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(Citation)
Journal of Obstetrics and Gynaecology Research,49(12):2969-2974

(Issue Date)
2023-12

(Resource Type)
journal article

(Version)
Accepted Manuscript

Two pregnant women with immune-mediated thrombotic thrombocytopenic purpura: a case report

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Running title: Two pregnant women with immune-mediated TTP

Abstract

Thrombotic thrombocytopenic purpura (TTP) during pregnancy is life-threatening. We encountered two pregnant women with immune-mediated TTP (iTTP).

A 40-year-old primigravida woman was referred at 19 gestational weeks (GWs) owing to iTTP. She received plasma exchange (PE) and steroid therapies and delivered a live infant at 27 GWs by cesarean delivery.

A-29-year-old primigravida woman was referred owing to intrauterine fetal death and thrombocytopenia at 20 GWs. She was diagnosed with iTTP and received PE therapy. She required additional PE and steroid therapies owing to relapse. Before her second pregnancy, she received prednisolone and hydroxychloroquine according to the therapy for systemic lupus erythematosus (SLE). She had induced labor at 37 GWs owing to decrease plasma level of a disintegrin-like and metalloproteinase with thrombospondin type 1 motif 13 (ADAMTS13) activity.

Close monitoring of plasma ADAMTS13 activity level and treatments for underlying SLE may prevent iTTP relapse and lead to a good prognosis.

Keywords: ADAMTS13, immune-mediated thrombotic thrombocytopenic purpura, plasma exchange, pregnancy, steroid

Introduction

Thrombotic thrombocytopenic purpura (TTP) is rare but life-threatening. Both congenital and immune-mediated TTP (iTTP) are caused by a deficiency of a disintegrin-like and metalloproteinase with thrombospondin type 1 motif 13 (ADAMTS13), which cleaves von Willebrand factor (1, 2). Inhibitors against ADAMTS13 are involved in the iTTP pathology (3). The early initiation of plasma exchange (PE) therapy can improve the prognosis of patients with both congenital and iTTP (4). However, the relapse rate in patients with a history of TTP is as high as 30%–60% (5).

During pregnancy, the prevalence of TTP is reported to be only 0.004% (1). The registry study of patients with TTP-hemolytic uremic syndrome (HUS) in Oklahoma reported that 10 women with a history of iTTP had subsequent pregnancies and that two of them had TTP relapse during the postpartum period. (6). However, there is no established prophylaxis for TTP relapse in subsequent pregnancies among women with prior histories of TTP.

Conversely, 1%–4% of patients with systemic lupus erythematosus (SLE) develop iTTP (7). The mechanisms wherein various tissue injuries occur in patients with SLE can cause iTTP (8).

We encountered two pregnant women with iTTP. The first one received PE and steroid therapies and delivered a live infant. The other had iTTP accompanied by intrauterine fetal death (IUFD) in her first pregnancy and received therapy for SLE before and throughout the subsequent pregnancy; she then delivered a healthy newborn at term without iTTP relapse.

Case Reports

This case report followed the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients, and patient anonymity was maintained.

Case 1

A 40-year-old primigravida woman, who had essential hypertension, was referred to a previous hospital because of severe hypertension (blood pressure, 161/97 mmHg), liver dysfunction (alanine aminotransferase [ALT], 123 U/L; aspartate aminotransferase [AST], 103 U/L), and thrombocytopenia (platelet [PLT] counts, $8.0 \times 10^4/\mu L$) at 17 + 1/7 gestational weeks (GWs). Hypertension and liver dysfunction were improved following the initiation of antihypertensive therapy with α-methyldopa, whereas thrombocytopenia and hemolytic anemia were exacerbated. At 18 + 5/7 GWs, plasma ADAMTS13 activity and inhibitor levels were <0.5% (normal, >10%) and 0.9 Bethesda unit (BU)/mL (normal, <0.5 BU/mL), respectively. Therefore, she was diagnosed with iTTP and was transferred to Kobe University Hospital at 19 + 3/7 GWs. The following were the laboratory findings at admission: red blood cell (RBC) counts, $237 \times 10^4/\mu L$; hemoglobin (Hb) concentration, 8.2 g/dL; PLT counts, $2.3 \times 10^4/\mu L$; serum levels of lactate dehydrogenase (LDH), 672 IU/L; ALT, 25 U/L; AST, 43 U/L; total bilirubin (T-Bil), 1.8 mg/dL; indirect bilirubin (ID-Bil), 1.6 mg/dL; creatinine (Cre), 0.68 mg/dL; blood urea nitrogen (BUN), 18.2 mg/dL; haptoglobin (Hp), <2 mg/dL; plasma ADAMTS13 activity, <0.5%; and ADAMTS13 inhibitor, 1.2 BU/mL. Ultrasonography (US) revealed an appropriate-for-gestational-age fetus. At 19 + 3/7 GWs, PE and steroid therapies (prednisolone [PSL] 1 mg/kg) were started.

