CASE REPORT

Successful Pregnancy in a Patient With Recurrent Pregnancy Loss Due to Afibrinogenemia Managed With Cryoprecipitate Prophylaxis in a Resource-limited Setting

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ABSTRACT

Recurrent pregnancy loss (RPL) can be defined as loss of pregnancy on or before 20 weeks of gestation. About half of the cases, cause of recurrent miscarriage is unknown. Bleeding disorders induced miscarriage has to be thoroughly investigated for the sake of both mother and fetus. Here is an interesting case report of a 24-year-old patient who was diagnosed to have afibrinogenemia after three consecutive miscarriages. Fibrinogen level was 5 mg/dl with prolonged prothrombin time greater than 180 seconds and activated thromboplastin time greater than 180 seconds. We managed with periodic cryoprecipitate transfusion. Pregnancy course was uneventful and delivered a healthy female child at 34 weeks of gestation under supervision of multidisciplinary team. Here we are discussing the management and how we approached the case to have a successful pregnancy outcome.

Keywords: Abortion, Afibrinogenemia, Cryoprecipitate, Pregnancy, Fibrinogen

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INTRODUCTION

Recurrent pregnancy loss (RPL) prior to 20 weeks of gestation occurs in 1-2 % of pregnancies. (1) According to previous reports, two consecutive pregnancy losses are seen in 2 % and 3 consecutive pregnancy loss in 0.4 to 1 % of cases. Etiology of RPL is mainly classified into primary and secondary.

Based on available literature, 55% - 62% of RPL are due to the abnormalities in blood coagulation. Other defects causing RPL are:

1. Chromosome / Gene (7%)
2. Anatomy 10%)
3. Hormones (15%)
4. Unexplainable (6%)

Bleeding defects are rare but hyper coagulable defects are extremely common. Out of all the coagulation factors, factor XIII and fibrinogen plays a major role in placental implantation and maintaining pregnancy. Based on available literatures, deficiency of factor XIII and fibrinogen results in RPL. This is a case of afibrinogenemia induced recurrent pregnancy loss which is managed with periodic cryoprecipitate transfusion leading to a successful delivery.

CASE REPORT

A 24-year-old G4A3 presented to our labor room with a history of vaginal bleeding after a cervical encirclage procedure from an outside local hospital. She was hemodynamic ally stable with BP of 100/50, pulse rate of 98 beats per minute and respiratory rate of 22 beats per minute. There were no obvious signs of disseminated intravascular coagulation. She was born of a non-consanguineous marriage. She had normal menstrual history with 3-4 days of bleeding. Patient did not have any umbilical stump bleed, joint bleed or any relevant bleeding history in the past.

In her previous pregnancies she noticed recurrent events of vaginal spots eventually leading to spontaneous abortions without undergoing any therapeutic procedures. From the available details, antiphospholipid antibody syndrome (APLA) workup was negative in her previous pregnancies. Family history was also negative for any bleeding or thrombotic disorders. Routine investigation & screening for coagulation tests were done. Due to ongoing bleed, she was initiated on Packed Red Blood Cells (PRBC) transfusion and other supportive measures and was stabilized.

Her initial lab investigations showed anemia with mild thrombocytopenia along with a prolonged PT & aPTT. The renal & liver function tests were normal. Peripheral blood smear was normal with no features of hemolysis or DIC. Fibrinogen assay (clauss method) showed a

value of 5 mg/dl. Ultrasonography showed a single live intrauterine fetus of 13 to 14 weeks of gestation with sub-chorionic bleed.

Rotational Thermoelectrometry (ROTEM) showed a prolonged coagulation Time (CT) in FIBTEM and EXTEM with low MCF (maximum clot formation in FIBTEM. There was no primary clot formation in the qualitative Factor XIII (urea clot solubility test). Clinical and laboratory findings were more likely to diagnose as case of Afibrinogenemia. Due to non-availability of fibrinogen concentrates she was started on cryoprecipitate (1unit/10 kg) along with other supportive measures which arrested the acute bleed. A multidisciplinary discussion was done and it was decided to start her on Cryoprecipitate prophylaxis and monitor the fetus closely.

The dosage and frequency of cryoprecipitate transfusion is as shown in (Table I). The target was to keep the value above 60 mg/dl till 28 weeks of Gestational Age. A multidisciplinary meeting decided to induce the patient at 34 weeks of gestation and also to keep the fibrinogen level at or above 200 mg/dl in peripartum and three days postpartum period. At 30 weeks of gestation; even though the dose was escalated; average weekly fibrinogen value remained less than 100 mg/dl without any bleeding. No further increase in prophylactic dosing was advised due to the chances of thrombosis.

She had a normal vaginal delivery at 34 weeks plus 2 days of gestation and a healthy female baby weighing 2.15 kg was born. Following delivery, she developed mild atonic PPH which was managed with Oxytocin infusion. Approximate blood loss was only 600 ml. Patient was on close observation to keep the fibrinogen above 200 mg/dl for at least 3 days. No further hemorrhagic or thrombotic complications were encountered in the postpartum period. Coagulation profile of baby showed PT (prothrombin time)-19.20 seconds, INR-1.42, aPTT (activated partial thromboplastin time) - 38.20 seconds, platelet count- 3,02,000 cells/cumm and fibrinogen was 103 mg/dl. There were no bleeding manifestations. Both the mother and child were discharged with an advice to return after 2 weeks for routine post-natal visit.

