

Hypofibrinogenemia and miscarriage: report of a first successful pregnancy under fibrinogen substitution and short review of the literature

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ABSTRACT

Disorders of fibrinogen have been reported to be associated not only with bleeding and thrombosis but also with miscarriage. Here, we report the case of a woman with genetically determined hypofibrinogenemia and recurrent miscarriages who had a first successful pregnancy under fibrinogen substitution. Current knowledge on fibrinogen disorders and recurrent miscarriages is briefly summarized and discussed.

KEYWORDS: miscarriage; hypofibrinogenemia; fibrinogen substitution

INTRODUCTION

Inherited and acquired coagulation defects have been reported to be associated with pregnancy complications, including recurrent miscarriage and placental vascular complications. In many cases, inherited thrombophilic risk factors are detected in female patients suffering from such complications, most commonly the G1691A mutation of the factor V gene (factor V Leiden) and the factor II (prothrombin) mutation G20210A in the 3' non translated region of the factor II gene. Much less frequently, rare quantitative or qualitative abnormalities of the coagulation inhibitors protein C, protein S, and antithrombin are associated with recurrent miscarriage and pregnancy complications [1]. However, the association of inherited thrombophilia and recurrent miscarriage and the clinical consequences in this setting are very controversially discussed and are matter of debate for decades [2]. By contrast, obstetric antiphospholipid syndrome – an acquired disorder involving hemostasis – has been widely recognized as a severe risk factor for miscarriages and placental vascular complications and the treatment of affected women with low-molecular weight heparins in combination of aspirin in pregnancy can be regarded as accepted standard treatment, leading to a high rate of successful pregnancies in this setting [3].

Compared to above mentioned inherited and acquired thrombophilic risk factors, an association of coagulation defects predisposing to bleeding and miscarriage has been reported much less frequently [4]. These defects may not

only lead to miscarriage by provoking bleeding with placental abruption, but the defects may also disturb the correct implantation of the embryo in the early phase of pregnancy, thus leading to pregnancy loss. Among these defects, disorders of fibrinogen appear to play an important role for abortions: Different types of fibrinogen defects such as afibrinogenemia, hypofibrinogenemia and also various defects of the fibrinogen molecule, i. e. dysfibrinogenemia, have been found to be associated with pregnancy complications [5].

Here, we present a rare case of a woman with recurrent miscarriage in whom hypofibrinogenemia was detected as most likely underlying cause and a first pregnancy was uneventful and successful under substitution of fibrinogen.

CASE REPORT

A 35-year-old female patient was admitted to our department for further diagnostic work-up due to recurrent miscarriages and hitherto no successful pregnancies. The miscarriages had occurred two years ago (one miscarriage, 7th gestational week), and in the year of admission (two miscarriages, 5th and 9th gestational week). The patient was otherwise completely healthy. In particular, there was no clinical evidence for a coagulation defect with increased bleeding tendency, the patient reported normal menstrual bleeding, and absence of epistaxis, abnormal bruising or hematoma, no perioperative bleeding complications, and no abnormal bleeding in association with the miscarriages. Moreover, she did not have a history of thrombotic or thromboembolic events. The family history was also unremarkable regarding bleeding, thrombosis, miscarriages, and pregnancy complications. The patient was overweight

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(1.63m; 101 kg), but the clinical examination was otherwise unremarkable.

Prior to first presentation at our department, she had already been extensively examined and there was no evidence for a gynecological or hormonal disorder as underlying cause of the abortions. In addition, in the unsuccessful pregnancies there had not been evidence for a defect of the embryo as cause of abortion.

In the diagnostic coagulation work-up, there was no evidence for inherited thrombophilia as potential cause of the miscarriages; a G1681A mutation in the factor V gene (factor V Leiden), a prothrombin mutation G20210A, and also protein C, protein S, and antithrombin deficiency as most relevant inherited thrombophilic risk factors could be ruled out. Furthermore, there was no evidence for an antiphospholipid syndrome as established cause not only for thrombosis but also for pregnancy complications, including recurrent miscarriages; relevant antiphospholipid antibodies, i. e. lupus anticoagulants and also beta 2 glycoprotein I and cardiolipin antibodies type IgM and IgG, were not elevated.

