

# IVF in a Woman with Congenital Hypofibrinogenemia —Case Report

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## Case report

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# Abstract

Background: Congenital hypofibrinogenemia is a rare inherited coagulation disorder and the complications of this disease are bleeding and thrombosis. Pregnant women with congenital hypofibrinogenemia are at high risk of abortion and placental abruption. This report is intended as a reference for IVF in women with congenital hypofibrinogenemia.

Case presentation: A 31-year-old woman with congenital hypofibrinogenemia and secondary sterility who was treated with IVF and cryoprecipitate. After ten months she delivered a live boy.

Conclusion: During IVF, elevated HCG increases the risk of thrombogenesis. So we didn't get as much fibrinogen supplementation as the literature suggested when we did FRT.

## Background

The coagulation disorders of fibrinogen include congenital disorders of fibrinogen disease and acquired disorders of fibrinogen disease. The congenital disorders of fibrinogen includes afibrinogenemia, hypofibrinogenemia, dysfibrinogenemia[1, 2], the first two of which are quantity of fibrinogen abnormality (afibrinogenemia is defined as fibrinogen in plasma less than 50mg/dl, hypofibrinogenemia is defined as fibrinogen in plasma from 50mg/dl to 150mg/dl[3]), the last of which are fibrinogen activity decreased (dysfibrinogenemia)[1, 2]. Congenital hypofibrinogenemia is autosomal recessive hereditary disease[4], which was first reported in 1953[5]and in the population, the morbidity rate is 1/1000000[6]. Clinical manifestations of this disease can be asymptomatic, bleeding, and rare thrombosis[3, 7]. The main treatment for congenital hypofibrinogenemia is fibrinogen replacement therapy(fresh frozen plasma, cryoprecipitate or fibrinogen concentrate)[2]. Fibrinogen, a 340Kd glycoprotein produced by liver, is the main substance in the process of coagulation and thrombosis[8]. The highest coagulation factor of plasma is fibrinogen which can promote platelet aggregation, promote the growth, proliferation and contraction of smooth muscle and endothelial cells, and promote red blood cell adhesion and thrombosis[9]. The treatment is not required in asymptomatic patients, but FIB should be maintained above 100mg/dl before major surgery and above 50mg/dl before minor surgery[10]. Thrombus occurrence in patients with hypofibrinogenemia is relatively rare, so there is no definite treatment for them. Next, we report a case of a woman with secondary infertility and congenital hypofibrinogenemia who gave birth to a healthy boy by cesarean section after IVF and cryoprecipitate treatment.

## Case Presentation

In December 2016, a 31-year-old woman in Changle city, Shandong province, was admitted into the Weifang Medical with primary hypofibrinogenemia. The woman was scheduled to IVF in our hospital due to "secondary sterility,infertility by salpingemphraxis, polymenorrhea, uterine fibroid"2 months ago. Her PT% was 65.2%, Fib was 0.66g/l, TT was 38.2s. There is no fever, epistaxis or other symptoms. It was dignosed as Coagulopathy by Hematology. For Coagulopathy she was admitted to our hospital and

treated with virus inactivated plasma several times. After treatment, her PT% was 61.4%, FIB was 1.01g/l, TT was 34.2/s. A Multiple Disciplinary Team was conducted in our hospital 1.5 months ago, the patient was diagnosed as primary fibrinogenemia because the clotting function examination of her mother and brother suggested plasma fibrinogen decreases. The MDT advice that two days before and the day of the oocyte retrieval, the patient need to transfuse cryoprecipitation 12U everyday and should observe the coagulation function of this patient after the surgery.

Two days before the oocyte retrieval the patient need to be injected 8000-10000 HCG subcutaneously, and her PT% was 63.9%, Fib was 0.88s, TT was 33.9s. There is no signs of abnormal bleeding and nothing unexpected happened since the onset of the disease. After ten months she delivered a live boy.