At 20 + 1/7 GWs, PE therapy was discontinued since PLT counts reached $>15 \times 10^4/\mu L$ (Figure 1). At 20 + 1/7 GWs, she was started on oral administration of

calcium blocker (20 mg/day) for hypertension. At 27 + 4/7 GWs, fetal US revealed fetal growth restriction (EFBW, 876 g [−1.5 SD]) with both absent end-diastolic flow in the umbilical artery (UA) and a ductus venosus pulsatility index above the 95% centile (9). In addition, loss of variability together with recurrent severe late deceleration was observed in cardiotocogram. Therefore, she was diagnosed with non-reassuring fetal status, and she delivered an 816-g (−1.4 SD) female infant with Apgar scores of 1 (1 min) and 8 (5 min), and pH 7.259 in the UA by cesarean delivery. The newborn admitted to the neonatal intensive care unit and received intensive care, including mechanical ventilation and surfactant administration for neonatal respiratory distress syndrome. Because the newborn had neither anemia (Hb concentration, 16.5 g/dL) nor thrombocytopenia (PLT counts, 17.8 × 10^4/μL), neither blood transfusion nor PE and steroid therapy were required.

After delivery, she was treated with a maintenance dose of PSL (30 mg/day). She and her baby were transferred back to the previous hospital 18 days after delivery.

Case 2

A 29-year-old primigravida pregnant woman visited a private clinic because of abdominal pain, petechiae, and hematuria at 20 + 0/7 GWs. At 20 + 1/7 GWs, she was diagnosed as having thrombocytopenia (PLT counts, 8 × 10^4/μL) and IUFD and was transferred to Kobe University Hospital. The following were the laboratory findings at admission to the university hospital: RBC counts, 304 × 10^4/μL; Hb concentration, 9.4 g/dL; PLT counts, 0.3 × 10^4/μL; serum levels of LDH, 2,010 IU/L; ALT, 26 U/L; AST, 61 U/L; T-Bil, 5.7 mg/dL; ID-Bil, 5.5 mg/dL; Cre, 0.89 mg/dL; BUN, 25.7 mg/dL; and Hp, <2 mg/dL. Initially, it was suspected that she had partial hemolysis, elevated liver

enzyme levels, and low PLT count (HELLP) syndrome. However, thrombocytopenia and hemolytic anemia did not improve despite PLT and RBC transfusions. Therefore, she was suspected to have iTTP, and PE therapy was initiated at 20 + 2/7 GWs. Her pregnancy ended in spontaneous abortion, and the female stillborn weighed 260 g at 20 + 4/7 GWs. On the ninth day of PE therapy, she was diagnosed with iTTP, since her plasma ADAMTS13 activity and ADAMTS13 inhibitor levels were <0.5% and 1.4 BU/mL, respectively. On the 14th day of PE therapy, her PLT counts reached $15.0 \times 10^4/\mu L$, and PE therapy was discontinued. However, the PLT counts decreased to $8.0 \times 10^4/\mu L$, and ADAMTS13 inhibitor levels increased again. Therefore, we resumed PE therapy and started steroid therapy (methylprednisolone 1,000 mg/day for the first 3 days and 1 mg/kg after the fourth day) 5 days after the termination of the first course of PE therapy. The second course of PE therapy was continued for 7 days, and the PLT counts reached $15.0 \times 10^4/\mu L$. The PSL dosage was tapered; however, plasma ADAMTS13 inhibitor levels were not increased (Figure 2). She was discharged 61 days after delivery, when the plasma ADAMTS13 activity and inhibitor levels were 83.7% and <0.5 BU/mL, respectively. Oral PSL was tapered and discontinued at 4 months after hospital discharge. Laboratory data showed that she was positive for both ANA (1:2,560 [normal, <1:40]) and anti-dsDNA (46.5 [normal, ≤12] IU/mL), and she also had low levels of C3 complement (54 [normal, 73–138] mg/dL) and C4 complement (10.8 [normal, 11–31] mg/dL). We decided to treat her with PSL and hydroxychloroquine (HCQ) according to the therapy for SLE before and during a subsequent pregnancy. Her medication with PSL (10 mg/day) and HCQ (300 mg/day) was initiated 1 year before her next pregnancy. No iTTP symptoms were observed, and ADAMTS13 inhibitor levels remained <0.5 BU/mL throughout her second pregnancy. ADAMTS13 activity levels were