However, further diagnostic work-up revealed a rare abnormality: at first presentation, a slight reduction of quick-derived fibrinogen to 165 mg/dl (normal range 180-350 mg/dl) was detected. Further examinations showed also a reduction of fibrinogen determined with the Clauss method to 102 mg/dl (normal range (200-400 mg/dl). The fibrinogen concentration was borderline (1.9 g/l, normal range 1.9-4.3 g/l). As a consequence, of fibrinogen deficiency, the thrombin time was slightly prolonged with 17.6 seconds (normal range 10-17 seconds). After confirmation of the findings in a second analysis, genetic analyses were initiated under suspicion of a genetically determined fibrinogen disorder. The exons of FGA (NM_000508.4), FGB (NM_005141.4) and FGG (NM_000509.5) including flanking splice-site regions were completely sequenced. The heterozygous missense mutation c.1330G>A, p.(Gly444Ser) according to the classification of the 'Human Genome Variation Society'

or B8Gly (GGC)414Ser(AGC) according to the 'Fibrinogen Variants Database' was detected in exon 8 of the FGB gene. This mutation has previously been shown to be associated with a reduced secretion of the fibrinogen molecule. Thus, our working diagnosis of inherited hypofibrinogenemia was confirmed by the genetic findings. An additional defect of primary and plasmatic hemostasis predisposing to bleeding and potentially enhancing the adverse effects of hypofibrinogenemia could be ruled out. Deliberately, we did not initiate further genetic analysis to rule out polymorphisms that modulate fibrinolysis and, thus, potentially influence the adverse effect of hypofibrinogenemia.

Since the patient did not show bleeding symptoms, there was no actual need for prophylactic or therapeutic measures. However, hypofibrinogenemia was regarded as most likely cause for the unexplained miscarriages and we proposed a treatment with fibrinogen concentrate to prevent further abortions in the following pregnancy.

Two months later, the patient presented in the 5th week of her next pregnancy. After informed consent, we initiated a substitution of fibrinogen concentrate (Haemocomplettan, CSL Behring) 2g absolutely by intravenous infusions once weekly. In the 6th week of pregnancy, the patient reported slight vaginal bleeding which stopped after another substitution of 2g fibrinogen concentrate. This substitution strategy led to continuous elevation of fibrinogen levels to approximately 250-300 mg/dl for quick-derived fibrinogen, and 150-200 mg/dl for fibrinogen measured with the method by Clauss (Figure 1). Under the treatment, the thrombin time was normalized. The treatment was well tolerated without any side effects and no further bleeding occurred. In the 24th week of pregnancy the fibrinogen substitution could be stopped, and the fibrinogen levels remained within normal range even without substitution.

Prior to delivery, laboratory examination in the 40th gestational week showed normal fibrinogen levels, but the thrombin time was slightly prolonged to 19.5 seconds. For this reason, we decided to give another 2g of the fibrinogen

