Abstract

Inherited fibrinogen disorders introduce risk for recurrent abortions, sub-chorionic haematoma, placental abruption and postpartum haemorrhage. This is a case report of a successful pregnancy outcome in a 37-year old woman with hypofibrinogenaemia. She was referred to a coagulation test in the first trimester because of history of preeclampsia and HELLP syndrome in previous pregnancy. Hypofibrinogenaemia was diagnosed with fibrinogen level of 0.7 g/L. During the pregnancy she was regularly monitored for fibrinogen levels and multiple cryoprecipitate concentrates were given. She delivered at 39th gestation week, with elective caesarean section under general anaesthesia. There was one episode of postpartum haemorrhage treated with 2 units of red blood cells, repeated infusions of cryoprecipitate to obtain the level of fibrinogen of 2 g/L. She was discharged on the 6th postpartum day in a good condition. In these disorders levels of fibrinogen should be higher than 1 g/L during pregnancy or 2 g/L in case of caesarean section for successful prenatal and peripartal management.

Key words: Hypofibrinogenaemia, pregnancy, peripartal management.

Introduction

The coagulation system has one final goal: convert fibrinogen to fibrin and form a clot. During pregnancy changes in the system of coagulation and fibrinolysis occur. Thrombin and fibrin generation increase to facilitate placental implantation and prevent excessive haemorrhage during delivery. Normal pregnancy causes progressive increase in maternal plasma D-dimer concentration from conception until delivery.¹

Fibrinogen (normal concentration in blood between 2.0 and 4.5 g/L) supports pregnancies by maintaining haemostatic balance and stabilising the foetal-maternal junction and embryo implantation.² Maternal fibrinogen and factor XIII are essential after 4-5 gestational week in decidual stroma.³ Fibrinogen plays a positive role in the process of implantation. Coagulation changes of pregnancy help in regulating attachment of placenta and stabilising some placental detachments that may happen. Low fibrinogen may cause rupture affecting embryonic trophoblast infiltration and leading to haemorrhage.⁴

Inherited fibrinogen disorders introduce risk for: menorrhagia, menometrorrhagia; recurrent foetal loss, antiphospholipid syndrome; multiple miscarriages.
tal loss, spontaneous abortions, bleeding in early gestations, sub-chorionic hematoma, placental abruption; increased incidence and severity of postpartum hemorrhage. There are two types of hereditary fibrinogen abnormalities: quantitative defects like afibrinogenaemia or hypofibrinogenaemia and qualitative defects like dysfibrinogenaemia or hypodisfibrinogenaemia (HD). First reported in 1935, prevalence of afibrinogenaemia is extremely rare, around 1/1,000,000. Prevalence of hypofibrinogenaemia is hard to say as there are many asymptomatic patients.

Congenital defects of fibrinogen are caused by mutations in the FGA, FGB, or FGG genes, located on the q arm of 4th chromosome at position 31.3. Hypofibrinogenaemia and dysfibrinogenaemia are autosomal dominant or recessive. There are more than 100 fibrinogen mutations that have been associated with hypofibrinogenaemia. Hypofibrinogenaemia could be: a) mild (fibrinogen levels > 1 g/L): asymptomatic, excessive bleeding can occur after injuries, surgery or delivery; b) moderate (fibrinogen levels between 0.1-1 g/L): bleedings can be spontaneous or caused by injuries, surgery, or delivery; c) severe (undetectable clot): spontaneous, severe, and even life-threatening bleeding may occur.

Dysfibrinogenaemia results in abnormal fibrinogen function. It can be asymptomatic in 55% of the cases, can cause haemorrhage in 25% and thrombosis in 20%. Dysfibrinogenaemias are result of defect of fibrinogen molecule which impairs polymerisation of fibrin associated with irregular cross linking with factor XIIIa. Dysfibrinogenaemias can be associated with hypofibrinogenaemia and congenital trombophylia. As first such case was diagnosed in 1958 until today over 100 mutations have been reported. Dysfibrinogenaemia increase the risk of spontaneous abortions, placental abruption, thrombosis and haemorrhage.

If possible, during pregnancy fibrinogen levels should be more than 1 g/L and in case of caesarean section 2 g/L. Best choice for treatment of acute bleeding episodes are fibrinogen concentrates. If unavailable, cryoprecipitate (a fibrinogen-rich plasma fraction) should be used.

