2
FDP > 10.0 μ g/mL	Singleton	4.2*	4.2	4.2*	4.2*	37.5*	8.3	29.2
	Twin	25.0	20.8	33.3	37.5	70.8	25.0	37.5
Fibrinogen < 420 mg/dL	Singleton	37.5	41.7	25.0*	29.2*	50.0	25.0	54.2
	Twin	33.3	37.5	58.3	62.5	58.3	50.0	79.2
Platelet count < 150x10 ⁹ /L	Singleton	0.0	8.3	12.5	16.7	16.7	0.0	0.0
	Twin	0.0	8.3	12.5	20.8	20.8	0.0	0.0
Antithrombin activity < 70%	Singleton	0.0	0.0	0.0*	4.2*	25.0	0.0	0.0
	Twin	4.2	8.3	25.0	29.2	50.0	12.5	0.0

FDP:fibrinogen/fibrin degradation products,

*, p<0.05 and **, p<0.01 for singleton pregnancies vs. twin pregnancies.

Figure 1 Morikawa *et.al.*

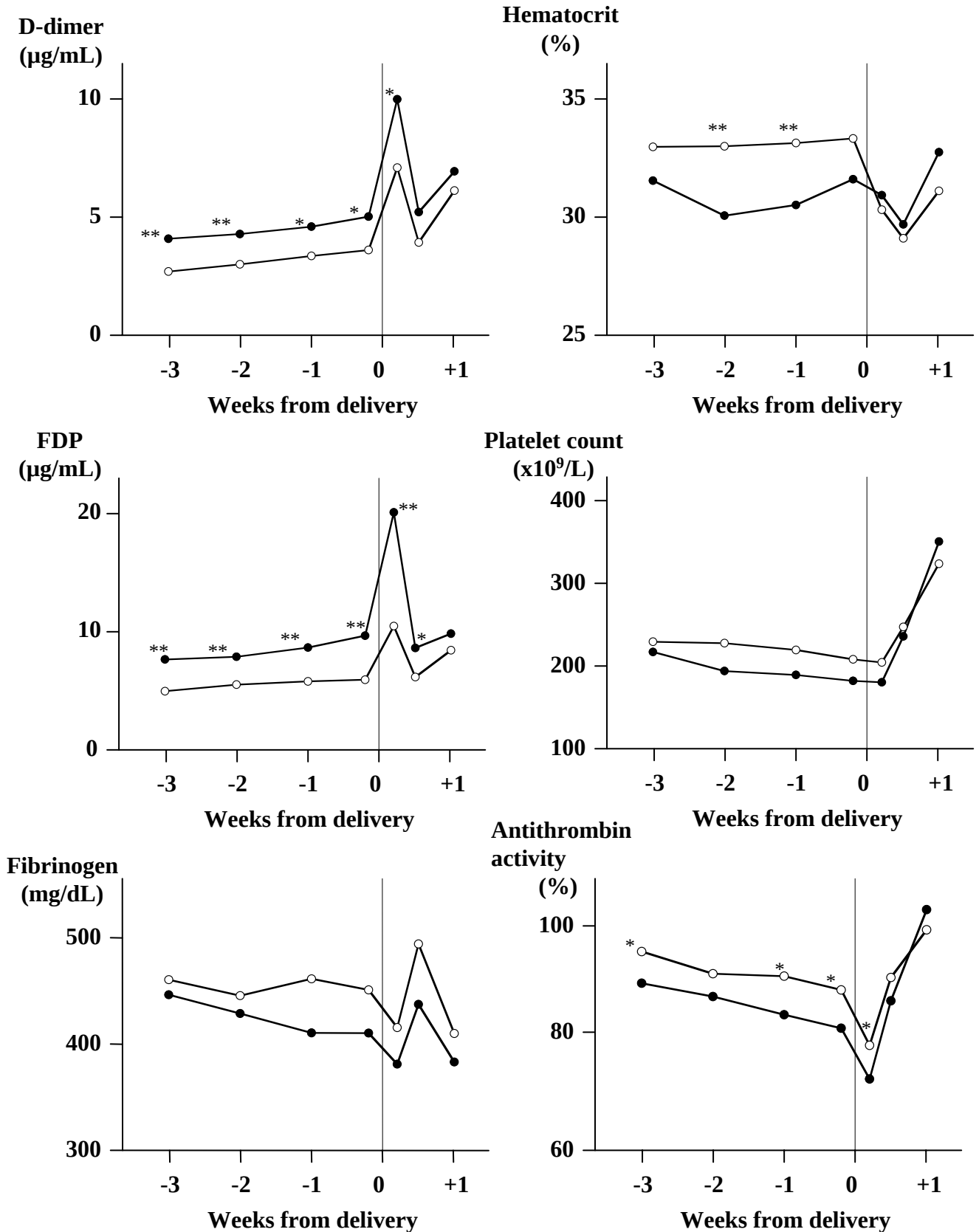


Figure 2 Morikawa *et.al.*