maintained at more than 50% until 34 GWs, except for abnormally low activity levels at 18 GWs. However, at 35 GWs, the plasma ADAMTS13 activity level decreased to 46.7% and continued to decrease thereafter. Therefore, we suggested the patient and her spouse to receive elective induction of labor, and she delivered a 2,488-g (−0.2 SD) female infant with Apgar scores of 9 (1 min) and 10 (5 min), and pH 7.252 in the UA at 37 + 1/7 GWs. She and her baby were discharged 7 days after delivery. At 104 days after delivery, her plasma ADAMTS13 activity levels recovered to 100% (Figure 3).

Discussion

TTP is a rare but life-threatening disease. The relapse rate in patients with a history of TTP is as high as 30%–60% (5).

TTP during pregnancy occurs most commonly in the third trimester or postpartum period (10). Furthermore, it is associated with fetal loss and preeclampsia (4) since it is believed that TTP may induce thrombus formation in the placentas and lead to severe obstetric complications (11).

PE therapy is the gold standard treatment for TTP. This therapy does not only supply ADAMTS13 but also remove ADAMTS13 inhibitors, thereby decreasing the mortality rate in patients with TTP from 90% to 25% (2, 12). Additionally, it is believed that the combination of PE and steroid therapies is more effective for patients with iTTP than PE therapy alone since steroids can suppress autoantibody production.

Moreover, iTTP is characterized by a low ADAMTS13 activity level and the presence of ADAMTS13 inhibitors (13). It has been reported that among patients with an ADAMTS13 activity level of <10%, an inhibitor titer of 2 BU/mL or more was associated with lower survival (12). Therefore, it may be better to use the combination of PE and steroid therapies as first-line therapy, when patients with iTTP had high ADAMTS13 inhibitor levels.

It is believed that PLT infusion is contraindicated in patients with TTP. During the first pregnancy of Case 2, she received PLT transfusion (50 units) before and during her first PE therapy. Some clinicians argued that PLT infusions are frequently required before invasive procedures (e.g., central venous catheter insertion) even for patients with TTP (14).

Distinguishing between HELLP syndrome and TTP during pregnancy is very important since termination of pregnancy is required for the treatment of HELLP syndrome (15). In contrast, if PE therapy is effective, pregnant women with TTP may continue their pregnancies (1). Clinicians should initiate PE and steroid therapies before considering termination of pregnancies when they encounter pregnant women who are suspected of having iTTP. However, it is often difficult to distinguish TTP from HELLP syndrome in daily practice. As in our cases, if pregnant women have severe thrombocytopenia, which is refractory to PLT transfusion, together with not so high levels of liver enzymes (ALT and AST), especially during early gestational ages when fetuses are difficult to survive in the ex utero environment, clinicians should probably consider PE and steroid therapy for suspected TTP before the test results of ADAMTS 13 are available. However, if PE and steroid therapy is not effective, clinicians should consider termination of pregnancy.

Patients with congenital TTP (Upshaw-Schulman syndrome) have been reported to have severe symptoms in the early neonatal period (16), and conversely, there are no reports on newborns with iTTP who had severe symptoms in their neonatal period. As in the newborn of Case 1, neonates born to mother with iTTP generally do not require specific treatments for iTTP.

