Revised article for Pregnancy Hypertension

Changes in D-dimer levels in pregnant women according to gestational week

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ABSTRACT

We performed a retrospective review of medical charts regarding blood D-dimer levels determined cross-sectionally by latex agglutination assay in 1952 samples from 1185 women to **determine changes in D-dimer levels** according to stage of pregnancy. Three of 17 women in whom further investigations were performed were found to have **clinical** venous thromboembolism (VTE). The median and 95th percentile values of D-dimer (μg/mL) in the 1182 women without clinical VTE, 0.54 and 2.41 at gestational week (GW) 4 – 13, increased gradually to 1.22 and 5.03 at GW 14 – 27, 1.81 and 6.18 at GW 28 – 35, and 2.13 and 5.85 at GW 36 – 42, respectively. A total of 9 women (0.76%), including 3 women with **clinical** VTE, exhibited a D-dimer level > 14.0 μg/mL, which was well above the 99th percentile for any stage of pregnancy. Thus, 3 (33%) of the 9 with a D-dimer level > 14 μg/mL developed **clinical** VTE, while none of the remaining 1176 women with a D-dimer level ≤ 14 μg/mL developed **clinical VTE**. Although further prospective studies are required, our results suggested that there is a certain cut-off D-dimer value that would allow us to differentiate between pregnant women with and without **clinical** VTE.

Keywords: thrombosis, pregnancy, cut-off value, D-dimer, antithrombin

Abbreviations: AT, antithrombin; CT, computed tomography; GW, gestational week; MRI, magnetic resonance imaging; VTE, venous thromboembolism

INTRODUCTION

Pregnancy is a state characterized by hypercoagulability [1] and an increased risk of venous thromboembolism (VTE) [2], which is one of the leading causes of maternal death in developed countries [3]. Although the risk of VTE is highest during the postpartum period [4, 5], many antenatal VTE events occur in the first trimester [6 – 8]. Therefore, VTE in pregnancy is a significant concern and recommendations for prophylaxis have been reported [9].

Measurement of the D-dimer level is useful for excluding VTE in non-pregnant patients with suspected VTE [10 – 12]. A D-dimer level of 0.2 – 0.5 μg/mL is usually used as the cut-off value for non-pregnant women [10 – 12]. However, as D-dimer level is elevated physiologically during pregnancy [13 – 19], the cut-off value for non-pregnant individuals is not useful because it has low specificity and positive predictive values. Theoretically, D-dimer can be a useful tool, and three studies have suggested that a higher cut-off value is useful for excluding pregnant women without VTE [17 – 19]. However, taking the consequent risks of VTE to the mother and fetus into consideration, further studies comparing D-dimer levels between pregnant women with and without VTE are required before definitive conclusions can be drawn regarding the usefulness of D-dimer test in pregnant women. Accordingly, we conducted this retrospective study **to determine changes in D-dimer levels according to gestational week** for pregnant women who do not have **clinical** VTE.

MATERIAL AND METHODS

Approval was granted for this study by the Ethics Committee of Hokkaido University Hospital, a tertiary teaching hospital managing mainly high-risk pregnant women. Laboratory tests, including a complete blood count, biochemistry, and parameters of coagulation-fibrinolysis such as the D-dimer level, are performed routinely in pregnant women visiting our clinic even for minor symptoms as well as women admitted to the hospital for management of various obstetric and incidental complications. This study included 1185 of such women who underwent blood tests including D-dimer level and miscarried before gestational week (GW) 22 or gave birth at or after GW 22 at Hokkaido University Hospital between April 2007 and May 2012 (Table 1). Pregnancy

stage was grouped into four categories: first trimester (until the end of GW 13), second trimester (GW 14 – 27), early third trimester (GW 28 – 35), and late third trimester (GW 36 – 42). Each subject usually underwent blood tests including determination of D-dimer level several times. However, only the highest D-dimer value within each GW category was used as the datum for the study subject. Finally, 1952 data on D-dimer obtained from the entire pregnancy period of 1185 women were analyzed in this study. These 1185 women accounted for 77.8% of 1523 women who gave birth at our hospital during the study period. Data regarding patient age, parity, and clinical outcomes were collected from the medial records.

