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**Congenital dysfibrinogenemia misdiagnosed and inappropriately treated as acute fatty liver in pregnancy: A case report and review of literature**

Jia Y *et al*. CD misdiagnosed as acute fatty liver

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**Abstract**

BACKGROUND

The purpose of this study was to report the rare case of a pregnant woman with congenital dysfibrinogenemia (CD) misdiagnosed as acute fatty liver. She was treated according to the principles of acute fatty liver but achieved good clinical results.

CASE SUMMARY

A 30-year-old woman presented with 39 (6/7) wk of menopause and 6 h of irregular abdominal pain and attended our hospital. Emergency surgery was performed due to fetal distress. Postoperative management followed the treatment principle of acute fatty liver. DNA sequencing was carried out on the pregnant woman and her pedigree. Coagulation values of the patient on admission were prothrombin time 33.7 s, activated partial thromboplastin time 60.4 s, thrombin time 45.2 s, and fibrinogen 0.60 g/L. DNA sequencing results showed that the woman carried a pathogenic heterozygous variation of the fibrinogen alpha chain gene (FGA), which is closely related to hereditary fibrinogen abnormality, and the mutation site was located in *p.R350H*. After a follow-up period of 12 mo, the mother and her newborn had a good prognosis without bleeding or thrombosis.

CONCLUSION

Pregnant women with CD may have atypical symptoms, which can easily lead to misdiagnosis. In addition, treatment can be attempted according to the principles of acute fatty liver management. This rare pregnant patient with CD was caused by a novel FGA (*p.R350H*) gene mutation.

**Key Words:** Gene mutation; Fibrinogen; Congenital dysfibrinogenemia; Pregnancy; Case report

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**Core Tip:** Pregnant women with congenital dysfibrinogenemia (CD) may have atypical symptoms, which can easily lead to misdiagnosis. The purpose of this study was to report the rare case of a pregnant woman with CD who was misdiagnosed with acute fatty liver. She was treated according to the principles of acute fatty liver but achieved good clinical results. DNA sequencing was carried out on the pregnant woman and her pedigree. The DNA sequencing results showed that the woman carried a pathogenic heterozygous variation of the fibrinogen alpha chain gene closely related to hereditary fibrinogen abnormality, and the mutation site was located in *p.R350H*.

**INTRODUCTION**

Congenital dysfibrinogenemia (CD) is an uncommon inherited coagulation disorder[1]. It is usually autosomal dominant and can be caused by liver disease, diffuse intravascular coagulation, primary fibrinolytic abnormalities, or certain drugs[2]. CD is a disease characterized by a dysfunctional fibrinogen molecule resulting in abnormal blood coagulation. The presentation of dysfibrinogenemia varies widely, ranging from asymptomatic (55% of patients) to hemorrhagic (25%) to thrombotic (20%). It can be quantitative or qualitative, congenital or acquired[3]. More than 400 families have been affected by this disorder[4]. However, fewer than 20 pregnant women with CD have been reported worldwide[5].

CD is difficult to diagnose due to the broad spectrum of clinical symptoms, and even after the diagnosis, treatment is selected based on symptoms. Commonly used methods include fibrinogen replacement therapy, anticoagulation, thromboprophylaxis, and a multidisciplinary team approach[6]. However, no unified standard CD treatment has been established, especially for pregnant women. Several adverse pregnancy outcomes have been associated with fibrinogen abnormalities, including post-partum hemorrhage or thrombosis, spontaneous abortion, recurrent miscarriage[7,8], and placental abruption[9,10].

We present the rare case of a pregnant woman with CD who was initially misdiagnosed with acute fatty liver. As a result, the patient was hospitalized and treated for “acute fatty liver” until discharge. Fortunately, the mother delivered a healthy newborn by cesarean section, and neither had clinical symptoms of severe hemorrhage or thrombosis. We then analyzed the diagnosis and treatment process of this rare pregnant woman. In addition, we performed sequence analysis of the amplified DNA for the proband and her pedigree. We also reviewed the literature of the last 30 years on clinical symptoms, coagulation function, DNA sequencing, treatments, and clinical outcomes of CD during pregnancy.