## Discussion And Conclusion

Fibrinogen is a clotting factor [11] that is synthesized by the liver and plays a key role in hemostasis by promoting clot formation, platelet aggregation and fibrinolysis [5, 12]. It is also a 340KDa protein that plays an important role in placenta formation during pregnancy [12, 13]. Its normal concentration in plasma is 150-350mg/dl, with a half life period is 3-4 days [14, 15]. FIB is a dimer molecule composed of three polypeptide chains A $\alpha$ , B $\beta$  and  $\gamma$  encoded by FGA, FGB, FGG on chromosome 4 respectively [8, 14]. Congenital hypofibrinogenemia is a rare autosomal inherited disease defined as FIB < 150mg/dl [3, 5] and it's the heterozygote state [4]. Diagnosis is not easy because of the rarity of this disease [3]. Acquired hypofibrinogenemia or afibrinogenemia such as liver disease should be first excluded [12]. Second, ask about family history and then rely on the results of laboratory tests (FIB decreases, BT, APTT, PT, TT all extend, but it can be corrected by fibrinogen) [4, 16]. Clinical manifestations of hypofibrinogenemia may be asymptomatic, bleeding (umbilical cord bleeding, nosebleed, menorrhagic, gastrointestinal bleeding, joint bleeding, muscle hematoma, intracranial bleeding and even spontaneous splenic rupture [15]) or thrombogenesis [7]. Patients with hypofibrinogenemia are prone to spontaneous abortion, placental abruption and postpartum hemorrhage during pregnancy [3, 5]. In normal women, plasma FIB level increases after pregnancy to maintain placental integrity, so patients need more fibrinogen as the pregnancy progresses [3, 5]. Treatment depends on the patient's condition [3]. If patients don't have any symptoms they don't need any treatment because unnecessary blood transfusions can cause infections and allergic reactions [4, 8]. Antifibrinolytic can be used for minor bleeding [7]. Fibrinogen replacement can be used in patients with moderate to severe bleeding, in pregnant women or in patients prior to surgery [5, 13]. FIB should be maintained 50-100mg/dl for patients with bleeding tendency [11, 15] and 60-100mg/dl for patients with pregnancy [11]. Patients with hypofibrinogenemia are prone to bleeding after 5 weeks of gestation and spontaneous abortion after 6-8 weeks of gestation [5]. Studies have shown that starting FRT after 5 weeks of gestation still carries a risk of genital bleeding so it is recommended that FRT should be started before pregnancy [17]. FIB should be maintained at 100-200mg/dl for patients undergoing major surgery [10, 15]. Fibrinogen levels need to be monitored daily after FRT, as 20%-30% patients will develop blood clots [10, 15]. Although there is no evidence suggest that FRT is associated with the formation of clots, we all agree that the formation of clots is associated with some predisposition (FRT, infection, pregnancy) [18]. There is no clear treatment or prevention program for

thrombotic hypofibrinogenemia, and some scholars believe that heparin can be prophylactic used after FRT[8, 13]. Fibrinogen concentrate is the best choice: 1. Although the price of fresh frozen plasma and cryoprecipitate is lower, larger amounts are needed, especially for pregnant women, which can lead to fluid overload and cardiopulmonary strain. 2. Fibrinogen concentrate does not transmit the disease, fresh frozen plasma and cryopolytes contain proteins that are not needed by patients, which can affect the formation of clots and cause allergic reactions[3, 13-15]. The amount of fibrinogen can be calculated by formula: ( target FIB level-measured FIB level) ÷ 1.7× weight( kg) [5, 13]. For this patient with hypofibrinogenemia, 8000-10000u HCG was injected subcutaneously 36 hours prior to egg retrieval. Elevated HCG increases the risk of thrombogenesis, so we didn't get as much fibrinogen supplementation as the literature suggested when we did FRT and only got to 88mg/dl.

IVF with hypofibrinogenemia is a very rare case. There were no abnormal conditions such as genital bleeding or placental abruption during treatment and pregnancy. In 2017, the patient had a full-term cesarean section at a local hospital, and both mother and child were in good condition.

## Abbreviations

IVF: In Vitro Fertilization; FIB/Fib: Fibrinogen; HCG: Human Chorionic Gonadotropin; BT: Bleeding time; PT: Prothrombin time; APTT: activated partial thromboplastin time; TT: Thrombin time; FRT: Fibrinogen replacement therapy

## Declarations

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Authors' contributions:

FRQ was responsible for writing the manuscript. JJY and JAF collected cases. FRQ and FLP collected the patient data. The surgery was performed by RCE and YTT. All authors read and approved the final manuscript.

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Competing interests:

The authors declare that they have no competing interests

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