Clinical VTE was defined as that confirmed with imaging techniques including compression ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and echocardiography. Seventeen of the 1185 women underwent **these** investigations during pregnancy for detection of **clinical** VTE because of clinical symptoms **(n=2), preoperative screening (n=3, before fetoscopic laser photocoagulation for twin-to-twin transfusion syndrome), decline in SpO_2 during amniocenthesis (n=1), bed rest for long time (n=3), referring physician's request (n=1), and high D-dimer levels (n=7)**: compression ultrasonography in 17, CT in 2, MRI in 1, and echocardiography in 1. Three of the 17 women were found to have VTE (pulmonary thromboembolism in two cases and deep vein thrombosis in one case).

The blood specimens for determination of D-dimer levels were obtained from another forearm when one forearm was used for an intravenous fluid replacement to avoid possible effects of heparin on the D-dimer levels. The D-dimer levels were measured using the latex agglutination assay (Mitsubishi Kagaku Iatron Inc., Tokyo, Japan) in citrated blood samples after centrifugation. Blood levels of D-dimer ranging from 0.0 μg/mL to 0.99 μg/mL are considered normal at our institution. Intra- and interassay coefficients of variation were 4.4% and 3.3%, respectively, at our institution. Correlation of D-dimer levels determined by our assay system (y) with those by the Vidas DD new assay (bioMérieux, Marcy l'Etoile, France) (x_1) [**20 – 22**] or Tinaquant assay (Roche Diagnostics, Mannheim, Germany) (x_2) **[22 – 24**] were as follows: $y = 3.577\ x_1 - 1.71$, $r = 0.943$ or $y = 2.471\ x_2 - 0.59$, $r = 0.951$ for 302 blood samples with D-dimer levels of 0.0 – 40.0 μg/mL determined by our method; and $y = 0.999\ x_1 + 0.31$,

r = 0.819 or y = 1.446 x_2 + 0.32, r = 0.882 for 90 blood samples with D-dimer levels < 2.0 μg/mL determined by our method.

Data are presented as means ± standard deviation. Statistical analyses were performed using the JMP8© statistical software package (SAS, Cary, NC). Differences between the means were tested using the Tukey – Kramer HSD (honestly significant difference) test between each group. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

RESULTS

*D-dimer levels in 1182 women without **clinical** VTE*

As our institution is a tertiary hospital, the rates of multifetal pregnancies, pregnancy-induced hypertension, and cesarean delivery were higher than those in the general Japanese population (Table 1). Three women in the study population developed **clinical** VTE during pregnancy. Of the 1182 women remaining after excluding the 3 women with VTE, 118, 372, 681, and 781 women without **clinical** VTE were examined at GW 4 – 13, 14 – 27, 28 – 35, and 36 – 42, respectively (Fig. 1). Of the 1182 women without **clinical** VTE, only 17 and 6 exhibited D-dimer levels > 10 μg/mL and > 14 μg/mL, respectively, while all 3 women with **clinical** VTE exhibited a D-dimer level > 14 μg/mL (Fig. 2). Of the 17 women undergoing investigations for detection of **clinical** VTE, 3 women with D-dimer levels of 14.6 (Case 1), 17.6 (Case 2), and 19.0 μg/mL (Case 3) were found to actually have **clinical** VTE. Mean values ± SD were 0.82 ± 0.79 μg/mL at GW 4 – 13, 1.78 ± 1.67 μg/mL at GW 14 – 27, 2.48 ± 2.36 μg/mL at GW 28 – 35, and 2.65 ± 1.94 μg/mL at GW 36 – 42 among the 1182 women without **clinical** VTE. The median, 90th, 95th, and 99th percentile values for D-dimer were determined for the 1182 women within each GW category (Fig. 2). The median and 99th percentile values (μg/mL), 0.54 and 4.30 at GW 4 – 13, increased gradually to 1.22 and 9.26 at GW 14 – 27, 1.81 and 10.95 at GW 28 – 35, and to 2.13 and 10.32 at GW 36 – 42, respectively. The number of women with a D-dimer level ≥ 1.0 μg/mL (threshold for non-pregnant individuals), 21.2% (25/118) at GW 4 – 13, increased to 59.4% (221/372) at GW 14 – 27, 85.2% (580/681) at GW 28 – 35, and 92.3% (721/781) at GW 36 – 42.