**CASE PRESENTATION**

***Chief complaints***

A 30-year-old female presented with “39 (6/7) wk of menopause and 6 h of irregular abdominal pain”.

***History of present illness***

Her abdominal pain occurred at intervals of 15 to 30 min and lasted for 30 s. She was admitted to the obstetric department of our hospital as an emergency case.

***History of past illness***

The patient denied a history of other diseases.

***Personal and family history***

The pregnant woman was previously healthy and denied a family history of hereditary diseases.

***Physical examination***

Measurements of fundal height, abdominal circumference, fetal heart rate, and external pelvis were normal. The position of the fetus was Left Occiput Anterior (LOA). No dystocia of the head was noted. An internal examination revealed no abnormalities.

***Laboratory examinations***

The pregnant woman was admitted to the operating room as an emergency due to intrauterine distress before her laboratory results were available. Intraoperatively, laboratory tests showed that the white blood cell count was 11.3 × 109/L ↑, the prothrombin time (PT) was 33.7 s ↑, the international prothrombin standard was 2.79 ↑, partial thromboplastin time was 60.4 s ↑, partial thromboplastin ratio was 2.06 ↑, PT was 45.2 s ↑, prothrombin activity was 22% ↓ and antithrombin was 17% ↓, fibrinogen assay was 0.6 g/L ↓, fibrin (pro) degradation product was 116.4 μg/mL ↑, uric acid was 615 μmol/L ↑, creatinine was 172 μmol/L ↑, glutathione aminotransferase was 705 U/L ↑, glutathione aminotransferase was 323 U/L ↑, total bilirubin was 89.51 μmol/L ↑, direct bilirubin was 70.25 μmol/L ↑ and indirect bilirubin was 19.26 μmol/L ↑.

***Imaging examinations***

Ultrasound examination showed ascites and bright liver. Obstetric three-dimensional color ultrasound showed the following: The fetal position was cephalic, the fetal heart rate was 171 bpm, fetal movements were palpable, the biparietal diameter was 9.1 cm, the head circumference was 32.0 cm, the abdominal circumference was 33.1 cm, femoral length was 6.8 cm, the placenta was in the fundus with a maturity of II, the amniotic index was 17.41 cm, umbilical artery S/D was 2.4, placental entrance and the inferior border was indistinct. The results of the non-stress test after admission showed a non-responsive type, a flat baseline, no fetal movements, and no fetal heart fluctuations.

***Genetic tests on the pedigree***

We analyzed genomic DNA obtained from the blood sample to check for mutations in the fibrinogen gene. Both the mother and the newborn had abnormal coagulation values, indicating that the disease was inherited in the family. Genotype analysis confirmed the diagnosis of hypofibrinogenemia by identifying a homozygous mutation in fibrinogen alpha chain gene (FGA) (*p.R350H*). In addition, genetic testing was performed on the patient’s parents and daughter, and the results confirmed that both the father and daughter were disease-causing gene carriers (Figure 1). We have studied the clinical symptoms, fibrinogen results, genetic analysis, treatment, and clinical outcomes of pregnant women with CD over the past 30 years (Table 1). In addition, we reviewed the CD-related gene mutation sites mentioned above (Table 2).

**FINAL DIAGNOSIS**

CD.

**TREATMENT**

A cesarean section of the lower uterine segment was performed under emergency lumbar epidural anesthesia. When the membrane was punctured during the procedure, brown-yellow amniotic fluid was seen overflowing, and a live female baby weighing 3090 g was delivered at LOA. The Apgar score was one point at one minute after birth and improved to four points at five minutes after birth. The neonatal medical staff was present to assist with the resuscitation and transfer of the newborn to neonatology. Fortunately, there were no surgical complications during the operation, such as severe bleeding.

Intraoperatively, laboratory tests showed that the patient had leukocytosis, elevated transaminases, elevated bilirubin, elevated urate, coagulopathy and renal impairment. After intraoperative multidisciplinary consultation, the clinical diagnosis of acute fatty liver during pregnancy was made according to the Swansea criteria and NHS guidelines[11]. She was then transferred to the intensive care unit (ICU). In the ICU, glucose supplementation, monitoring of coagulation function, oxygen inhalation, infection control, blood transfusion, fluid infusion, multifunctional monitoring, and other general treatments were given to stabilize her vital signs.