It has been reported that plasma ADAMTS13 activity levels in healthy pregnant women gradually decreased from 12 to 16 GWs to the end of the early postpartum period, and they are increased thereafter (17). During the second pregnancy of Case 2, plasma ADAMTS13 activity and ADAMTS13 inhibitor levels were closely monitored. Plasma ADAMTS13 activity levels gradually decreased after 14 GWs and rapidly decreased after 32 GWs. After delivery, plasma ADAMTS13 activity levels rapidly increased, and they

reached to 100% at 104 days after delivery. However, the rapid decrease in plasma ADAMTS13 activity levels after 32 GWs in the second pregnancy of Case 2 could not be pathogenic in nature; we selected elective induction of labor at 37 GWs owing to the risk of iTTP relapse.

Conversely, 1%–4% of patients with SLE develop iTTP (7). Additionally, in the registry study of patients with TTP-HUS in Oklahoma, 2 of the 10 women who had both a history of iTTP and subsequent pregnancies had iTTP relapse. Notably, one of the 2 women with iTTP relapse in their subsequent pregnancies had SLE (6). Case 2 was positive for ANA and anti-dsDNA after her first pregnancy complicated by iTTP; however, she did not meet the diagnostic criteria for SLE owing to the lack of clinical symptoms of SLE. However, if she had an iTTP relapse, she met the diagnostic criteria for SLE. The mechanisms wherein various tissue injuries occur in patients with SLE can cause iTTP in patients with SLE (8). However, although no evidence-based treatment to prevent iTTP relapse is available, Case 2 received medication with PSL and HCQ according to the therapy for SLE and delivered a full-term infant without iTTP relapse. Steroids may suppress ADAMTS13 inhibitor production. HCQ is believed to exert its immunomodulatory effects by accumulating in lysosomes. Treatments with PSL and HCQ may contribute to iTTP relapse prevention in her subsequent pregnancy.

This is the first report showing that the close monitoring of plasma ADAMTS13 activity levels and aggressive therapeutic interventions in underlying diseases associated with iTTP could lead to positive pregnancy outcomes. This case report provides useful information for clinical practitioners in perinatal medicine.

Acknowledgments

We acknowledge and thank all the members of the multidisciplinary teams at Kobe University Hospital and in particular: Dr. Tomonori Tanaka (Department of Pathology), Dr. Kazumichi Fujioka (Department of Pediatrics), Dr. Yutoku Shi, Dr. Hitomi Imafuku, Dr. Masashi Deguchi, and Dr. Yoshito Terai (Department Obstetrics and Gynecology).

Disclosure

The authors state that they have no conflict of interest.

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Figure legends

Figure 1. Clinical course of Case 1.

In the upper chart, black circles indicate platelet counts (× 10^4/μL; normal range, 15.8–34.8 × 10^4/μL), and white triangles indicate serum haptoglobin levels (mg/dL; normal, >19 mg/dL). In the lower chart, black and white circles indicate the serum levels of ADAMTS13 activity (%; normal, >10%) and ADAMTS13 inhibitor (BU/mL; normal, <0.5 BU/mL), respectively.

Abbreviations: GW, gestational week; POD, postoperative day; RBC, red blood cell.

Figure 2. Clinical course of the first pregnancy of Case 2.

In the upper chart, black circles indicate platelet counts (× 10^4/μL; normal range, 15.8–34.8 × 10^4/μL), white triangles indicate serum haptoglobin levels (mg/dL; normal, >19 mg/dL), and white circles indicate serum creatinine levels (mg/dL; normal, <0.79 mg/dL). In the lower chart, black and white circles indicate the serum levels of ADAMTS13 activity (%; normal, >10%) and ADAMTS13 inhibitor (BU/mL; normal, <0.5 BU/mL), respectively.

