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Fibrinogen levels in the late stage of twin pregnancy

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ABSTRACT

Introduction: Twin pregnancy is a risk factor of complications, such as pregnancy-induced hypertension, venous thromboembolism, and postpartum hemorrhage, the pathogenesis of which may involve aberrations of the coagulation–fibrinolysis system.
Materials and Methods: Fibrinogen data for 129 and 1202 blood specimens from 84 and 902 women with twin and singleton pregnancies, respectively, at gestational week (GW) ≥ 32 were analyzed retrospectively. None of the 986 women developed complications in which blood fibrinogen levels may be altered. Thirty-six and 288 women with twin and singleton pregnancies were examined longitudinally, respectively.
Results: The fibrinogen levels of 403 ± 63 and 403 ± 77 mg/dL at GW 32 – 33 and 34 – 35, respectively, decreased significantly to 366 ± 57 mg/dL at GW 36–37 in women with twins, while corresponding levels (422 ± 79, 420 ± 65, and 415 ± 64, respectively) and that at GW ≥ 38 (408 ± 60 mg/dL) did not change significantly in women with singleton pregnancies. The fibrinogen levels determined within 3 weeks before delivery were consistently and significantly lower in women with twin than singleton pregnancies. The fibrinogen levels were significantly inversely correlated with GW in women with twins ($R = -0.36$, $P = 0.002$), but not in those with singleton pregnancies.
Conclusions: The fibrinogen level of twin pregnancy decreases significantly and is significantly lower than that in singleton pregnancy in the last few weeks of pregnancy.

Introduction

Twin pregnancy differs considerably from singleton pregnancy in many respects, such as risks of venous thromboembolism (VTE) [1–3], HELLP syndrome [4], acute fatty liver of pregnancy [5], pregnancy-induced hypertension [6,7], and postpartum hemorrhage (PPH) [8,9]. The pathogenesis of all of the above complications is thought to be related to an aberrant coagulation–fibrinolysis system, and women with twins are consistently at higher risk of these complications compared to those with singleton pregnancies.

Changes in hemostasis and coagulation–fibrinolysis parameters, such as platelet count, antithrombin activity, and D-dimer, differ between women with singleton and twin pregnancies. Platelet count and antithrombin activity are likely to decrease [10–12] and D-dimer level is likely to increase in the late stage of twin compared to singleton pregnancy [13–16]. Therefore, fibrinogen, which is one of the most important components of the coagulation cascade and the principal factor for the final stage of clot formation, may exhibit different changes in twin pregnancies compared to singleton pregnancies in the late stage of pregnancy. Although fibrinogen level increases during pregnancy [17–20] and is believed not to decrease during pregnancy, whether fibrinogen decreases in the late stage of twin pregnancy remains to be determined.

This retrospective study was conducted to determine whether changes in fibrinogen level in the late stage of pregnancy are different between twin and singleton pregnancies.

Materials and Methods

This retrospective study was conducted with the approval of the Ethics Committee of Hokkaido University Hospital (a tertiary care center). The institutional delivery database was queried for women who gave birth to singleton or twins at or after gestational week (GW) 32 at Hokkaido University Hospital during the study period between 1 April 2007 and 31 March 2013. Totals of 1471 and 118 women with singleton and twin pregnancies, respectively, were identified (Fig. 1).

Laboratory tests, including complete blood count, biochemistry, and analysis of coagulation–fibrinolysis parameters, are performed routinely even for minor symptoms in pregnant women at our clinic, and for those admitted to hospital for management of obstetric and incidental complications. All blood fibrinogen and D-dimer data from the institutional central laboratory was obtained for each patient during the study period. A part of results on the D-dimer levels was reported previously [16].