Mean D-dimer level for the 221 data from 120 women with multifetal pregnancies was

significantly higher than that of women with singleton pregnancies (3.65 ± 2.65 vs. 2.14 ± 1.91 μg/mL, $P < 0.0001$). However, mean D-dimer level for the 146 data from 93 hypertensive women with singleton pregnancies was not significantly higher than that of their counterparts with singleton pregnancies (2.35 ± 2.03 vs. 2.31 ± 2.07 μg/mL, $P = 0.8244$). **Mean D-dimer level in the late 3rd trimester was not affected by maternal age; 2.80 ± 2.39 μg/mL, 2.54 ± 1.67 μg/mL, and 2.62 ± 1.75 μg/mL for women with age of ≤ 29 years (n=234), 30-34 years (n=265), and ≥ 35 years (n=282), respectively (*P*=0. 3197, ANOVA), while that (1.88 ± 1.01 μg/mL) of women with pre-pregnancy body mass index (BMI, kg/m^2) ≥ 30 (n=35) was significantly lower compared with that (2.67 ± 1.83 μg/mL) of women with pre-pregnancy BMI < 25 (*P*=0.0300) (n=663), but was not different from that (2.58 ± 1.68 μg/mL) of women with pre-pregnancy BMI of 25 – 29.9 (n=72).**

*Three patients who developed **clinical** VTE during pregnancy (Fig. 3)*

Asymptomatic **Case 1** (27 years old, primiparous) with one prior VTE at 18 years old and diagnosed with antithrombin (AT) deficiency **was first seen** at GW 7. She had not been treated with anti-coagulation therapy. **Laboratory work-up was performed emergently.** Enhanced CT scan performed after reaching a high D-dimer level of 14.6 μg/mL (Fig. 2) and a reduced AT level (50% of normal) revealed the presence of bilateral pulmonary thromboembolism on the day of the visit. Treatment with AT product and heparin was initiated on the same day (hospital day 0). The D-dimer level decreased gradually to around 1.0 μg/mL on hospital day 11 (Fig. 3). The patient left the hospital on hospital day 15 after termination of her pregnancy on hospital day 7.

Case 2 (28 years old, primiparous) diagnosed with AT deficiency was emergently admitted to our hospital at GW 9 due to dyspnea, chest pain, nausea, and vomiting. She had not been treated with anti-coagulation therapy. She exhibited a high D-dimer level of 17.6 μg/mL (Fig. 3), and a reduced AT level (33% of normal) on admission. Treatment with AT product and heparin was initiated followed by a further increase in D-dimer level to 23.6 μg/mL 6 h after initiation of heparin. Echocardiography revealed marked overload in the right ventricle and a diagnosis of pulmonary thromboembolism was made. Her D-dimer level, which decreased to < 1.0 μg/mL on hospital day 9 (Fig. 3), increased gradually after GW 21 to 3.4 μg/mL just before delivery while on heparin. However, she did not have **clinical** VTE recurrence, and gave birth to a male infant

weighing 2565 g at GW 38 by cesarean section for breech presentation and left the hospital on postpartum day 8.

Case 3 (35 years old, primiparous) with twin gestation was referred and admitted to our hospital for premature labor at GW 33 on the day of referral. She exhibited a high D-dimer level of 19.0 μg/mL (Fig. 2), reduced AT level (62% of normal), and a high C-reactive protein level (13.6 mg/dL) on admission. As MRI revealed the presence of deep vein thrombosis in the left common iliac vein, a filter was placed in the inferior caval vein to prevent pulmonary thromboembolism, and emergency cesarean section was performed on hospital day 1; the patient gave birth to female twins weighing 1726 g and 1944 g. Treatment with heparin was initiated 8 h after delivery followed by fluctuating D-dimer levels (Fig. 3). She left the hospital on hospital day 12 after removal of the filter on hospital day 5. The AT activity of 59% of normal before cesarean section increased to 79% of normal on postpartum day 12.

