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At present, both hematologists and obstetricians seem to avoid excess interventions in managing moderate immune thrombocytopenic purpura (ITP, defined as a platelet count of 40,000-60,000 ml 1) in pregnancy [1,2]. On the other hand, it is true that pregnant women with severe ITP (defined as a platelet count of less than 20,000 ml 1) often require aggressive intervention, e.g., treatment with a combination of drugs, splenectomy, and Cesarean section [2]. Accordingly, combination therapy of high-dose intravenous immunoglobulin (IVIG) and corticosteroids is the main course of management, even in severe patients. We report here on a pregnant woman with severe and refractory ITP (platelet count of about 1000 ml 1 or more less) who was managed with combination therapy of high-dose IVIG and corticosteroids together with short-term danazol in the third trimester. We also discuss the benefits of high-dose IVIG combined with corticosteroids, and risks of management with danazol. A 30-year-old nulligravid Japanese woman, who was diagnosed 5 years earlier with severe chronic ITP associated with a positive serologic test for antiphospholipid antibody, became pregnant under permission of the physician in charge. Before pregnancy, she was given 10 mg/day prednisone and 200 mg/day danazol. No splenectomy was performed, based on the patient's wishes. The above therapeutic regiment maintained platelet count at 40,000-50,000 ml 1. At the time of conception, danazol treatment was terminated, which resulted in a reduction of platelet count to around 20,000 ml 1. At 6 weeks of gestation, the platelet count was only 1000-2000 ml 1 while she was continuously being treated with 10 mg/day prednisone. An increase in the dose of prednisone to 25 mg/day failed to increase the platelet count. At 7 weeks of gestation, to maintain the platelet count above 20,000 ml 1, she received one course of high-dose IVIG at 0.4 g/kg/day for five

consecutive days, together with 25 mg/day of prednisone. After a temporary rise in platelet count (35,000 ml 1), the count returned to about 700-3000 ml 1. Two other courses of high-dose IVIG transiently increased platelet count to 10,000 ml 1, but the effect was transient, lasting for only 1 week. At 28 weeks of gestation, many petechiae and minor purpura were identified on the limbs, which did not disappear until childbirth. At 31 weeks of gestation, an intractable genital bleeding occurred. Oligohydramnios was detected on ultrasound examination during the same week. After written informed consent had been obtained, to prevent the genital bleeding, a combination therapy with high-dose IVIG and danazol (200 mg/day) was immediately provided. Three days of such treatment resulted in a rapid rise of platelet count to 22,000 ml 1. At 32 weeks and 1 day, an emergency Cesarean section was performed following the detection of abnormal fetal heart rate. Immediately prior to the operation, the patient received 30 U of packed platelets. The transfusion of platelets just before laparotomy increased the platelet count to 132,000 ml 1 when measured intraoperatively. A female infant weighing 1866 g was delivered with Apgar scores 9 and 10 at 1 and 5 min, respectively. The newborn had no visible physical abnormalities including virilization, and the platelet count was 220,000 ml 1 at delivery. Total blood loss during the operation was 1150 ml. All parameters of the coagulation system were within the normal limits apart from the platelet count. On the seventh postpartum day, the platelet count was still about 20,000 ml 1 under treatment with prednisone (25 mg/day) and danazol (200 mg/day). Both the mother and infant had an uncomplicated postnatal course. The baby went home at 4 weeks of age and clinical examination at 18 months of age showed normal growth and no abnormalities.

The causal relationship between 3 days of danazol therapy and the rise in the patient's platelet count remains unknown. A rise in platelet count induced by danazol often takes place after several weeks of administration [3], while immunoglobulin increases platelet count within several days. In our patient, who had been refractory to IVIG and oral glucocorticoid therapy, the effect of the combination therapy of high-dose IVIG with danazol was not clear.

A number of studies have reported that inadvertent use of danazol during the first trimester of pregnancy resulted in female fetal virilization, including clitoral hypertrophy,

fused labia, and urogenital sinus malformation [4]. Danazol, a synthetic androgen derived from ethisterone, is used for the treatment of endometriosis, certain breast disease, and ITP. Female fetal genital tissue is very responsive to exogenous androgens between 7 and 12 weeks of gestation, and continues to exhibit some response until 20 weeks of gestation, which can cause variable virilization. However, the impact of androgen on fetal virilization seems to be very little after 20 weeks of gestation, since the female phenotype is complete by 20 weeks of gestation [5], and that excess maternal androgen after that stage is converted to estradiol-17b by aromatase in both placenta and fetus [6]. The influence of danazol on the brain (gender identity, sexual behavior, and levels of aggression) remains to be elucidated. In contrast, there is no evidence for this side effect when danazol is administered in the third trimester.
Unfortunately, in the present case, effects of danazol combined with high-dose IVIG and corticosteroids in the third trimester were not unclear. Even in a pregnant woman who is refractory to IVIG and oral glucocorticoid therapy, combination treatment of high-dose IVIG with corticosteroids may not result in successful management. In that case, a short-term danazol combined with high-dose IVIG and corticosteroids in the third trimester may be recommended.

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