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ORIGINAL ARTICLE

Physiological correction of hereditary mild hypofibrinogenemia during pregnancy

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Abstract

Introduction: Hereditary hypofibrinogenemia is a rare fibrinogen disorder characterised by decreased levels of fibrinogen. Pregnant women with hypofibrinogenemia are at risk of adverse obstetrical outcomes, depending on the fibrinogen level.

Aim: We investigated how the physiological changes of hemostasis throughout the pregnancy impact the hemostatic balance in a woman with hereditary mild hypofibrinogenemia.

Methods: Fibrin clot properties were analyzed by turbidimetry and scanning electron microscopy, clot weight and red blood cells retention were measured by whole clot contraction, and in vitro thrombin generation was assessed by calibrated automated thrombogram and ex vivo by TAT.

Results: Throughout the pregnancy, the fibrinogen levels increased reaching normal values in the third trimester (activity 3.1 g/L, antigen 3.2 g/L). In parallel, the fibrin polymerisation increased, the fibrinolysis decreased, the fibrin clot network became denser with thicker fibrin fibers, and the fibrin clot weight and red blood cells retention increased, reaching control's value at the third trimester. Similarly, in vitro and ex vitro thrombin generation increased, reaching maximum values at the delivery.

Conclusion: In this case of hereditary mild hypofibrinogenemia we observed a physiological increase of fibrinogen and thrombin generation. Future studies should focus on moderate and severe hypofibrinogenemia, to assess fibrinogen variation and the overall impact of increased TG on the hemostasis balance.

KEYWORDS
fibrinogen, fibrinogen disorders, hypofibrinogenemia, pregnancy, thrombin generation

1 | INTRODUCTION

Hereditary hypofibrinogenemia is a quantitative fibrinogen disorder characterized by a proportional decrease of the functional and antigen fibrinogen levels.[1] Severe and moderate hypofibrinogenemia (functional fibrinogen below 1 g/L) are often associated with a bleeding phenotype, while mild hypofibrinogenemia (fibrinogen higher than 1 g/L) is usually asymptomatic except after trauma or surgery.[2] Hypofibrinogenemia is very often caused by heterozygosity for a fibrinogen gene mutation, which in homozygosity or compound heterozygosity would cause afibrinogenemia.[3] The exact prevalence of hereditary hypofibrinogenemia is not known, but it is probably underestimated.[4]

Pregnancy in fibrinogen disorders is considered as a high-risk clinical situation.[5] It has been reported that women with hereditary hypofibrinogenemia are at risk of miscarriage, vaginal bleeding, retroplacental hematoma, placenta abruption and post-partum hemorrhage.[6] Complications are dependent on the type of fibrinogen disorder and the fibrinogen level throughout the pregnancy. However, detailed data on variation of fibrinogen level during pregnancy are limited.

In most cases of hereditary hypofibrinogenemia, the variant fibrinogen is not secreted into the circulation.[7] Therefore, the fibrin clot is formed only by fully functional fibrinogen molecules, even though in lower concentrations.[8] One of the major determinants of the fibrin clot properties is the fibrinogen concentration. Fibrin fiber diameter correlates positively with fibrinogen concentration. Fibrin clots made in low fibrinogen concentration have a looser network with thinner fibrin fibers and increased permeability compared to those at high fibrinogen concentration.[9] During pregnancy, women with hereditary hypofibrinogenemia are able to partially increase the fibrinogen synthesis and secretion, and thus could have a denser and more stable fibrin clot. A second major contributor to the fibrin clot network is the concentration of active thrombin present at the time of fibrin gelation.[10] Higher concentrations of thrombin produce fibrin clots that are composed of relatively thinner, more tightly-packed fibrin strands.[11] The physiological increase of factor VIII and thrombin generation throughout the pregnancy lead to a procoagulant state, also characterised by the modification of the fibrin clot network.[12]

The influence of the pregnancy-related hypercoagulability on the overall hemostatic profile in women with hereditary hypofibrinogenemia has not been studied so far. To evaluate the impact of increasing fibrinogen levels and variation of other coagulation factors on fibrin clot properties in a pregnant woman with hypofibrinogenemia, we studied the fibrin clot structure and performed global hemostasis assays during the pregnancy, at the time of the delivery, and in the post-partum.

2 | MATERIALS AND METHODS

Institutional review board approval and written consent was obtained from the patient in accordance with the Declaration of Helsinki.

