A 26-year-old pregnant woman with mild gingival bleeding

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Summary
Congenital dysfibrinogenemia is a genetic coagulopathy that leads to compromised fibrinogen function. This case report describes a 26-year-old pregnant woman at the 38th week of gestation who presented with mild gingival bleeding and constant bruising on her joints. As part of her laboratory workup, fibrinogen was found to be significantly decreased and thrombin time was prolonged. Using whole exome DNA sequence analysis, a heterozygous mutation was identified in the fibrinogen α (FGA) (c.104G > A; p.R35H) gene. This mutation has been reported previously in congenital dysfibrinogenemia (CD) patients who are usually asymptomatic and lack any obvious thrombotic complications. However, both post-partum disseminated intravascular coagulation and mild bleeding have been observed in this type of mutant. The patient in our case received fibrinogen concentrate as replacement therapy during her cesarean section to prevent severe bleeding. Neither major bleeding nor a thrombotic event was observed throughout her surgery.

Key words: Dysfibrinogenemia; Heterozygous mutation; Fibrinogen; Bleeding; Thrombosis.

Introduction
Fibrinogen, the final reaction protein in the clotting cascade, plays a major role in clot formation after conversion into insoluble fibrin by the action of thrombin (insert ref). The 340 kDa fibrinogen molecule consists of two sets of three polypeptide chains: an α chain (644 amino acids (aa)), β chain (491 aa), and γ chain (437 aa) encoded by fibrinogen α (FGA), fibrinogen β (FGB) and fibrinogen γ (FGG) genes respectively clustered in a region of approximately 50 kb on chromosome 4q31.3 [1].

Congenital fibrinogen deficiency represents a group of disorders with quantitatively (afibrinogenemia/hypofibrinogenemia) or qualitatively (dysfibrinogenemia/hypodysfibrinogenemia) compromised circulating fibrinogen, caused by mutations in the exons of FGA, FGB, and FGG genes [2]. Although fibrinogen is increased during pregnancy as a normal physiological response, patients with fibrinogen deficiency may still have potential complications of mild bleeding during surgery or as post-partum hemorrhage [3]. In this case, we identified a congenital dysfibrinogenemia patient by whole exon sequencing followed by Sanger sequence analysis. Having confirmed this diagnostic information, prophylactic management was applied to prevent major bleeding during her cesarean section surgery.

Case report
A 26-year-old Chinese female at the 38th week of gestation paid a routine antenatal visit to the Beijing Obstetrics and Gynecology Hospital. She complained about mild gingival bleeding and occasional spotted vaginal bleeding in the third trimester. In addition, she mentioned that she bruised easily especially on her extremities. However, there were no any major bleeding or thrombotic events throughout her pregnancy. Notable bruising areas were observed on her elbows. The patient’s past medical, family history and physical examinations were not remarkable.

The patient’s major laboratory findings are summarized in Table 1 and Figure 1. In addition, thyroid function evaluation, infectious disease serological screening and the triple test for Down syndrome were all negative. The mild gingival and vaginal bleeding during her pregnancy, together with the frequent bruises on her joints, implied a potential underlying coagulation disorder. As seen in her coagulation testing panel performed on the Sysmex CS-5100 (Table 1), the patient’s functional fibrinogen level, 0.70 g/L (Clauss method), was significantly below the lower limit of the reference interval (1.80–4.00 g/L), which was accompanied by a prolonged thrombin time. However, her fibrinogen antigen level was not decreased (Medical System, Fibrinogen ELISA Kit). As expected, the patient’s D-dimer was elevated due to a physiological change of normal pregnancy in the third trimester (Table 1). Clotting was not found with the patient’s citrated plasma, suggesting that this was not a pre-analytical (plasma clotting error) induced low fibrinogen. The patient’s liver and renal function tests and complete blood count were essentially within normal limits at the time of the current antenatal visit (data not shown).