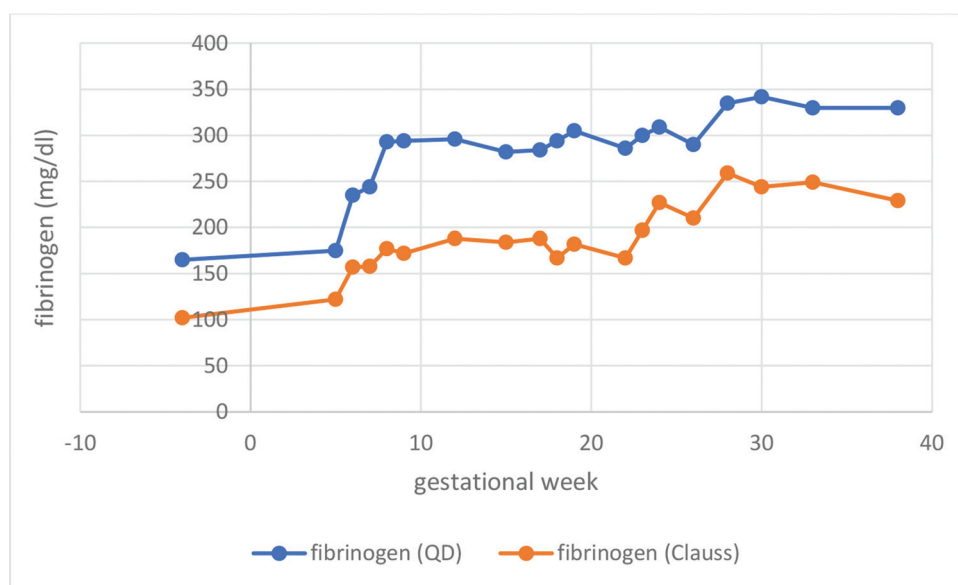


Fig. 1. Fibrinogen activity before and during pregnancy measured as quick-derived fibrinogen (QD) and fibrinogen measured with the method by Clauss. Fibrinogen substitution was performed between the 6th and 24th gestational week.

concentrate prior to caesarean delivery which was performed for obstetric indication and not because of the coagulation defect. In the literature, both vaginal and cesarean delivery have been reported for women with fibrinogen disorders, but there is no evidence which delivery mode is preferable in this setting [5].

The child was delivered completely healthy and on term, abnormal peripartum bleeding was not observed. For prophylaxis of a thrombotic event, the patient additionally received heparin prophylaxis with dalteparin 5.000 IE/d s. c. after delivery over two weeks due to age > 35 years, obesity, and increased thrombotic risk due to caesarean delivery.

■ DISCUSSION

The first reports on abnormalities and disorders of fibrinogen as cause of isolated and recurrent miscarriages date back to the 1960s. Since then, a number of cases and case series regarding this issue have been published in the literature [6-7]. A variety of fibrinogen disorders has been found to be associated more or less strongly with pregnancy complications, such as spontaneous and recurrent miscarriages, placental abruption and bleeding complications during pregnancy, delivery and postpartum [8]. To explain this association, the biophysiological properties of the fibrin network during normal pregnancy and patients with recurrent miscarriages were studied. It is known that fibrin monomer assembly and fibrinolysis are modulated in pregnancy and increased in pregnant compared to non-pregnant women [9]. Fibrinogen also plays an important role for maintaining placenta integrity and, in particular, for the development of adequate feto-maternal vascularization [5]. Thus, fibrinogen disorders impairing fibrin formation, fibrin monomer assembly, and fibrinolysis, can promote pregnancy complications and impair the pregnancy outcome. Apart from bleeding manifestations during pregnancy and delivery, genetically determined hypofibrinogenemia and other fibrinogen disorders can be associated with miscarriage, fetal growth restriction, placental abruption and premature delivery [5].

Among fibrinogen disorders associated with pregnancy complications, rare cases of afibrinogenemia, but also hypofibrinogenemia, dysfibrinogenemia and gene polymorphisms were reported. In a retrospective study of 795 cases of women with recurrent miscarriage, significant differences of the fibrinogen levels were observed [10]. In a cohort of 36 women with pregnancy loss, Kamimoto et al. (2017) identified a surprisingly high number of five patients with reduced fibrinogen levels, median 110 mg/dl, caused by genetic abnormalities [11]. According to these findings, it might be that the role of fibrinogen disorders in the context of abortions and pregnancy complications is currently underestimated due to unawareness and, thus, lack of appropriate diagnostic work-up of these disorders in respective women. Additional abnormalities, particularly those affecting fibrinolysis, such as the factor XIII Val34 Leu polymorphism, can interfere with fibrinogen disorders and further increase the risk of pregnancy complications in women with fibrinogen disorders by influencing fibrin formation and fibrinolysis [12].

The question if only severe fibrinogen disorders, in particular afibrinogenemia, or also mild fibrinogen disorders can be associated with recurrent miscarriages and pregnancy complications. In the presented case, the patient suffered

from only mild hypofibrinogenemia which was not associated with relevant abnormal bleeding, but with miscarriages. In the literature, it has previously been reported that even mild hypofibrinogenemia caused by genetic defects can be associated with recurrent miscarriages [13], even with very slightly reduced fibrinogen levels of 100-150 mg/dl, and also with bleeding in pregnancy [14]. Thus, the pregnant state may unmask and amplify otherwise inapparent and clinically silent to mild hemostatic disorders, such as mild hypofibrinogenemia.