Table I: Serum fibrinogen levels and dosage of cryoprecipitate transfused according to gestational age from the day of admission till delivery

Gestational Age (weeks)	Fibrinogen (mg/dl)*	Cryoprecipitate dose .	Cryoprecipitate frequency
On admission : GA : 14 weeks	**<10**	1 unit /10 kg	Weekly
15	**123**		
16	**57**		
17	**56**		
18	**75**		
19	**59**		
20	**43**		
21	**89**		
22	**49**	**1 unit /7 kg**	**Twice a week**
23	**54**		
24	**73**		
25	**73**		
26	**59**		
27	**40**		
28	**44**	**1 unit / 7 kg**	**Thrice a week**
28 weeks + 3 day	**66**		
29	**75**		
30	**72**		
31	**83**		
32	**74**		
33	**87**		
33+6 days	**76**		
Management of Labour			
Evening of 33 +6 weeks	**73**	2units/10 kg	
Morning of 34 weeks	**226**	Extra amniotic induction	
Evening of 34 weeks	**193**	Top-upcryo 1unit/10kg	
Morning of 34+1 weeks	**263**	Pharmacological induction	
After noon of 34 + 2 weeks	**275**	FTND ; Female child Fibrinogen :103 mg/dl	

DISCUSSION

Fibrinogen is essential for hemostasis. The final result of extrinsic and intrinsic pathway is the conversion of fibrinogen to fibrin. Thus, deficiency results in increased bleeding or functional defects of fibrinogen which may cause bleeding or thrombotic complications. The likelihood of successful pregnancy appears to correlate with adequate level fibrinogen. The timing of pregnancy loss is typically at approximately five to eight weeks gestation, if fibrinogen replacement therapy is not administered. Thus, as per previous reports it's a hematological emergency and should be diagnosed at the earliest in recurrent miscarriages and there is no consensus regarding when to diagnose and start treatment. Before the availability of routine fibrinogen replacement, women with afibrinogenemia rarely had a successful pregnancy.

The role of fibrinogen appears to be in the integrity of placental insertion rather than in earlier stages such as ovulation, fertilization or initial implantation. In a mouse model of fibrinogen deficiency; there was fatal uterine bleeding at approximately ten days of gestation (2).

The disorders associated with fibrinogen deficiency are mainly classified into quantitative and qualitative. Quantitative disorders are afibrinogenemia and hypofibrinogenemia and qualitative is dysfibrinogenemia.

Congenital afibrinogenemia is a rare bleeding disorder with an autosomal recessive inheritance and is diagnosed when fibrinogen falls below <20 mg/dl. Its frequency is estimated as 1 per 1 million normal populations. First case of congenital afibrinogenemia in pregnancy was reported by Inamoto & Terao in 1985, a second case by Trehan & Fergusson in 1991 and the third case by Kobayashi et al in 1996. (3)

Guidelines from the United Kingdom Hemophilia Centers Doctors' Organization (UKHCDO) and a 2016 consensus from a panel with expertise in bleeding disorders were followed to guide us in the management of our case. (4) These documents recommend such individuals to be treated with fibrinogen concentrate or cryoprecipitate similar to prophylaxis in hemophilia if they have previous bleeding event. As prophylaxis against bleeding, it's considered to keep trough level of fibrinogen at 50 mg/dl.

The Royal College of Obstetricians and Gynecologists (RCOG) guideline published in 2017 provides specific guidance for the management of pregnancy and delivery. It's recommended to start replacement therapy as early as four to five weeks of gestation and to continue throughout pregnancy till delivery. Fibrinogen should be maintained at 100 mg/dl or >50 mg/dl with frequent monitoring at every one to two weeks.

The guideline states that if a previous pregnancy has been unsuccessful, it may be necessary to use a higher trough level. The required dose is likely to increase significantly as the pregnancy progresses due to increased clearance. The recommendation during labor and for a minimum of 3 days postpartum is to keep target levels of fibrinogen at 150 to 200 mg. (5) After the first 24 hours postpartum, a fibrinogen level >50 mg/dl is appropriate until healing is complete but a higher trough level should be maintained if there is previous history of PPH.

Cryoprecipitate can be used when fibrinogen concentrates are unavailable. Fibrinogen present in one unit of cryoprecipitate is approximately 200 to 400 mg. Transfusion of one unit of cryoprecipitate raises 7 to 10 mg/dl of fibrinogen and its half-life is approximately four days.

Complications with Cryoprecipitate include transfusion reactions and thrombosis. Thromboembolic risk can be reduced if we avoid overcorrecting fibrinogen levels.

CONCLUSION

From this case report, we wanted to emphasize that congenital bleeding disorders has to be kept in mind while evaluating recurrent pregnancy loss. Apart from routine PT & aPTT tests, addition of fibrinogen assay and qualitative factor XIII test will enable clinicians to diagnose hidden causes of miscarriage. Once a diagnosis of a coagulation disorder is made, these cases have to be managed at areas having expertise in managing blood disorders and also have a full-fledged Transfusion Medicine department which can cater to the blood needs of the patients. A multi-disciplinary approach with adequate inter departmental communication is a must for the successful outcome of such patients.

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