Postoperative treatment included benzalkonium chloride solution (0.05%, 0.25 g/500 mL × 1 bottle, Guangdong Lorst Pharmaceutical Co., Ltd.) 0.25 g for infection prevention, oxytocin injection (5 U/mL × 1 piece, Anhui Hongye Pharmaceutical Co., Ltd.) 20 U for contraction promotion, sodium chloride injection (0.90%, 500 mL × 1 bag, Anhui Fengyuan Pharmaceutical Co., Ltd.) 500 mL for fluid infusion, Yigong Granules (CO 10 g × 9 sachets, Shaanxi Jianmin Pharmaceutical Co., Ltd.) 3 boxes for strengthening qi and enriching blood, Compound Ferrous Sulfate and Folic Acid Tablets (CO 50 mg × 36 tablets, Jilin Province West point Pharmaceutical Science and Technology Development Co., Ltd.) 3 boxes for prevention of iron deficiency anemia, and Vitamin D2 Calcium Hydrogen Phosphate and Calcium Gluconate Tablets (60 tablets, China Resources Double Crane Pharmaceutical Co., Ltd.) for supplementation of calcium for symptomatic treatment. The patient’s vital signs were monitored closely, and uterine involution and vaginal bleeding were observed.

**OUTCOME AND FOLLOW-UP**

Eight days after surgery, the patient’s condition had improved significantly, and her vital signs were stable, but her liver function was still abnormal, so she was transferred to the department of hepatobiliary and pancreatic medicine for treatment. Laboratory examination revealed abnormal liver function, abnormal renal function, blood tests, and coagulation tests. Abdominal ultrasound revealed fatty liver. The patient was then treated with anti-infectives, liver protection, and coagulation improvement.

Twenty-one days after surgery, liver function improved significantly, and coagulation function returned to normal. The patient was subsequently discharged.

During hospitalization, the patient’s fibrinogen fell below the critical level several times. The doctors immediately injected fresh frozen plasma or cryoprecipitate and took blood samples every other day to monitor the coagulation function. The coagulation routine was performed 15 times before and after treatment, and the results are shown in Figure 2A.

The newborn was transferred to the neonatal unit for treatment after birth. The initial diagnosis was neonatal meconium aspiration syndrome, neonatal asphyxia, metabolic acidosis, hyperlactatemia combined with abnormal coagulation function, and fibrinogen fell below the critical level several times. After active symptomatic treatment, the child’s general condition and response were acceptable, and nutrition was tolerated. There were no obvious abnormalities on physical examination, and the child was discharged from the hospital. The infant’s coagulation profiles are shown in Figure 2B.

After a follow-up period of 12 mo, the mother and her newborn had a good prognosis without bleeding or thrombosis. The diagnosis and treatment of this patient are summarized in Figure 3.

**DISCUSSION**

Of the various cases of dysfibrinogenemia reported previously, 16 pregnant women with CD were reviewed (Table 1). The most important finding is that a new, previously unreported heterozygosity of the FGA (*p.R350H*) gene mutation was found in one pregnant woman, leading to CD in this patient. Another important finding is that the treatment strategy for acute fatty liver could have a therapeutic effect in the treatment of CD in pregnant women. Therefore, we have shared our experience on the diagnosis and treatment methods in this rare case.