It should be noted that concomitant defects of hemostasis can promote pregnancy related complications in patients with hypofibrinogenemia. As an example, postpartum hemorrhage, menorrhagia, and also miscarriage was reported in a woman suffering not only from hypofibrinogenemia but also from factor XIII deficiency [15]; in our patient, however, additional defects could be ruled out by the diagnostic work-up. In addition, it has been reported that the clinical presentation of hypofibrinogenemia, in particular also the association of this disorders with miscarriages could be modulated by genetic polymorphisms impairing fibrinolysis, such as the 4G/5G polymorphism of the plasminogen activator inhibitor (PAI-1) gene and the factor XIII Val34Leu polymorphism. It was demonstrated that in carriers of the 34Leu allele fibrinogen levels below the median, i.e. ≤ 300 mg/dl, and the first tercile, i.e. ≤ 284 mg/dl, in this study, was associated with an increased risk for recurrent pregnancy loss, i.e. a 2.9 or 3.9 fold increased risk [12]. As a reason, the fibrin structure in patients with fibrinogen level in the low normal range could be altered by the presence of distinct fibrinogen polymorphisms, leading to an increased resistance to fibrinolysis [12]. The presence of additional hemostatic defects or polymorphisms and variants which modulate fibrinolysis could explain considerable differences in the clinical course of pregnancies of women with hypofibrinogenemia.

The management of patients with recurrent miscarriages due to mild hypofibrinogenemia can be derived from women with congenital afibrinogenemia as the most severe fibrinogen disorder which is also associated with pregnancy complications and miscarriages. It is well known that these complications can be prevented by substitution of fibrinogen in respective patients. Consequently, fibrinogen substitution is also the optimal choice of treatment in patients with hypofibrinogenemia to prevent pregnancy complications and miscarriages. Experience from afibrinogenemia showed that fibrinogen trough levels of > 1 g/l are efficient to prevent abortion and other pregnancy related complications [16]. If possible, higher fibrinogen levels of 1.5-2 g/l have been recommended during labor to prevent placental abruption [17]. Due to the long half-life of fibrinogen of 100-120 hours once weekly substitution of fibrinogen is sufficient to establish these fibrinogen levels. Since miscarriages occurs most frequently between the 6th and 8th gestational week and fibrinogen levels may raise spontaneously during pregnancy even in patients with hypofibrinogenemia, substitution may not be required during the whole pregnancy but a temporary substitution may be sufficient. In our patient substitution was performed between first presentation at the 6th gestational week and the 24th gestational week and the fibrinogen levels remained spontaneously within normal range after cessation of substitution. To prevent peripartum hemorrhage, however, another substitution of fibrinogen may be necessary, particularly in

patients with abnormal results for fibrinogen or thrombin time prior to delivery.

■ CONCLUSION

We reported the first successful pregnancy in a patient with previous miscarriages associated with genetically determined hypofibrinogenemia. In this patient, fibrinogen substitution led to normal fibrinogen levels, allowing an uneventful and successful pregnancy. We recommend considering the presence of a fibrinogen disorder as underlying cause in patients with recurrent miscarriage and to add suitable further diagnostic laboratory work-up in these patients to establish the exact diagnosis. In case of a fibrinogen disorder, further genetic analyses should be performed. In addition, it should be considered to check for additional risk factors, modulating the risk of hypofibrinogenemia in pregnancy, such as concomitant factor XIII deficiency and variants of the fibrinolytic system. As demonstrated, adequate substitution with a fibrinogen concentrate can result in a normal pregnancy in affected women, even in case of mild hypofibrinogenemia.

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Conflicts of interest

There are no conflicts of interest to report.