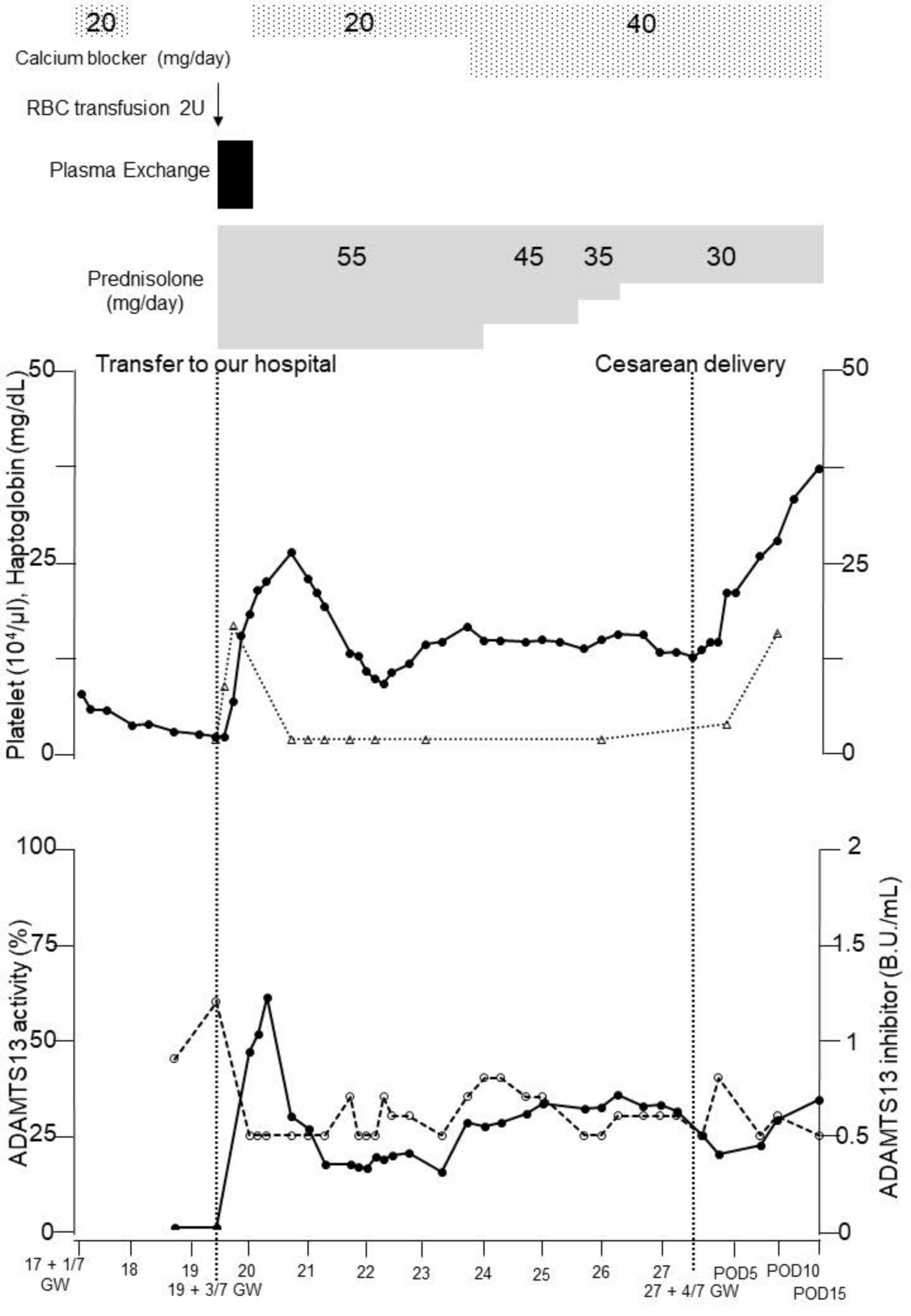
Abbreviations: GW, gestational week; PPD, postpartum day; PC, platelet concentrate; RBC, red blood cell.