CD can be easily misdiagnosed for the following two reasons: First, the clinical symptoms of CD are characterized by high heterogeneity and low specificity. They usually present as asymptomatic, thrombosis, chronic thromboembolic pulmonary hypertension, or renal amyloidosis, suggesting that CD is likely to be initially diagnosed as a respiratory, digestive, or urinary tract disease, making accurate diagnosis difficult. Secondly, the diagnosis of CD in clinical practice relies mainly on laboratory tests. However, the most commonly used methods for detecting fibrinogen, such as the PT algorithm or the Clauss method, have serious shortcomings. The PT algorithm can easily lead to a misdiagnosis of CD. Yan *et al*[12] found that the Clauss method can easily misdiagnose CD as hypofibrinogenemia. Recently, Xiang *et al*[13] reported that the combined use of the Clauss and PT-derived method can improve the accuracy of CD diagnosis. Values of the PT algorithm/Clauss method > 1.43 indicated a diagnosis of CD, with a sensitivity and specificity of about 100%. In this study, the pregnant woman with CD was misdiagnosed with acute fatty liver due to atypical clinical symptoms and incomplete laboratory results. The absence of laboratory examinations can lead to the misdiagnosis or missed diagnosis of CD[14]. In clinical practice, we recommend combining the PT-derived method and the Clauss method when CD is suspected to improve the accuracy of the diagnosis. Our opinion was supported by Yan *et al*[15], who reported that simultaneous determination of fibrinogen concentrations utilizing the Clauss method, the PT-derived method and immunoturbidimetry, as well as measurement of PT, reptilase time, thrombin time (TT) and activated partial thromboplastin time, can effectively distinguish dysfibrinogenemia from other diseases.

***Treatment of CD in pregnancy***

Treatment of CD during pregnancy or surgery should be individualized[15]. The optimal concentration and function of fibrinogen are crucial to the success of a pregnancy.

With regard to pregnant women with asymptomatic CD, special treatment of asymptomatic dysfibrinogenemia is not needed during pregnancy or surgery in the absence of bleeding or thrombotic events in the patient’s personal or family history[15]. The authors reported that using fibrinogen replacement therapy and prophylactic anticoagulation starting in the third trimester could achieve a successful clinical outcome for CD pregnant women without bleeding symptoms[6].

Concerning hemorrhage in pregnant women with CD, if CD pregnant women or their family members have a history of bleeding symptoms, it is recommended that the patient be referred to a hemophilia center for prenatal care. Bleeding and spontaneous abortion must be prevented if the fibrinogen level is below 0.5 g/L. In patients with vaginal delivery or cesarean section, the fibrinogen level should be raised to 1.5 g/L or more[2].

Regarding thrombosis in pregnant women with CD, low-molecular-weight heparin can be used during pregnancy for thromboprophylaxis in CD pregnant women or their family members who have a history of symptoms of thrombosis. These patients are at increased risk of thrombosis, so anticoagulants and fibrinogen should be used simultaneously. Optimizing treatment in different groups of patients under different clinical conditions and improving our knowledge of thrombotic events requires further study.

In this study, we report a pregnant patient with CD who underwent an emergency cesarean section due to intrauterine stress. Intraoperative laboratory examination revealed PT 33.7 s, activated partial thromboplastin time (APTT) 60.4 s, TT 45.2 s, and fibrinogen 0.60 g/L. After multidisciplinary consultation, the clinical diagnosis was “acute fatty liver in pregnancy”. After surgery, the patient was transferred to the ICU. Her condition improved after general and symptomatic treatment. However, her liver function remained abnormal. She was then transferred to the hepatobiliary and pancreatic medicine department. The results of additional examinations showed that the patient had liver damage and cholestatic hepatitis. Following treatment according to the principles of acute fatty liver, her coagulation gradually improved to normal values, and she was discharged. During the 12 mo follow-up, the patient achieved a good clinical outcome. This effective treatment has not been mentioned in previous studies. In our opinion, in pregnant women with CD special attention should be paid to the following during pregnancy: (1) Their general health during pregnancy; (2) The frequency of prenatal examinations; (3) The number of coagulation function tests, including PT, APTT, TT, and fibrinogen; and (4) A comprehensive evaluation of the risk of bleeding or thrombosis under the guidance of the obstetrician. We believe that this effective treatment regimen will help provide an alternative for other pregnant women with CD.

As CD is inherited in families, we advocate that other family members should also have a blood coagulation test. Furthermore, the entire family should be subjected to genetic sequencing, and this view is consistent with Yan *et al*[12]. In this study, a new heterozygous FGA mutant (*p.R350H*) was found by gene analysis. The pedigree map showed that the proband’s heterozygous FGA (*p.R350H*) mutation was inherited from her father, which was consistent with the autosomal dominant inheritance reported by progenitors[12,16]. In addition, genetic analysis revealed that the proband’s daughter also carried the disease-causing gene. Therefore, we performed comprehensive genetic counselling for the proband’s family members and informed the patient’s daughter that she should pay special attention to the risk of bleeding and thrombosis during pregnancy and that she should check her coagulation function regularly.

