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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

Vaping associated acute respiratory distress syndrome (ARDS) is a new consideration in the field of radiology with respect to tetrahydrocannabinol (THC) containing electronic nicotine delivery systems (ENDS). The appeal of ENDS product use was initially advertised as being superior to cigarettes because of the limited ingredients compared to the numerous carcinogenic elements found in cigarettes. ENDS products typically contain only four primary components including propylene glycol, vegetable glycerine, nicotine, and flavorants. In recent months, patients with a reported history of vaping have presented to the hospital with respiratory symptoms and demonstrate one of four computed tomography (CT) patterns including acute eosinophilic pneumonia, diffuse alveolar damage, organizing pneumonia, and lipoid pneumonia. The field of radiology is therefore identifying lung pathologies associated with vaping as the sole etiology, particularly in young patients. The different patterns of vaping associated lung pathology are reviewed in this article with the hope that treatment can be initiated after early image findings are identified and to guide treatment planning within the field of interventional radiology (IR).

Keywords: Recurrent Pregnancy Loss (RPL); Afibrinogenemia; Cryoprecipitate; Pregnancy; Abortion

Introduction

Recurrent pregnancy loss (RPL) is defined as three consecutive pregnancy losses prior to 20 weeks from the last menstrual period which are not required to be intrauterine [1-3]. Approximately 15% of clinically recognized pregnancies results in spontaneous abortions [1]. And out of which recurrent pregnancy loss is 1-2%. RPL can be divided into primary and secondary [4]. 2% of women experience two consecutive pregnancy losses and 0.4 to 1% have three consecutive pregnancy losses [5].

Based on available literature; RPL is mainly due to the abnormalities in [6].

- 1.Blood coagulation (55% - 62%)
- 2.Chromosome / Gene (7%)
- 3.Anatomy 10%)
- 4.Hormones (15%)
- 5.Unexplainable (6%)

Coagulation defects comprise the major cause of RPL [6]. Bleeding defects are rare but hypercoagulable defects are extremely common. Of all the coagulation factor deficiencies, only factor XIII and fibrinogen are associated with RPL as they play an important role in placental implantation and maintaining pregnancy [7]. This case report describes a patient with RPL due to afibrinogenmia managed using targeted cryoprecipitate transfusion therapy and resulting in a successful outcome.

Case Report

A 24 year-old female G4A3 presented to our labor room with a history of vaginal bleeding after a cervical encirclage procedure from an outside local hospital. 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. All her three previous abortions occurred within the first 5 weeks of gestation. Anti-phospholipid 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 on going bleed, she was initiated on Packed Red Blood Cells (PRBC) transfusion and other supportive measures and was stabilized.

Her initial lab investigations showed anaemia 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 haemolysis or DIC. Fibrinogen assay (Clauss method) showed a value of less than 10 mg/dl. Ultrasonography showed a single live intrauterine fetus of 13 to 14 weeks of gestation with sub-chorionic bleed.

Rotational Thromboelastometry (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). From the clinical & laboratory findings, a provisional diagnosis of congenital afibrinogenemia was made. It is a rare bleeding disorder with an autosomal recessive inheritance characterized by absence or a very low fibrinogen value below detectable levels.

Due to non-availability of fibrinogen concentrates she was started on cryoprecipitate (1 unit/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 1).The target was to keep the value above 60 mg/dl till 28 weeks of Gestational Age [8-16]. A multidisciplinary meeting decided to induce the patient at 34 weeks of gestation. It was also decided to keep the fibrinogen level at or above 200 mg/dl during and three days postpartum.. At 30 weeks of gestation; even though the dose was escalated; average weekly fibrinogen value remained less than 100 mg/dl but without any bleeding. No further increase in prophylactic dosing was advised due to the chances of thrombosis.

Table 1: Management of Labour.

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	2 units/10 kg	
Morning of 34 weeks	226	Extra amniotic induction	

Evening of 34 weeks	193	Top-upcryo 1 unit/10 kg
Morning of 34+1 weeks	263	Pharmacological induction
After noon of 34 + 2 weeks	275	FTND ; Female child Fibrinogen :103 mg/dl

She delivered a healthy female baby weighing 2.15 kg. She developed a 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. Fibrinogen level of the infant 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.

Discussion

Fibrinogen is essential for hemostasis [8]. 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

Women with fibrinogen abnormalities have an increased incidence of bleeding and thrombotic complications during pregnancy and postpartum, as well as an increased risk of recurrent pregnancy loss and abruptio placenta [13]. 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. Before the availability of routine fibrinogen replacement, women with afibrinogenemia rarely had a successful pregnancy [18].

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 [9]. In a mouse model of fibrinogen deficiency; there was fatal uterine bleeding at approximately ten days of gestation [10].

The disorders associated with fibrinogen deficiency can be either quantitative (afibrinogenemia, hypofibrinogenemia) or qualitative (Dysfibrinogenemia). Congenital afibrinogenemia is a rare bleeding disorder 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 [11].

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 [12,13]. These documents recommend such individuals to be treated with fibrinogen concentrate or cryoprecipitate similar to prophylaxis in hemophilia if they have previous bleeding event. A target trough fibrinogen level of 50 mg/dl is considered reasonable for prophylaxis against bleeding [12].

The Royal College of Obstetricians and Gynecologists (RCOG) guideline published in 2017 provides specific guidance for the management of pregnancy and delivery. (14)Replacement therapy should ideally be commenced as early as four to five weeks of gestation and continued throughout pregnancy and delivery. Target trough fibrinogen level of 100 mg/dl or >50 mg/dl with monitoring every one to two weeks is suggested. The guideline states that if a previous pregnancy has been unsuccessful, it may be necessary to use a higher trough level [17]. 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 a target levels of 150 to 200 mg [14]. 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. One unit of Cryoprecipitate contains fibrinogen present in one unit of whole blood (approximately 200 to 400 mg) in a volume of 10 to 20 ml. One unit of cryoprecipitate raises the fibrinogen concentration by approximately 7 to 10 mg/dl, with a half-life of approximately four days.

Complications with Cryoprecipitate include transfusion reactions and thrombosis. Transmission of viral infections such as hepatitis and HIV is rare but still occurs (15, 16). Thromboembolic risk can be reduced if we avoid overcorrecting fibrinogen levels. Rarely, patients with afibrinogenemia have developed antibodies to fibrinogen following replacement therapy [17].

Even though afibrinogenemia is not usually diagnosed and treated in primary care, we wanted to emphasize that congenital bleeding disorders has to be kept in mind while evaluating recurrent pregnancy loss. Fibrinogen assay & Urea clot lysis test has to be included as a screening coagulation test apart from the routine PT & aPTT tests. 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 [18,19].

A multi-disciplinary approach with adequate inter departmental communication is a must for the successful outcome of such patients.

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Conflict of Interest

Dr. Athira Sasidharan, Dr. Aboobacker Mohamed Rafi, Dr. Ramesh Bhaskaran, Dr. Nithya M Baiju, Dr Susheela Jacob Innah declare that they have no conflict of interest.

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