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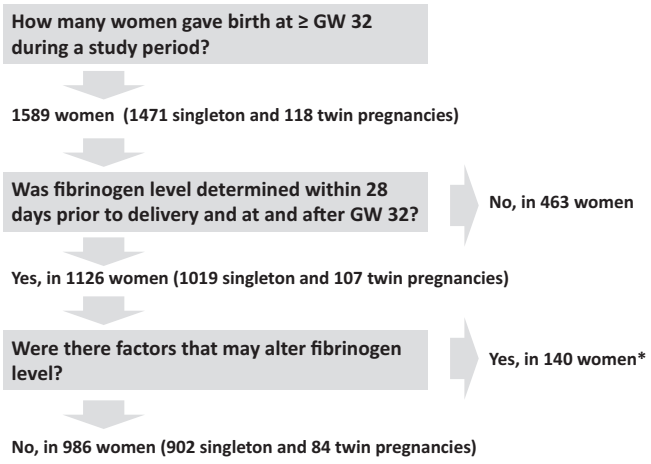

Fig. 1. Flow diagram showing criteria for selection of study subjects. *, 140 women with the following characteristics were excluded: 92 with pregnancy-induced hypertension, 27 with placenta previa or low-lying placenta with or without placenta accreta, 12 with fetal death, 5 with VTE, 2 with placental abruption, and 2 with other complications.

After matching fibrinogen data with medical charts, 1019 and 107 women with singleton and twin pregnancies, respectively, were found to have had blood fibrinogen concentrations measured at and after GW 32 and within 28 days prior to delivery. Demographic characteristics were recorded from medical charts. Of these 1126 women, the following 140 women were excluded because their complications may alter fibrinogen level: 92 with pregnancy-induced hypertension, 27 with placenta previa or low-lying placenta with or without placenta accreta, 12 with fetal death, 5 with VTE (deep vein thrombosis), 2 with placental abruption, and 2 with other complications. No women with liver dysfunction were included in this study. Finally, the study was performed with data from 902 with singleton and 84 twin pregnancies with determination of fibrinogen level at least once on and after GW 32 and with birth on or after GW 32, accounting for 61.3% and 71.2% of the 1471 and 118 women with singleton and twin pregnancies who gave birth at and after GW 32 at our institution during the study period, respectively (Table 1).

Changes in fibrinogen levels in the late stage of pregnancy were analyzed in the two groups (singletons and twins). Stages of pregnancy were divided by GW or days before delivery. Each subject usually underwent blood tests several times during pregnancy. However, only the fibrinogen level determined latest within each GW category or each category divided by days from delivery was used as the datum for the study subject.

Fibrinogen concentration was measured using the Clauss thrombin clotting time method in citrated blood samples and a hematology analyzer (CS2000i; Sysmex Co. Ltd., Kobe, Japan) after centrifugation.

Table 1
Demographic characteristics of 986 study subjects and number of blood samples.

	Singleton	Twin	*P*-value
Number of women	902	84	
Maternal age (years)	32.1 ± 5.3	30.7 ± 5.0	0.0155
Primiparity	494 (54.8%)	43 (51.2%)	0.5290
Gestational week at delivery	38.1 ± 1.7	36.3 ± 1.4	<0.0001
<37 weeks	134 (14.9%)	43 (51.2%)	<0.0001
Cesarean delivery	552 (61.2%)	81 (96.4%)	<0.0001
Gestational week at determination of fibrinogen level			
32–33	32.9 ± 0.6 [94]	33.0 ± 0.6 [48]	0.7914
34–35	35.1 ± 0.5 [307]	35.2 ± 0.6 [26]	0.1174
36–37	36.9 ± 0.6 [526]	36.5 ± 0.4 [55]	<0.0001
≥38	39.2 ± 1.0 [275]	NA [0]	

Data are presented as means ± SD. Number of women who underwent determination of fibrinogen levels is indicated in square brackets. NA, not applicable.

Intra- and interassay coefficients of variation were less than 6% and 10%, respectively. Normal fibrinogen concentration at our institution, not specific for pregnant women, is 200–400 mg/dL.