Although the patient was misdiagnosed and inappropriately treated, she eventually achieved a satisfactory treatment outcome. However, the study still has some shortcomings: First, due to the misdiagnosis of acute fatty liver during hospitalization, the patient did not have fibrinogen detected by the Clauss method; second, this treatment method needs to be verified by multicenter studies with large samples and randomized controlled trials.

**CONCLUSION**

Pregnant women with CD may have atypical symptoms, which can easily lead to misdiagnosis. In addition, a treatment approach can be attempted according to the principles of acute fatty liver. This rare pregnant woman with CD was caused by a novel FGA (*p.R350H*) gene mutation.

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**Figure Legends**



**Figure 1 Pedigree.** Affected II1 (proband) had congenital dysfibrinogenemia and carried the genetic mutation in the fibrinogen alpha chain gene (*p.R350H*). I1, I3, II1, and III1 carry the causative pathogenic gene.



**Figure 2 Coagulation results.** A: The pregnant patient during hospitalization. Fibrinogen dropped below the critical value several times, and fresh frozen plasma or cryoprecipitate was injected immediately; B: The newborn during hospitalization. PT: Prothrombin time; APTT: Activated partial thromboplastin time; TT: Thrombin time; FIB: Fibrinogen.

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**Figure 3 The process of patient admission, diagnosis, and treatment.** ICU: Intensive care unit; FGA: Fibrinogen alpha chain gene.

**Table 1** **Review of congenital dysfibrinogenemia in pregnancy**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Age (yr)** | **Symptoms** | **BCF** | **GT** | **Treatments** | **Clinical outcomes** |
| Bouvier *et al*[1], 2018 | 21 | Placental abruption | 1. Fibrinogen plasma level (Clauss): 0.6 g/L ↓; 2. A normal immunological level: 1.91 g/L | FGA exon 5: c.1415\_1416 ins C | Fibrinogen substitution with heparin and aspirin | (1) First pregnancy: A low-birth-weight baby by cesarean delivery followed by postpartum hemorrhage; (2) Second pregnancy: Cesarean delivery due to decreased fetal movements; (3) Third pregnancy: Fetal death; and (4) Fourth pregnancy: Pregnancy was normal with a programmed cesarean delivery |
| Edwards and Rijhsinghani[3], 2000 | 24 | (1) Vaginal bleeding; and (2) Placental abruption | Fibrinogen level: 84 mg/dL ↓; thrombin time: 67 s ↑ | - | Operation | - |
| Langer *et al*[6], 2021 | 28 | Heavy vaginal bleeding after her first sexual intercourse | Fibrinogen activity level: < 60 mg/dL ↓ | - | (1) Fibrinogen replacement therapy; and (2) Prophylactic anticoagulation | Uneventful delivery |
| Takala *et al*[17], 1991 | - | Thrombotic | - | - | Heparin | Fetal loss |
| Yamanaka *et al*[18], 2003 | 38 | (1) Vaginal bleeding; and (2) Three times repeated abortions due to placental abruption | (1) Clottable fibrinogen: 66 mg/dL↓; and (2) Immunologic fibrinogen: 225 mg/dL (normal) | - | (1) Cesarean section; and (2) Before and during the operation 6 g of fibrinogen was infused | (1) No findings of placental abruption at the time of surgery; and (2) The newborn developed normally |
| Franchini *et al*[19], 2007 | 30 | Miscarriage at 9 wk of gestation 2 yr previously | (1) Functional fibrinogen: 161 mg/dL ↓; and (2) Immunologic fibrinogen: 466 mg/dL | Prothrombin G20210A mutation | LMWH | The woman delivered a healthy female baby |
| Franchini *et al*[19], 2007 | 36 | Idiopathic thrombocytopenic purpura | (1) Functional fibrinogen: 85 mg/dL ↓; and (2) Immunologic fibrinogen: 221 mg/dL | - | -  | The woman delivered a healthy male baby |
| Franchini *et al*[19], 2007 | 25 | No | (1) Functional fibrinogen: 56 mg/dL ↓; and (2) Immunologic fibrinogen: 268 mg/dL | - | LMWH | The woman delivered a male baby |
| Franchini *et al*[19], 2007 | 33 | No | (1) Functional fibrinogen: 63 mg/dL ↓; and (2) Immunologic fibrinogen:180 mg/dL | - | LMWH | A normal male baby was delivered |
| Kotlín *et al*[20], 2011 | 36 | (1) Bleeding; and (2) Spontaneous abortions | (1) Functional fibrinogen level: 0.85 g/L ↓; and (2) Thrombin time: 39.3 s ↑ | A heterozygous G4864A transition in exon 2 of the FGA (GenBankaccess number M64982)  | Curettage | - |
| Yan *et al*[15], 2015 | 26 | (1) Viral cold and *Mycoplasma genitalium*infection; and (2) No other clinical signs. | (1) Fibrinogen concentration: 0.56 g/L ↓; and (2) Immunoturbidimetry: 3.82 g/L | - | Operation | Artificial abortion |
| Yan *et al*[21], 2018 | 30 | No | Function fibrinogen level: 0.55 g/L ↓ | FGA exon 2: 1233C→A | No specific intervention in this case because the patient had no previous episodes of abnormal bleeding or thrombosis | Uneventful delivery |