DISCUSSION

This study confirmed results of previous studies that the D-dimer level increases with advancing gestation [13-16,18]. The study population included only 3 women with clinical VTE. These 3 women with clinical VTE in addition to other 6 women without clinical VTE exhibited a high D-dimer level > 14 μg/mL, while none of the remaining 1176 women with a D-dimer level ≤ 14 μg/mL developed **clinical** VTE. These results suggested that there is a certain cut-off D-dimer value that would allow us to differentiate between pregnant women with and without **clinical** VTE.

To our knowledge, there have been 3 previous studies regarding the possibility that a higher cut-off value than that for non-pregnant individuals may be **helpful** to exclude pregnant women without VTE [17 – 19]. In 2007, Chan *et al.* [17] demonstrated that a less sensitive assay method (SimpliRED; Agen Biomedical, Brisbane, Australia) yielded a sensitivity of 100% with a specificity of 60% in a cohort including 8.7% women with VTE. Chan *et al.* [19] later demonstrated that D-dimer level was significantly higher in pregnant women with than in those without VTE in all of five more sensitive assay methods (two rapid enzyme-linked immunosorbent assays and three latex agglutination assays), and that use of higher cut-off values improved specificity up to 62% – 79%, while maintaining high sensitivity (80% – 100%) in all five assays for diagnosing VTE

in pregnancy. In another study using the HemosIL D-dimer HS assay method [**25**], Kovac *et al*. [18] reported that D-dimer levels were higher in 9 of 10 pregnant patients with VTE than the highest value according to each trimester of pregnancy. These results together with those of the present study strongly suggested that pregnant patients with VTE were likely to show an even higher D-dimer level than those without VTE. **Similar phenomenon was also suggested in women after cesarean sections [26].**

The numerical data of D-dimer differed between assay methods employed. As described in the Material and Methods section, our method gave relatively high D-dimer values. For example, among pregnant women in the third trimester, the median values were 1.48 μg/mL with Vidas D-dimer (bioMérieux), 1.25 μg/mL with Asserachrome D-dimer (Stago), 0.42 μg/mL with IL Test (Instrumentation Laboratories, Lexington, MA), 0.99 μg/mL with Sta-Lia Test (Stago), and 1.56 μg/mL with Innovance D-Dimer (Siemens) [19] and was 1.81 at GW 28 – 35 and 2.13 at GW 36 – 42 in this study. In addition, the patterns of rising D-dimer levels during pregnancy differ depending on the assay methods used [**27**]; the Innovance D-Dimer assay increases significantly with the advancement of pregnancy, and is more sensitive than D-Dimer PLUS assay in the pregnant population [**27**]. Our data were comparable to data obtained by the Innovance D-Dimer assay; mean and 97.5th percentile values (μg/mL) were 0.53 and 1.63 in the first trimester, 1.01 and 2.28 in the second trimester, and 1.95 and 4.15 in the third trimester for Innovance D-Dimer assay, respectively [**27**], while the mean, 95th, and 99th percentile values (μg/mL) were 0.82, 2.41, and 4.30 in the first trimester, 1.78, 5.03, and 9.26 in the second trimester, 2.48, 6.18, and 10.95 at GW 28 – 35, and 2.65, 5.85, and 10.32 at GW 36 – 42, respectively, in this study. Thus, our assay method showed similar sensitivity to Innovance D-Dimer assay for the detection of D-dimer change during pregnancy.

