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Case report

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Hypofibrinogenemia Complicating Pregnancy – Case Report and Review of Literature

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ABSTRACT

Congenital fibrinogen disorder may be either afibrinogenemia / hypofibrinogenemia / dysfibrinogenemia. Afibrinogenemia may present at birth as bleeding from umbilical cord. Patients with hypofibrinogenemia may present only during surgical intervention or during pregnancy. Pregnancy with this condition is associated with a very high incidence of abortion & abruption. Fibrinogen replacement can be done using either cryoprecipitate or fibrinogen concentrate. Successful pregnancies have been reported using cryoprecipitate & fibrinogen concentrate (FC). We report a woman with 6 abortions previously who was treated with fibrinogen replacement therapy & delivered a live child.

INTRODUCTION

Fibrinogen plays a pivotal in role in normal haemostasis by promoting clot formation, platelet aggregation & fibrinolysis. It has been established that maintenance of haemostatic balance is necessary for successful outcome of pregnancy.

Congenital afibrinogenemia or hypofibrinogenemia has been shown to have adverse pregnancy outcomes like spontaneous abortion, abruption placenta and post partum haemorrhage [1]. Successful pregnancies have been reported using cryoprecipitate and recent studies have shown use of fibrinogen concentrate to be very effective. We report an interesting case of a multiparous woman with previous six abortions. The seventh pregnancy was treated with fibrinogen concentrate and she had a successful pregnancy outcome.

CASE SUMMARY

A 36 year old woman who was married for 10 years had four repeated spontaneous abortion. She had profuse bleeding during the abortions. 15 days after the 4th abortion she developed severe headache; a CT scan was taken which showed a left frontoparietal subdural haematoma. She was referred to a tertiary centre for further haematological evaluation. She did not have any history of bleeding tendency or a family history of

bleeding disorders. The investigations showed fibrinogen level of 18.7mg/dl, Factor VIII 126.3%, PT > 2 minutes, APTT > 3 minutes, TT 31.8 sec. Based on these investigations, she was diagnosed to have hypofibrinogenemia / dysfibrinogenemia. The fifth pregnancy also ended in a spontaneous abortion. During the sixth pregnancy she was started on cryo precipitate, and in the fourth month had profuse bleeding. She had massive chorioamniotic separation and since she failed to respond to medical treatment hysterotomy was done. Post abortal bleeding was treated with blood and blood products.

Pre-pregnancy counseling was done and she was advised fibrinogen concentrate from the time of conception. After conceiving she was administered fibrinogen concentrate every 4th day and fibrinogen levels were monitored twice weekly and the dose was adjusted accordingly. The fibrinogen level was kept between 85 to 100 mg/dl.

Considering her bad obstetric history, risk of abruption and history of previous hysterotomy patient was planned for elective caesarean section at 36 weeks of pregnancy. She was Rh negative, so sufficient blood had to be arranged. Hematologist consultation was obtained and was advised to maintain fibrinogen level around 1 gm/L and to consider thromboprophylaxis after surgery. With back up of sufficient blood, blood products and fibrinogen, patient was posted for elective caesarean section. Her hemoglobin was 13.4gm/dl and fibrinogen level on the day of surgery was 94mg/dl. She was given 2.5gm of Fibrinogen concentrate (FC) prior to surgery. Caesarean section was done under general anesthesia. She was started on tranexamic acid infusion just prior to surgery. Steps were taken to minimize blood loss. The blood loss during surgery was around 750 ml. Post-operatively she had close monitoring of vital parameters, fibrinogen levels 4th hourly. Hemoglobin, PT and APTT were repeated 8 hours later. The amount of blood loss was accurately calculated by collecting and weighing the soaked pads and linen. She was given 1.5 gm of Fibrinogen concentrate (FC), fibrinogen level was maintained at 100 to 110 mg/dl. The post-operative blood loss was around 1000ml. She also received eight units of cryo precipitate and one unit of blood. Her hemoglobin dropped to 9.7gm/dl. Although thromboprophylaxis was advised, in view of bleeding it was not administered.

