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Pregnancy-Related Thrombosis in a Woman With Congenital Afibrinogenemia: A Report of Two Successful Pregnancies

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We managed two pregnancies in a woman with congenital afibrinogenemia with increasing amounts of cryoprecipitate to achieve a pre-infusion fibrinogen level of 60 mg/dL. The first pregnancy resulted in placental abruption at 36 weeks, in spite of recent cryoprecipitate infusion. Both placentas showed infarction. Post-partum ovarian and renal vein thromboses complicated the second pregnancy. Mean FVIII (344%) and vWF Antigen (323%) were elevated prior to cryoprecipitate infusion, with mean post-infusion levels of 367% and 363%. The clearance of fibrinogen after cryoprecipitate infusion increased during the course of pregnancy. A paradoxical prothrombotic state with embolization may play a role in the observed complications of pregnancy. Am. J. Hematol. 76:267–270, 2004. © 2004 Wiley-Liss, Inc.

Key words: afibrinogenemia; pregnancy; thrombosis

INTRODUCTION

Congenital absence of fibrinogen causes a bleeding disorder as well as paradoxical thromboembolism [1]. Pregnancy ends in miscarriage due to hemorrhage at 6–8 weeks of gestation without replacement therapy. A published recommendation advocates that a higher level of fibrinogen be maintained as the pregnancy progresses in order to avoid placental abruption [2]. This report details evidence of a prothrombotic state in two pregnancies in a woman with afibrinogenemia. The observed prothrombotic tendency in this woman suggests that risks of bleeding and thrombosis must be balanced during pregnancy.

CASE REPORT

This patient presented in the newborn period when a heelstick continued to bleed for 6 days. Fibrinogen was undetectable by an immunologic technique capable of detecting nanogram amounts of fibrinogen antigen. Clinical bleeding episodes were similar to those described in a large Iranian cohort [1], including splenic rupture and a hemorrhagic corpus luteum at menarche. She was placed on oral contraceptive medication prophylaxis to prevent future ovulation associated bleeding. She then developed a spontaneous intraventricular and intraparenchymal CNS hemorrhage at 21 years of age. To prevent recurrent CNS bleeding, regular infusions of cryoprecipitate were given to maintain fibrinogen levels at >60 mg/dL [3]. Conception occurred while the patient was on this prophylaxis when she had self-discontinued the oral contraceptive medication.

First Pregnancy

Based on previous reports [2,4,5], increasing amounts of cryoprecipitate (20–25 bags twice a week)

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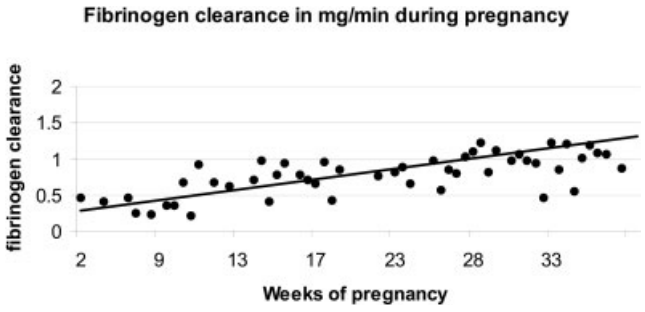

Fig. 1. Increasing quantities of cryoprecipitate infusion were required to maintain a steady level of fibrinogen during this pregnancy. The decline in fibrinogen level after cryoprecipitate infusion becomes more rapid as pregnancy advances. Each point represents one observation. Fibrinogen clearance in mg/min was calculated based on fibrinogen levels, interval between infusions, mean fibrinogen concentration of sampled cryoprecipitate units, and estimated volume of distribution for different stages of pregnancy from published data. A regression line described by the equation $y = 0.0146x + 0.27$ ($r^2 = 0.25$, ANOVA significance < 0.001) has been added.

were given to keep the fibrinogen level >60 mg/dL. We graphed fibrinogen clearance as a function of the stage of pregnancy (Fig. 1) based on sampled cryoprecipitate fibrinogen concentration (Clauss method), interval between infusions, and volume of distribution. Fibrinogen clearance increased as pregnancy progressed. At 35.6 weeks of gestation, the patient presented with severe back pain and fetal heart tones of 80 bpm with minimal variability. An emergency Cesarean delivery revealed placental abruption. The patient had received cryoprecipitate less than 24 hr previously, with a post-infusion level of 205 mg/dL. Fibrinogen level at the time of clinical presentation was 51 mg/dL. The platelet count fell from 233,000 to 76,000, suggestive of consumption. She delivered a 2715-g male infant with APGAR scores of 3, 5, and 7 at 1, 5, and 10 min, respectively. Placental pathology revealed a 14 × 5 cm peripheral depression of the maternal surface due to retroplacental hematoma associated with multiple recent infarctions measuring less than 1 cm. This child had a low fibrinogen level (84 by Clauss) in the perinatal period. His fibrinogen level later normalized (fibrinogen 223 at 17 months of age). This boy has had normal growth and development without obvious sequelae.

Second Pregnancy

Two years later, conception again took place during cryoprecipitate prophylaxis. During this pregnancy, the fibrinogen level was again maintained >60 mg/dL. During the third trimester mean pre-infusion levels were as follows: fibrinogen, 81 mg/dL (range 17–112); Factor VIII 344% (range 279–370%); and von Willebrand factor antigen 323% (range 245–453%). Mean post-infusion levels were 175 mg/dL (range 108–235%); 366% (range 275–540%); and 362% (286–493%), respectively. Based on paired samples, the mean increases after infusion were as follows: fibrinogen 99 mg/dL, Factor VIII 44%, and von Willebrand factor antigen 56%. Elective Cesarean delivery was performed at 34.5 weeks of an appropriately grown 2625-g male infant (APGAR scores 9 and 9). Placental pathology revealed three 1- to 2-cm peripheral infarcts and focally increased perivillous fibrin beneath the chorionic plate. The infant required surfactant for respiratory distress syndrome. This child also had a low fibrinogen level (116 by Clauss) in the perinatal period. His fibrinogen level later normalized (fibrinogen 151 at 14 months of age). This boy has also had normal growth and development without obvious sequelae.