The normal level of functional fibrinogen (Clauss) was 150-450 mg/dL; the normal thrombin time was 12.5-16.5 s; the normal reptilase time was 12–22 s. BCF: Blood coagulation function; GT: Genetic testing; LMWH: Low-molecular-heparin; FGA: Fibrinogen alpha chain gene; ↓: Decreased values; ↑: Prolonged values.

**Table 2** **Review of gene mutation sites**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **cDNA** | **Gene** | **Exon** | **CM** | **Clinical symptoms** |
| Yoshida *et al*[5], 2017 | - | *FGB* | - | Ala68Thr | Superior sagittal sinus thrombosis, pulmonary embolism, DVT |
| Qiao *et al*[16], 2020 | c.92G>A | *FGA* | - | p.Gly31Glu | No symptoms so far |
| Kotlín *et al*[22], 2012 | - | *FGA* | - | Gly13Glu and Ser314Cys | Easy bruising, excessive bleeding during pregnancy and delivery, menorrhagia |
| Kotlín *et al*[22], 2022 | - | *FGA* | - | Gly13Glu | Epistaxis, bleeding from gums, prolonged bleeding after venipuncture |
| Luo *et al*[23], 2016 | c.104G>A | *FGA* | 2 | Arg16His | Mostly asymptomatic, sometimes severe bleeding and postpartum DIC |
| Cai *et al*[24], 2018 | c.103C>A | *FGA* | 2 | Arg38Thr | No symptoms so far |
| Shlebak *et al*[25], 2017 | c.221G> T | *FGB* | 2 | p.Arg74Leu | Venous and arterial thrombosis |
| Casini *et al*[26], 2017 | c.284 G>C | *FGB* | 2 | p.Cys95Ser | One miscarriage followed by metrorrhagia lasting nearly 2 mo |
| Undas *et al*[27], 2009 | c.1052A>T | *FGG* | 8 | Asn325Ile | DVT after appendectomy |
| Luo *et al*[28], 2020 | c.1178T>C | *FGG* | 9 | p.IIe367Thr | Menorrhagia |
| Yan *et al*[29], 2016 | g.5877G>A | *FGG* | 8 | Arg275His | No symptoms so far |
| Imafuku *et al*[30], 2002 | γ chain from Arg 275 to Cys (gR275C) | *FGG* | 8 | γ R275C | No symptoms so far |

CM: Causative mutations; cDNA: Complementary DNA; FGA: Fibrinogen alpha chain; FGB: Fibrinogen beta chain; FGG: Fibrinogen gamma chain; DIC: Disseminated intravascular coagulation; DVT: Deep venous thrombosis.