Case history

A thirty-seven-year old woman went to a gynaecologist to perform a routine exam due to the new pregnancy (gravida 2, para 1). There were no hemorrhagic and thrombotic events in the personal or family medical history.

Her previous pregnancy resulted in premature labour in 30th gestation week by caesarean section due to HELLP syndrome under general anaesthesia. The newborn had a body weight of 1,300 g and length of 42 cm. It was admitted and treated in ICU and had a good outcome.
levels were analysed and risk for preeclampsia was ruled out (PLGF 103, sFLT 4708, sFLT 1/PLGF 4.6).

Non-invasive prenatal screening test was done due to maternal age and it came out as low risk for aneuploidy (chromosome 21, 18, 13, sex chromosomes, microdeletions).

Monitoring of fibrinogen levels on a two week or monthly interval was made by a specialist in transfusion medicine. She received multiple transfusions of cryoprecipitate (20 units each) during the 1st and 2nd trimester, as well as multivitamin supplementation with B6, B12, methylfolate.

Platelet count ranged from 200 x 10^9/L at the beginning to 150 x 10^9/L at the end of pregnancy. Haematocrit was maintained above 30% during the pregnancy (42.7% - 30.9%).

Screening haemostasis parameters were as follows: prothrombin time (PT) was in the normal range (12-14 s) during whole pregnancy; activated partial thromboplastin time (aPTT) was shortened according to the gestational age (29-24 s) and thrombin time (TT) was significantly prolonged (48-31 s) according to the cryoprecipitate substitution (Figure 1a). During the pregnancy the level of fibrinogen varied from 0.7 to 1.6 g/L according to the cryoprecipitate substitution (Figure 2a). D-dimers were increased according to the gestational age (from 227 to 2,900 ng/ml).

Foetal growth was adequate for gestational age, placental echogenicity and doppler of the fetoplacental unit was closely monitored through the pregnancy by ultrasound. Pregnancy was uneventful with no signs of bleeding. Patient received thromboprophylaxis with enoxaparin in the late second and third trimester.

She was admitted at the University Clinic for Obstetrics and Gynaecology at 38th gestation week for adequate preparation for delivery. Anaesthesiology consultation was made with physical exam, ECG and cholinesterase analysis (history of prolonged waking after general anaesthesia in previous caesarean section, results in reference values 6,389 U/L).

Blood products were supplied: erythrocyte concentrate, fresh frozen plasma, cryoprecipitate. Thromboprophylaxis with enoxaparin was discontinued 12 hours before delivery. Cryoprecipitate infusion was administered with 10 units/8 h interval until concentration of fibrinogen reached 3 g/L before scheduling the caesarean section.

The patient was delivered at 39th gestation week by elective caesarean section under general anaesthesia. The newborn had weight of 3,550 g, length of 50 cm and Apgar score 9/10. Operative period was uneventful.

Postpartum screening haemostasis parameters were analysed daily: PT and APTT were in the normal range (12.1-13.2 s) as well as aPTT (24-30.7 s), while D-dimers were decreasing. Platelet count ranged from 122 up to 361 x 10^9/L. Postpartum TT and fibrinogen level is shown on Figure 1b and 2b.

There was one episode of postpartal haemorrhage with estimated blood loss of 700 mL treated with standard uterotonics (oxytocin, methylergometrine, carboprost tromethamine). The haemoglobin levels were reduced from 114 g/L to 74 g/L, haematocrit from 0.34 to 0.21. She received two units of red blood cells (RBC), 3x20 units of cryoprecipitate (the level of fibrinogen was main-
Congenital fibrinogen disorders carry pregnancy risk, but it can be successfully managed by engaging the multifunctional team of specialists. As there are no randomised controlled studies, management is made on expert consensus. Successful perinatal outcomes can be accomplished by analysis of the fibrinogen levels and supportive therapy. Management must be individualised considering the personal history and the specific clinical situation. Interdisciplinary approach and close collaboration between the institutions is necessary since it was crucial to the positive outcome in this case.

Conclusion

Congenital fibrinogen disorders carry pregnancy risk, but it can be successfully managed by engaging the multifunctional team of specialists. As there are no randomised controlled studies, management is made on expert consensus. Successful perinatal outcomes can be accomplished by analysis of the fibrinogen levels and supportive therapy. Management must be individualised considering the personal history and the specific clinical situation. Interdisciplinary approach and close collaboration between the institutions is necessary since it was crucial to the positive outcome in this case.

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Conflict of interest
None.
References