Statistical Analysis

Data are presented as means ± standard deviation (SD) or median (25th - 75th percentile value). Statistical analyses were performed using the JMP10© statistical software package (SAS, Cary, NC). Paired t-test, ANOVA and Tukey–Kramer HSD (honestly significant difference) tests were used for comparison of means. Mann–Whitney U test was used for comparison of medians. Chi square test and Fisher's exact test were used for comparison of categorical variables. Linear regression analysis was used to determine whether fibrinogen levels were correlated with GW among women who underwent determination of fibrinogen level twice. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

Women were significantly younger, duration of pregnancy was significantly shorter, and preterm delivery at GW < 37 and cesarean delivery were significantly more common in twin than singleton pregnancies (Table 1). None of the 84 women with twins gave birth at GW ≥ 38. Finally, 129 and 1202 data on fibrinogen determined at GW ≥ 32 were available for 84 and 902 women with twins and singleton pregnancy, respectively (Table 1). The numbers of data per woman were 1.5 ± 0.7 and 1.3 ± 0.5 for twin and singleton pregnancies, respectively ($P = 0.0006$). The fibrinogen level (mean ± SD) (median [25th – 75th percentile value]) was significantly lower in the 129 samples from the 84 women with twin pregnancies than in the 1202 samples from 902 women with singleton pregnancies (387 ± 66 vs. 415 ± 65 mg/dL, $P < 0.0001$) (390 [341 - 433] vs. 410 [372 - 452] mg/dL, $P < 0.0001$).

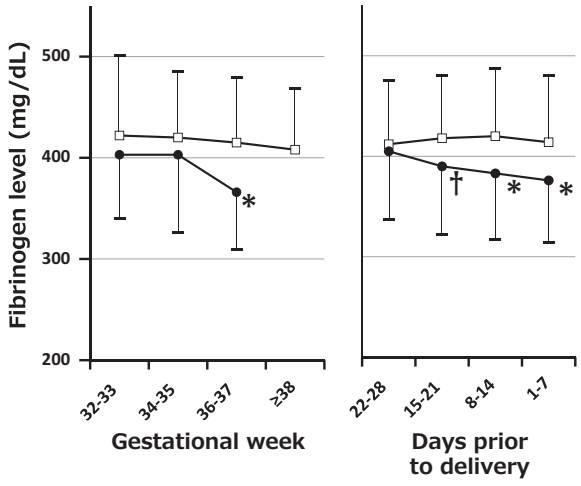

Fig. 2. Changes in fibrinogen levels according to gestational week and days prior to delivery (cross-sectional study). Data are presented as mean with SD. Open squares and closed circles indicate singleton and twin pregnancies, respectively. † and *, $P < 0.05$ and $P < 0.01$ between values of two groups, respectively. In twin pregnancies, the fibrinogen levels at GW 36 – 37 were significantly lower than those at GW 32 – 33 ($P = 0.0095$) and GW 34 – 35 ($P = 0.0411$). The median (25th – 75th percentile value) fibrinogen values (mg/dL) of singleton vs. twin pregnancies were 417 (367 - 482) vs. 402 (358 - 461), 414 (381 - 456) vs. 398 (351 - 480), and 411 (372 - 452) vs. 358 (327 - 405) for GW of 32 – 33, 34 – 35, and 36 – 37, respectively. It was 403 (368 - 441) mg/dL for singleton pregnancies at GW 38 or more. The median (25th – 75th percentile value) fibrinogen values (mg/dL) of singleton vs. twin pregnancies were 411 (373 – 451) vs. 404 (355 – 455), 413 (379 – 452) vs. 390 (341 - 435), 418 (372 – 461) vs. 380 (339 - 427), and 408 (372 - 449) vs. 381 (333 – 422) for values determined 22 – 28, 15 – 21, 8 – 14, and 1 – 7 days before delivery, respectively.