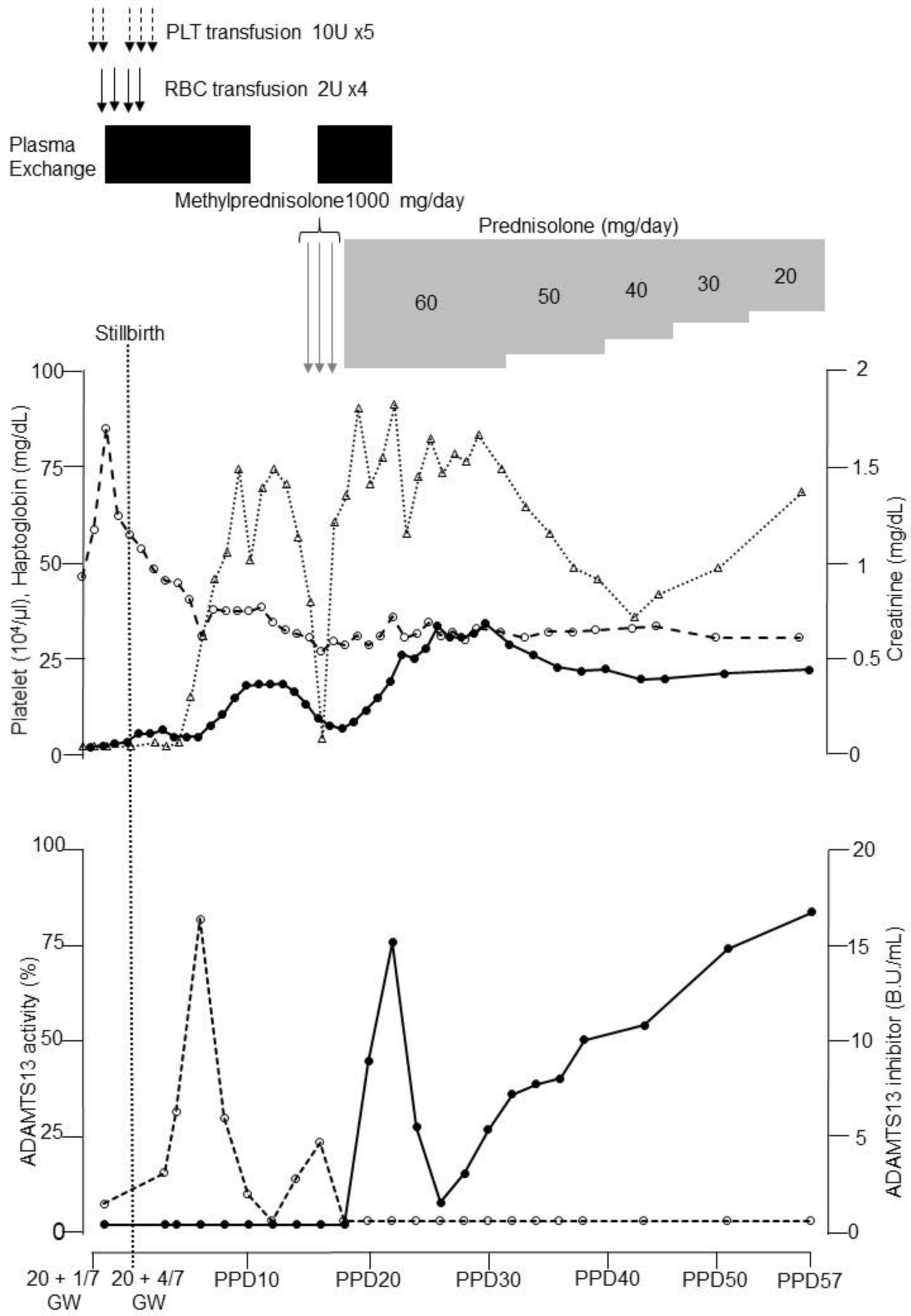
Figure 3. Clinical course of the second pregnancy of Case 2.