24 hours following delivery, patient stabilized with no excessive bleeding with a fibrinogen level of 122mg/dl. She was ambulated early. She made an uneventful recovery with no evidence of sepsis or thrombosis and she was discharged on the 5th post operative day. She did not receive any further replacement and on discharge her fibrinogen level was 68mg/dl. Baby was normal at birth.

USE OF FIBRINOGEN CONCENTRATE

Fibrinogen concentrate is available as a powder to be dissolved in 50 ml of water and be given as a slow IV injection. The constituted solution may be kept at room temperature for 24 hours. The advantages of fibrinogen concentrate over cryoprecipitate are that it has less viral transmission, less immunogenic, lesser thromboembolic events [2]. The dose is determined as follows:

Dose (mg) = [Target fibrinogen level (mg/dL) – measured fibrinogen level] ÷ 1.7 x body weight (kg) [3].

DISCUSSION

Fibrinogen is a glycoprotein and is present at concentration of 200 to 400 mg/dl with half-life of 4 days [4].

Fibrinogen abnormalities comprise two classes of plasma fibrinogen defects: Type I, afibrinogenemia or hypofibrinogenemia, which has absent or low plasma fibrinogen antigen levels (quantitative fibrinogen deficiencies), and Type II, dysfibrinogenemia or hypodysfibrinogenemia, which shows normal or reduced antigen levels associated with disproportionately low functional activity (qualitative fibrinogen deficiencies) [5]

It plays an important role in hemostatic balance [6].

- It is a substrate for clot formation.
- It binds to platelet to support aggregation.
- It has role in wound healing.
- Fibrin clot is a template for both thrombin binding and fibrinolytic system.

Accordingly any abnormality of fibrinogen may result in defect of any of these key functions. Afibrinogenemia is total absence of fibrinogen.

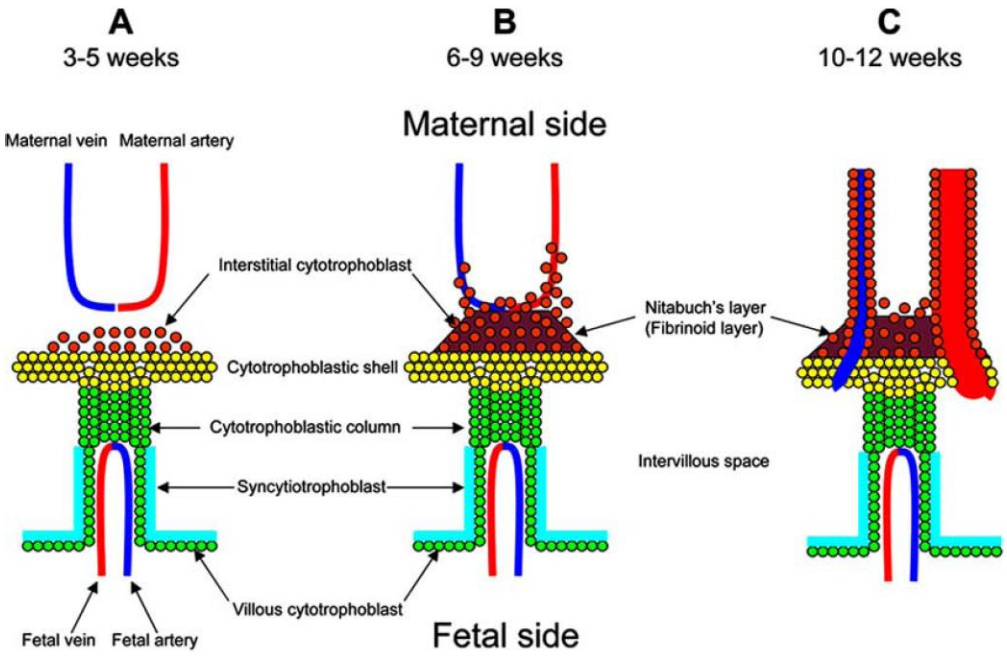
Hypofibrinogenemia is fibrinogen levels is <150 mg/dl. Dysfibrinogenemia is malfunctioning of the fibrinogen with levels being normal.