The major strength of our study was that the study population included a relatively large number of women without clinical VTE for determination of the highest D-dimer value among women without VTE, including those with obstetric and incidental complications. The D-dimer level is elevated in women with preeclampsia or multifetal gestations [**26, 29 – 31**]. Both preeclampsia and multifetal gestation are well-known risk factors for VTE [9], and one of the three patients with VTE in the present study had

twin gestation. Theoretically, any pregnant woman would have an elevated D-dimer level after compared to that before the development of VTE. If we assume that pregnant women with higher D-dimer levels would be prone to the development of VTE, inclusion of women with various complications other than VTE in whom higher D-dimer is anticipated is reasonable in a study for determination of the upper reference value for pregnant women without VTE.

A sharp decline of D-dimer level occurred in the three women with VTE in this study. Although it is not clear whether treatment with heparin initiated soon after the diagnosis of VTE modified changes in D-dimer levels, heparin may have inhibited new thrombus formation, and thereby may have had an inhibitory effect on the D-dimer level. False-negative results can occur 7 – 10 days after the onset of symptoms [**28**]. Therefore, care is required when pregnant women exhibit a negative result but have had symptoms suggestive of VTE, although data on the D-dimer in this study and those in previous studies [17 – 19] suggested that a higher cut-off value was clinically helpful for excluding pregnant women without VTE.

We presented data on the D-dimer levels of 3 and 1182 pregnant women with and without **clinical** VTE, respectively. The D-dimer levels in the three women who developed VTE during pregnancy were well above the 99th percentile values determined for each trimester of pregnancy, suggesting that there may be a certain cut-off D-dimer value that allows differentiation between pregnant women with and without VTE as suggested in previous studies [17 – 19]. However, pregnant women are at four- to sixfold higher risk of VTE than non-pregnant women [5]. Further research is clearly necessary, as the evidence-based use of biomarkers to exclude VTE in pregnant women could obviate the need for alternative investigations involving radiation exposure, with their consequent risks to both mother and baby [**32**].

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DISCLOSURE

None of the authors have a conflict of interest.

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FIGURE LEGENDS

Fig. 1: D-dimer levels according to stage of pregnancy.
A cross-sectional study was conducted in 1182 women who did not develop venous thromboembolism (VTE) during pregnancy and postpartum. Of the 1182 women without VTE, only 17 and 6 exhibited D-dimer levels of > 10 μg/mL and 14 μg/mL, respectively.

Fig. 2: Changes in median, 90^{th}, 95^{th}, and 99^{th} percentile values of D-dimer according to stage of pregnancy.
●, Women who developed venous thromboembolism (VTE); ○, Women who were suspected to have VTE for various reasons, but were found to be free from VTE after investigation.

Fig. 3: Changes in D-dimer levels in three women who developed venous thromboembolism during pregnancy.
Cases 1, 2, and 3 developed venous thromboembolism (pulmonary thromboembolism in Cases 1 and 2, deep vein thrombosis in Case 3) at gestational week 7, 9, and 33, respectively. Case 3 was twin gestation. Closed arrow indicates initiation of heparin for Cases 1 and 2, and open arrow indicates initiation of heparin in Case 3.