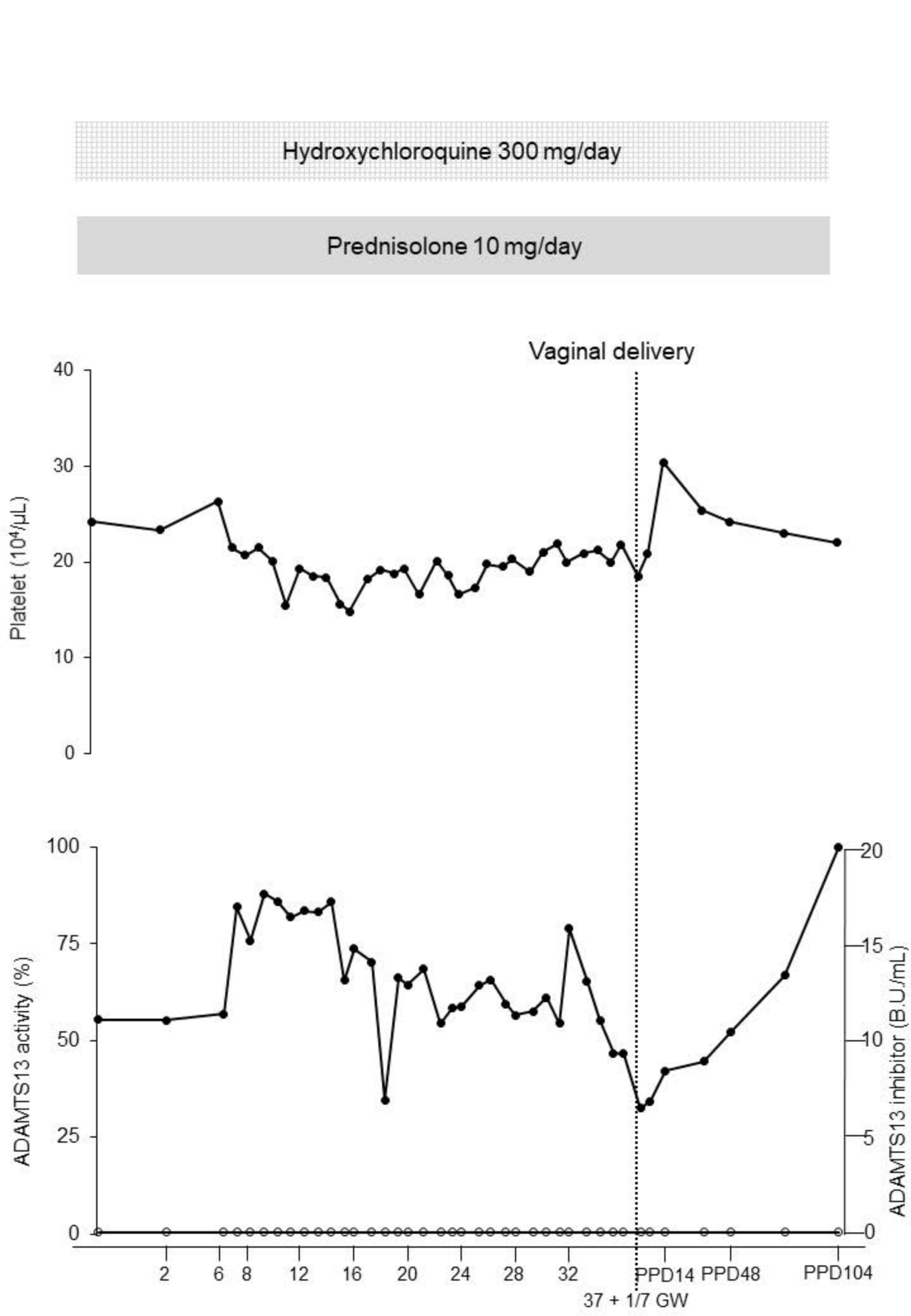
In the upper chart, black circles indicate platelet counts (× 10^4/μL; normal range, 15.8–34.8 × 10^4/μL). In the lower chart, black and white circles indicate the serum levels of

ADAMTS13 activity (%; normal, >10%) and ADAMTS13 inhibitor (BU/mL; normal, <0.5 BU/mL), respectively.

Abbreviations: GW, gestational week; PPD, postpartum day.


20
20
40
Calcium blocker (mg/day)
RBC transfusion 2U
Plasma Exchange
55
45
35
30
Prednisolone (mg/day)
Transfer to our hospital
Cesarean delivery
Platelet (10^4/μl), Haptoglobin (mg/dL)
50
25
0
ADAMTS13 activity (%)
100
75
50
25
0
ADAMTS13 inhibitor (B.U./mL)
2
1.5
1
0.5
0
17 + 1/7 GW
18
19
19 + 3/7 GW
20
21
22
23
24
25
26
27
27 + 4/7 GW
POD5
POD10
POD15


PLT transfusion 10U x5
RBC transfusion 2U x4
Plasma Exchange
Methylprednisolone1000 mg/day
Prednisolone (mg/day)
60
50
40
30
20
Stillbirth
Platelet (10⁴/μl), Haptoglobin (mg/dL)
Creatinine (mg/dL)
ADAMTS13 activity (%)
ADAMTS13 inhibitor (B.U./mL)
20 + 1/7 GW
20 + 4/7 GW
PPD10
PPD20
PPD30
PPD40
PPD50
PPD57


Hydroxychloroquine 300 mg/day
Prednisolone 10 mg/day
Vaginal delivery
Platelet (10^4/μL)
40
30
20
10
0
ADAMTS13 activity (%)
100
75
50
25
0
ADAMTS13 inhibitor (B.U./mL)
20
15
10
5
0
2
6
8
12
16
20
24
28
32
PPD14
PPD48
PPD104
37 + 1/7 GW