The first clinical report of afibrinogenemia was Rabe & Salomen in 1920 of a boy with repeated bleeding episodes [7] since birth and hypofibrinogenemia was reported. Several cases with this disease have been previously reported, all of which have resulted in abortions during the early stage of gestation (Dube et al, 1970; Matsuno et al 1977, Ebron et al 1985 [8, 9, 10]). The first successful pregnancy with congenital afibrinogenemia was reported by Inamoto and Terao 1985. In this pregnancy the patient presented in early pregnancy with bleeding with a fibrinogen level of 25mg/dl. Fibrinogen was infused, gradually stepped up and delivered at 36 weeks by caesarean section [11].

Why is abortion common in these individuals?

It has been shown that at 6 weeks of gestation, the interstitial cytotrophoblasts reach the maternal vessels and begin the remodeling process of vessels. Maternal endothelial cells are replaced by these interstitial cytotrophoblasts. During the remodeling of the vessels, active bleeding near the cytotrophoblastic shell is observed, following which Nitabuch's layer (fibrinoid layer) is generated at that site. The genital bleeding in afibrinogemic patients starts around 5-6 weeks of gestation and this period closely matches the period of vessel remodeling by interstitial cytotrophoblasts and the formation of Nitabuch's layer. This uncontrollable bleeding leads to spontaneous miscarriage in the patients [12]. Elevated levels of fibrinogen help maintain placental implantation which may be deficient in women with hypofibrinogenemia. This theory fits in with the description seen in most untreated patients.

Figure 1: Intercommunication of maternal and fetal cells and vessels in the placenta [8].



What causes abruption in these individuals?

Abruption is most often thought to be a thrombotic event. It has been reported that several syncytial knots and hyaline membrane were found in the placenta. These strongly indicated that thrombotic events continuously occurred in the placenta.

Remjin et al [13] in his study helped to explain this paradox. This in vitro study demonstrated that blood from afibrinogenemic patient forms abnormal clots under flow conditions. The platelet aggregates were larger and more loosely packed than normal, creating unstable clots. In turn, these abnormal clots

caused a higher tendency of thrombus breakdown and possible microembolizations. Along with the abnormal placental attachment shown in the previous studies, this thrombotic tendency helps to explain the increased placental abruption, as well as the possibility for other pregnancy complications commonly associated with thrombotic tendencies such as fetal growth restriction.

Takao has described 3 cases of congenital hypofibrinogenemia, all treated with fibrinogen and has proposed certain guidelines [14]:

1. Genital bleeding usually begins at 5 weeks gestation and spontaneous abortion always occurs at 6±8 weeks gestation without fibrinogen infusion.
2. The fibrinogen level must be at least 0.6 g/l and, if possible, higher than 1.0 g/l during the pregnancy to prevent bleeding and abortion
3. The amounts of fibrinogen necessary increase as the pregnancy progresses.
4. The fibrinogen level under the continuous infusion of fibrinogen during labour must be maintained at a minimum of 1.5 g/l and, if possible, higher than 2.0 g/l to prevent placental abruption;
5. The puerperium is usually uneventful with a reduced dose of fibrinogen infusion;

Bornikova et al [15] has done a review on congenital fibrinogen deficiency between 1961 to 2010 using MEDLINE search. Data on 18 obstetric patients confirmed a very high rate of 1st trimester abortion in women with afibrinogenemia. Even when Fibrinogen replacement therapy (FRT) was given by 5 weeks of gestation, bleeding was common. Placental abruption was a particularly vexing complication and was not completely prevented by Fibrinogen replacement therapy (FRT). Fibrinogen clearance markedly increases as pregnancy advances requiring higher and more frequent dosing.

CONCLUSION

Hypofibrinogenemia in pregnancy is a rare disease occurring in 1 in 1 million. Untoward complications in pregnancy like abortion, abruption and post-partum haemorrhage are common. However fibrinogen replacement therapy is effective in preventing these episodes and reduces the high rate of pregnancy loss. Early start of Fibrinogen replacement therapy (FRT), continuous monitoring of fibrinogen levels and step up of dose as pregnancy advances is the key to success.

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ETHICAL CLEARANCE

Patient consent is not required because the patient identification is not disclosed in any way in this article.

CONFLICT OF INTEREST

None

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