Fig. 1

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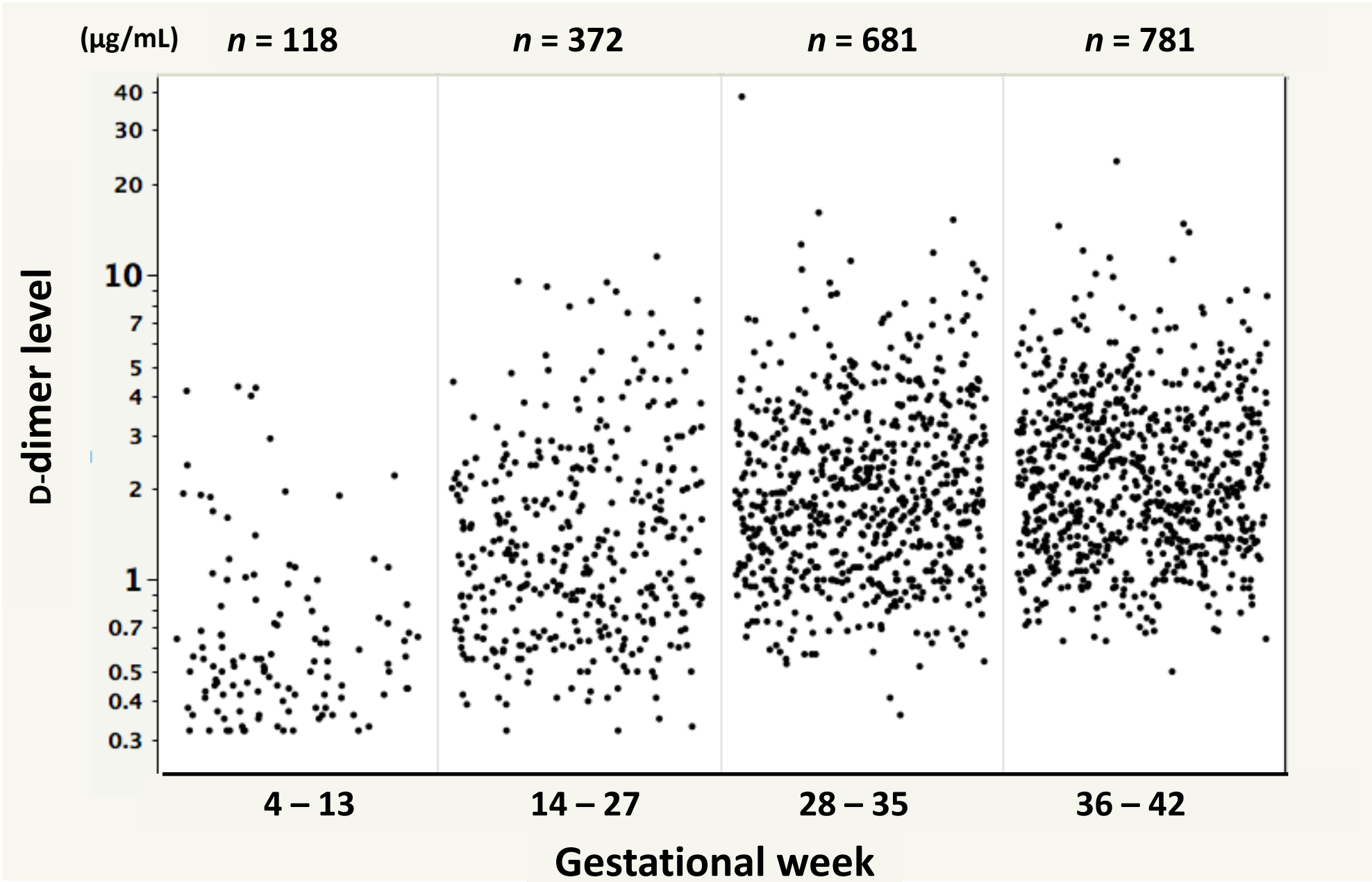