On the 7th post-partum day, the propositus developed fever, chest pain, and uterine tenderness. Abdominal CT scan at 9 days was suggestive of gonadal vein thrombosis. A right upper lobe infiltrate was found on chest X-ray at 11 days. MRI imaging 13 days postpartum revealed an enlarged uterus, with loculated ascites. A thrombus within the left renal vein without extension into the IVC was noted. Inferior to the left renal vein, a thrombus was also noted within the left gonadal vein. Assays of antithrombin, protein C, protein S, APCR, and tests for the lupus anticoagulant were all normal. The patient was treated with unfractionated heparin and cryoprecipitate. Repeat MRI 14 days later showed that the thrombi had disappeared (27 days post-partum) and heparin was discontinued. Both deliveries were also complicated by wound dehiscence.

DISCUSSION

Women with congenital afibrinogenemia typically are able to conceive and permit embryonic implantation; however, pregnancy invariably results in genital bleeding and spontaneous abortion at 6–8 weeks of gestation unless fibrinogen replacement is given. Previous to this report, six successful pregnancies in women with congenital afibrinogenemia had been documented in the literature [1,2,4–6]. We have described two pregnancies in an afibrinogenemic woman with successful infant outcomes but thrombotic complications.

Our patient had complete placental abruption within 24 hr of receiving sufficient cryoprecipitate to raise her fibrinogen level to 205 mg/dL. During her second pregnancy, she developed overt gonadal and

renal vein thrombosis. We are concerned that the recommendation to maintain high levels of fibrinogen may have played a role in the development of paradoxical thromboses. Patients with afibrinogenemia have been reported to have had both arterial and venous thrombosis, with and without prior infusion of fibrinogen, and with and without underlying tendencies to thrombophilia [7].

We noted a trend toward more rapid fibrinogen clearance as pregnancy advances (Fig. 1). The critical role of fibrin and fibrinogen degradation products in the maintenance of pregnancy is under investigation [8].

Fibrinogen-knockout mice reproduce the human experience. Conception ends with complete placental abruption and abdominal bleeding at day 9.75, which is fatal to the mother. Pregnancy can be maintained in these mice with two infusions of human fibrinogen, given at days 8.5 and 17.5 [9]. Histologic assessment of embryonic, placental, and decidual tissues in this mouse model elucidates the role of fibrinogen in the maintenance of pregnancy. Fibrinogen is essential as a hemostatic agent and is also important in the formation of a stable fibrinoid layer to anchor the spongiotrophoblast layer to the decidua. Embryonically derived fibrinogen is not required for successful pregnancy. The study of knockout mice speculates on the role of thrombosis in the complications of pregnancies.

Knockout mice also provide insight into the paradoxical phenomenon of thromboembolism. With vascular injury, abundant platelet deposition is similar to wild-type animals. These thrombi, however, are not stable but are stripped off the vessel wall and embolize to result in downstream occlusion [10]. Human afibrinogenemic blood in an in vitro perfusion system results in increased surface coverage with large, loosely packed thrombus [11]. Fibrin plays a role in inactivating thrombin, and patients with low fibrinogen may be at risk for thrombosis due to the persistent presence of thrombin [12].

Based on their experience, Kobayashi et al. [2] made recommendations regarding pregnancy in women with congenital afibrinogenemia. They recommended keeping the fibrinogen level greater than 60 mg/dL and, if possible, greater than 100 mg/dL. They recommend continuous infusion of fibrinogen concentrate during labor to maintain fibrinogen higher than 150 mg/dL or, ideally, greater than 200 mg/dL.

Our concern is that the paradoxical thrombotic tendency may play a role in the observed frequency of placental abruption. Placental abruption is thought to be caused by a rupture of the maternal spiral arterioles in the decidua basalis. The risk of placental abruption is also increased in women with thrombophilia [13]. In the two cases presented here, there was an insufficient amount of maternal decidua to fully assess the maternal vessels. The multiple infarcts observed in both placentas, however, may be due to embolization of the spiral arterioles by unstable thrombi or enhanced clot formation at the trophoblast–decidua interface, with subsequent infarction of the corresponding placental parenchyma.

Levels of Factor VIII and von Willebrand factor prior to cryoprecipitate infusion were elevated in our patient. Cryoprecipitate infusion likely made a further contribution to the high levels, which were observed because cryoprecipitate contains appreciable quantities of Factor VIII and von Willebrand factor in addition to fibrinogen. Cryoprecipitate was used because fibrinogen concentrate is not available in the United States. Fibrinogen concentrate is the product used by Kobayashi et al. [2]. Factor VIII and von Willebrand factor have been implicated in thrombophilia. It is not clear what additional role this aspect of cryoprecipitate therapy played in the development of thrombosis in our patient.

In our review of the literature, it is interesting to note that one Iranian woman had a full term vaginal delivery after replacement therapy only during the first 6 months of gestation [1]. Knockout mice were also found to be capable of sustaining normal gestation with only two infusions of fibrinogen [9]. We did not attempt to maintain these pregnancies with a shortened period of infusion because of the patient's history of spontaneous CNS bleeding and because of strong contrary recommendations in the literature [2]. We recognize that the risk of bleeding and of thromboembolic events must be balanced in these patients. Recommendations for high-level replacement during pregnancy should be moderated with the caution that thromboembolic phenomena are also a possibility.

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