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■ REFERENCES

- McNamee K, Dawood F, Farquharson R. Recurrent miscarriage and thrombophilia: an update. *Curr Opin Obstet Gynecol*. 2012; 24:229-234. doi: 10.1097/GCO.0b013e32835585dc.
- Middeldorp S, Naue C, Köhler C. Thrombophilia, Thrombosis and Thromboprophylaxis in Pregnancy: For What and in Whom? *Haemostaseologie* 2022; 42:54-64. doi: 10.1055/a-1717-7663.
- Alijotas-Reig J, Esteve-Valverde E, Anunciación-Llunell A, et al. Pathogenesis, Diagnosis and Management of Obstetric Antiphospholipid Syndrome: A Comprehensive Review. *J Clin Med*. 2022; 11:675. doi: 10.3390/jcm11030675.
- Presky KO, Kadir RA. Women with inherited bleeding disorders - Challenges and strategies for improved care. *Thromb Res*. 2020; 196:569-578. doi: 10.1016/j.thromres.2019.07.004.
- Zhang Y, Zuo X, Teng Y. Women with Congenital Hypofibrinogenemia/Afibrinogenemia: From Birth to Death. *Clin Appl Thromb Hemost*. 2020; 26:1076029620912819. doi: 10.1177/1076029620912819.
- Norburn LM. Hypofibrinogenemia with a 19-weeks abortion. *J Obstet Gynaecol Br Emp*. 1957; 64:220-221. doi: 10.1111/j.1471-0528.1957.tb02623.x.
- Rabau E, Szeinberg A. Hypofibrinogenemia in a case of missed abortion. *Harefuah*. 1957; 52:313-314.
- Frenkel E, Duksin C, Herman A, et al. Congenital hypofibrinogenemia in pregnancy: report of two cases and review of the literature. *Obstet Gynecol Surv*. 2004; 59:775-779. doi: 10.1097/01.ogx.0000143774.04144.b9.
- Marchi R, López Ramirez Y, Nagaswami C, et al. Haemostatic changes related to fibrin formation and fibrinolysis during the first trimester in normal pregnancy and in recurrent miscarriage. *Thromb Haemost*. 2007; 97:552-557. doi: 10.1160/TH06-09-0542.
- Fang J, Xie B, Chen B, et al. Biochemical clinical factors associated with missed abortion independent of maternal age: A retrospective study of 795 cases with missed abortion and 694 cases with normal pregnancy. *Medicine (Baltimore)*. 2018; 97:e13573. doi: 10.1097/MD.00000000000013573.
- Kamimoto Y, Wada H, Ikejiri M, et al. Hypofibrinogenemia and the α -Fibrinogen Thr312Ala Polymorphism may be Risk Factors for Early Pregnancy Loss. *Clin Appl Thromb Hemost*. 2017; 23:52-57. doi: 10.1177/1076029615594003.
- Dossenbach-Glaninger A, van Trotsenburg M, Oberkanins C, et al. Risk for early pregnancy loss by factor XIII Val34Leu: the impact of fibrinogen concentration. *J Clin Lab Anal*. 2013; 27:444-449. doi: 10.1002/jcla.21626.
- Skotnicki AB, de Moerloose P, Neerman-Arbez M. Severe bleeding and miscarriages in a hypofibrinogenemic woman heterozygous for the gamma Ala82Gly mutation. *Blood Coagul Fibrinolysis*. 2009; 20:374-376. doi: 10.1097/MBC.0b013e328329f27a.
- McRoyan DK, McRoyan CJ, Kitay DZ, et al. Constitutional hypofibrinogenemia associated with third trimester hemorrhage. *Ann Clin Lab Sci*. 1986; 16:52-57.
- Kaveney AD, Philipp CS. Mild factor XIII deficiency and concurrent hypofibrinogenemia: effect of pregnancy. *Blood Coagul Fibrinolysis*. 2016; 27:457-460. doi: 10.1097/MBC.0000000000000448.
- Saes JL, Laros-van Gorkom BAP, Coppens M, et al. Pregnancy outcome in afibrinogenemia: Are we giving enough fibrinogen concentrate? A case series. *Res Pract Thromb Haemost*. 2020; 4:343-346. doi: 10.1002/rth2.12300.
- Kobayashi T, Kanayama N, Tokunaga N, et al. Prenatal and peripartum management of congenital afibrinogenemia. *Br J Haematol*. 2000; 109:364-366. doi: 10.1046/j.1365-2141.2000.01993.x