Fig. 2

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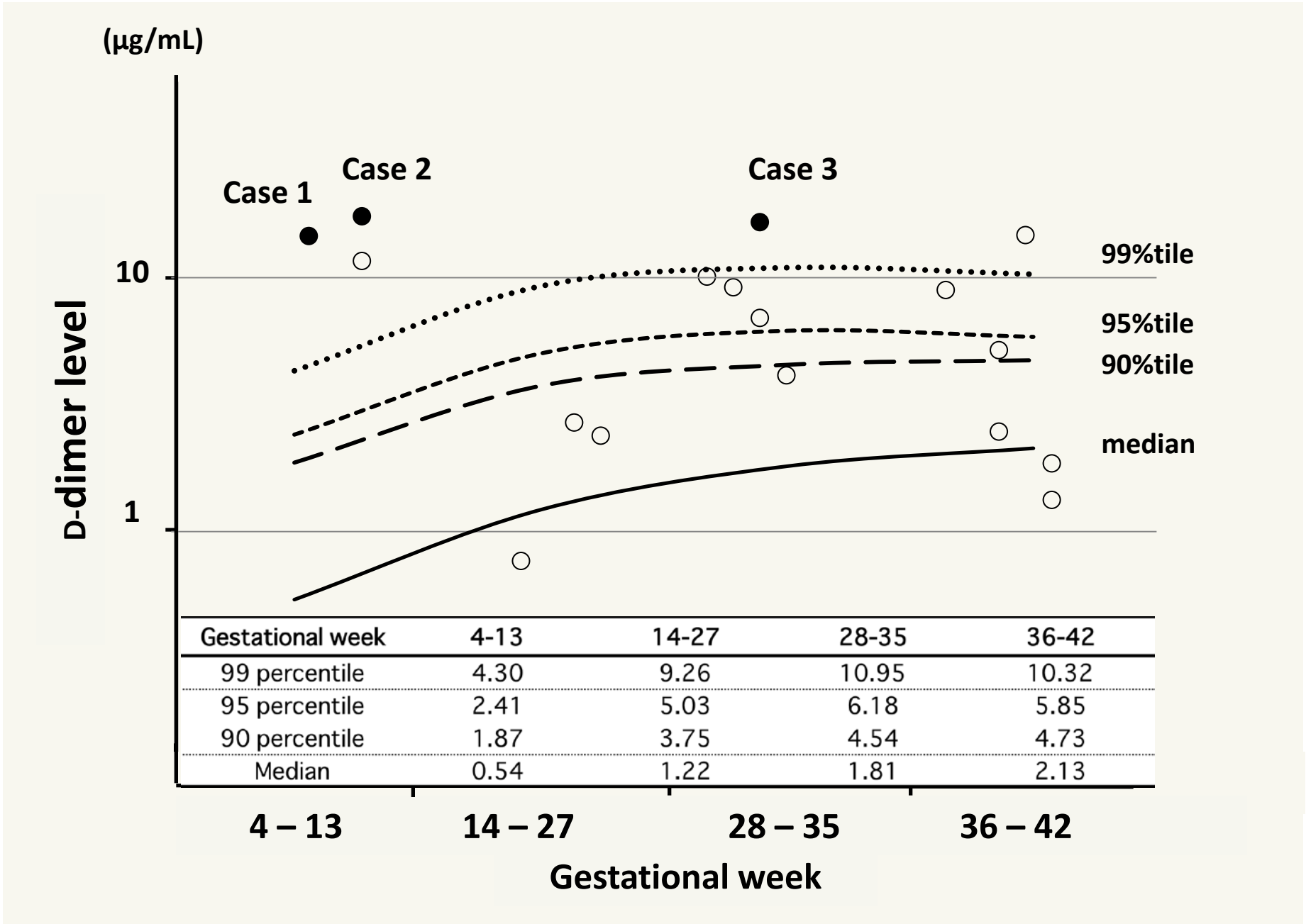

Gestational week	4-13	14-27	28-35	36-42
99 percentile	4.30	9.26	10.95	10.32
95 percentile	2.41	5.03	6.18	5.85
90 percentile	1.87	3.75	4.54	4.73
Median	0.54	1.22	1.81	2.13