With the patient’s consent, the coding regions of the FGA, FGB and FGG genes were analyzed by whole exon sequencing, followed by Sanger sequencing to confirm any mutation identified. The sequencing data revealed a heterozygous mutation in the FGA gene (c.104G > A; p.R35H) (Figure 1). The c.104G > A mutation leads to an arginine to histidine amino acid change, which has been
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Figure 1. — DNA sequencing analysis: single nucleotide substitution on FGA exon 2. FGA exon 2 c.104G >A mutation led to Arg35His in amino acid substitution in nascent chain. Genetic testing suggested Arg16His mutation in mature Aα chain.

Table 1. — Coagulation testing results

| Test     | Patient’s Result | Reference Interval |
|----------|------------------|--------------------|
| FIB (Clauss) | 0.7              | 1.80-4.00 g/L      |
| FIB (Antigen) | 4.6              | 2-4 g/L            |
| PT       | 11.9             | 10.0-14.0 sec      |
| TT       | 28.4             | 14.0-21.0 sec      |
| APTT     | 25.4             | 22.80-35.00 sec    |
| D-dimer  | 1.11             | 0.00-0.55 mg/L     |

FIB, fibrinogen; PT, prothrombin time; TT, thrombin time; APTT, activated partial thromboplastin time.

reported as a pathogenic allele in previous studies [4].

Discussion

Commonly observed clinical conditions that lead to reduced fibrinogen levels may include but are not limited to: fibrinolysis, cirrhosis, hepatitis, disseminated intravascular coagulation (DIC) and congenital fibrinogen deficiency [5]. The patient’s negative hepatitis screen and unremarkable liver function evaluation ruled out hepatology factors that would contribute to decreased fibrinogen (insert Ref). Furthermore, the level of normal fibrin degradation product (FDP) did not support fibrinolysis or DIC in which the FDP is expected to increase. Eventually, the patient’s low fibrinogen was explained by a point mutation (c.104G >A; p.R35H) identified in the FGA gene by DNA sequencing.

Since the first mutation reported in 1968, over a hundred mutations that lead to congenital dysfibrinogenemia (CD) have been reported (insert Ref). Of the previously published mutations, greater numbers have been found in the FGA and FGG genes rather than in the FGB gene (insert Ref). The most common mutation type is a missense mutation caused by a single nucleotide substitution (non-synonymous substitution), resulting in altered fibrinogen activity such as fibrinopeptide release, fibrin polymerization, fibrinogen clotting ability. The CD patient described in present case was identified with a heterozygous mutation of c.104G >A (Arg35His replacement) at one of the mutation hotspots of FGA exon 2 as described previously by Neerman-Arbez et al. [6]. It has been found that fibrinopeptide A release, the vital step of fibrinogen conversion into a fibrin monomer, would be slowed in patients with the c.104G >A mutation that further would lead to impaired thrombin-induced fibrin polymerization. It is interesting to note that patients with the FGA exon2 c.104G >A mutation are usually asymptomatic and lack obvious thrombotic complications [7, 8]. Both post-partum DIC and mild bleeding events have been observed in patients with this type of mutation [9].

Fibrinogen replacement is used to assist in maintaining pregnancy and reducing bleeding. For pregnant women with fibrinogen activity <0.5 g/L or with previous adverse pregnancy outcomes, prophylactic treatment with fibrinogen concentrate is recommended to maintain fibrinogen activity >1.0 g/L. For pregnant women with thrombotic dysfibrinogenemia and other risk factors for venous thrombosis, low molecular weight heparin is considered for thromboprophylaxis [3, 10].

Considering in more detail the care of this patient, she received 400 mL fresh frozen plasma as replacement therapy in the cesarean section procedure during which general anesthesia instead of combined epidural-spinal anesthesia was applied. Her fibrinogen level was able to be maintained at upper level of 1.0 g/L throughout the surgery and up to 72 hours post-partum prior to discharge. In the absence of major bleeding or thrombotic events during or after surgery, no thromboprophylactic treatment was administered. A healthy infant with Apgar scores of 10 at 1, 5 and 10 minutes was delivered.

Ethics Approval and Consent to Participate

The subject gave her informed consent for inclusion before she participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Beijing Obstetrics and Gynecology Hospital Research Ethics Committee (approval number: 2016-KY-073).

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Conflict of Interest

The authors declare no competing interests.

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