Fig. 3

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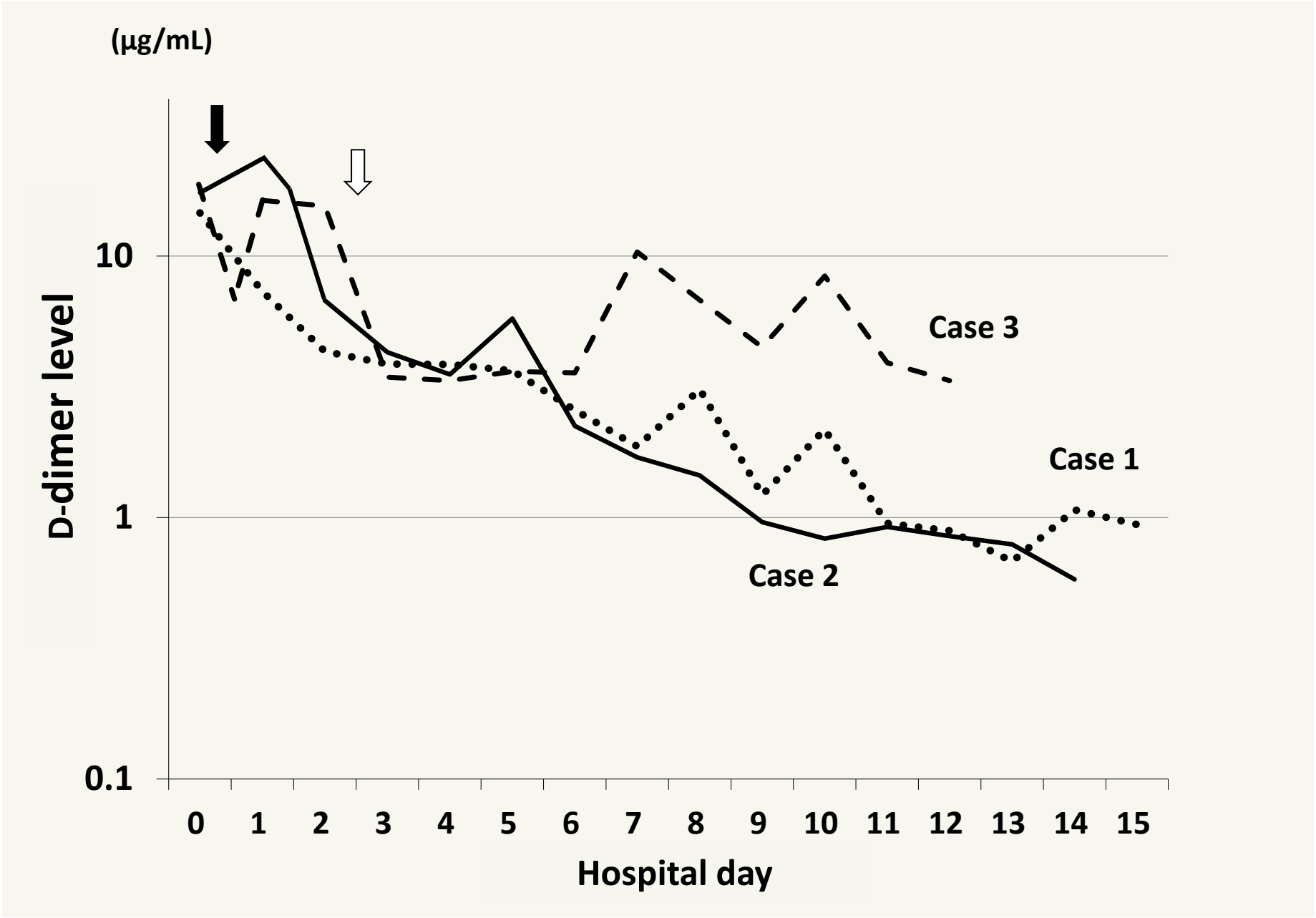

Table 1. Demographic characteristics of 1185 study subjects

Age (years old)	31.9 ± 5.3 [14 – 48]
< 20	11 (0.9%)
≥ 35	404 (34.1%)
Primiparous	673 (56.8%)
Multifetal pregnancy*	120 (10.1%)
Pregnancy-induced hypertension	93 (7.8%)
Venous thromboembolism	3 (0.3%)
Pre-pregnancy BMI	21.7 ± 4.1 [14.1 – 46.5]
– 24.9	995 (84.0%)
25.0 – 29.9	103 (8.7%)
30.0 –	57 (4.8%)
Gestational week at delivery	
Abortion at < 14	6 (0.5%)
Abortion at 14 – 21	37 (3.1%)
22 – 27	31 (2.6%)
28 – 35	186 (15.7%)
36 – 42	925 (78.1%)
Cesarean delivery	709 (59.8%)

Range is indicated in square brackets; BMI, body mass index (kg/m^2);

*, Including 114 twin, 5 triplet, and 1 quadruplet gestations.