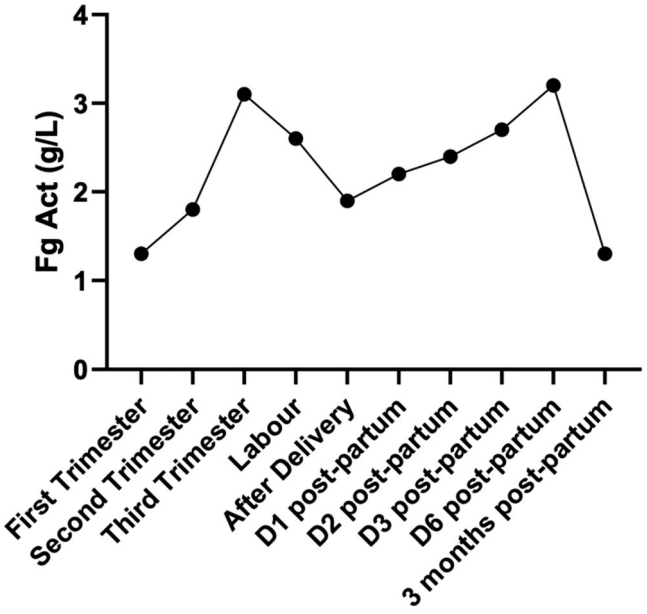

FIGURE 1 Variation of the patient's fibrinogen activity during pregnancy, at the time of labor, in the immediate post-delivery, the days after the delivery and 3 months post-partum. D, day; Fg Act, fibrinogen activity.

2.1 | Case-report

The patient was diagnosed with a mild hypofibrinogenemia (functional fibrinogen .8 g/L; antigen fibrinogen 1 g/L) when she was a teenager as investigation of a mild bleeding disorder. She mentioned a tendency to cutaneous hematoma, epistaxis, and heavy menstrual bleeding since menarches, requiring the introduction of a contraceptive pill. The familial screening revealed that her grandfather and her father also have hypofibrinogenemia, but they were asymptomatic despite multiple hemostasis challenges. The genetic analysis by whole exome sequencing identified a known donor splice site mutation in *FGB* intron 7: IVS7 + 1G > T (c.1244 + 1G > T).[13] Patient became pregnant when she was 28 years old. A progressive increase of fibrinogen levels, factor VIII and D-dimers was observed (Figure 1 and Table 1). At 39 weeks of gestation, she came to the maternity with spontaneous labor. Fibrinogen level was 2.5 g/L, allowing to perform a neuroaxial anesthesia without fibrinogen supplementation. The delivery was complicated by a prolonged labor and abnormality in fetal heart rate leading to an unsuccessful attempt of forceps delivery and finally a cesarean cut without fibrinogen supplementation but injection of 1 g of tranexamic acid. The overall bleeding was estimated to be about 600 mL. The decreased levels of fibrinogen observed at labor reflect the fibrinogen consumption during the delivery. A mechanical thromboprophylaxis was started in the early post-partum and replaced by a pharmacological thromboprophylaxis (i.e., enoxaparin 40 mg once a day) 2 days after the delivery for five days until discharge.

TABLE 1 Biological parameters at different time points of pregnancy, of the delivery and after delivery.

Parameter	First trimester	Second trimester	Third trimester	12 h post delivery	14 h post delivery	3 Months post-partum	Normal range
Fibrinogen activity (g/L)	1.3	1.8	3.1	1.9	2.2	1.3	2–4
Fibrinogen antigen (g/L)	1.3	1.8	3.2	NA	NA	1.6	2–4
D-dimers (ng/mL)	47	349	587	NA	NA	164	<500
Factor VIII (%)	104	156	161	NA	NA	112	50–150
F1+2 (Pm)	173	426	612	1091	666	343	69–229
TAT (μg/L)	3.56	8.41	9.10	16.58	10.26	3.39	2–4.2

Abbreviations: NA, not available; F1+2, prothrombin fragments 1 + 2; TAT, thrombin-antithrombin complex.

2.2 | Turbidity

Turbidity assays were performed with human tissue factor (TF) (Innovin, Siemens Healthcare Diagnostics, Newark, Germany).[14] Briefly, 70 μL of plasma samples were diluted with 49 μL Tris-buffered saline (TBS) for fibrin polymerisation or 49 μL tissue type plasminogen activator (tPA), 170 ng/mL, (Technoclone, GmbH, Austria) for clot lysis.[15] Then, 15 μL of activation mix [30.000x diluted TF, 17 mM $CaCl_2$, and 5 μM phospholipids (Rossix Diapharm, West Chester, US), final] were added. Optical density (OD) was recorded each min during 1 h and then each 3 min during 3 h at 405 nm in BioTek Instruments ELx800 series (Witec AG, Sursee, Switzerland). Lag time, the slope (OD/min), and MaxAbs (mOD) were calculated from the polymerization curves. The clot lysis time T50% (min) was defined as the time elapsed between 50% of MaxAbs in the polymerisation curve side and 50% MaxAbs in the fibrinolysis.[16] The slopes were calculated with GraphPad Prism 8.01. Plasma sample from a healthy subject was used as control.

2.3 | Scanning electron microscopy

Plasma samples (100 μL, 1:2 diluted with TBS, supplemented with 200 U/mL aprotinin), clotted with TF (same conditions as for turbidity), were immediately transferred into a pre-etched plastic serologic tip and incubated during 2 h at 37°C, then washed with TBS and with 50 mM sodium cacodylate-HCl buffer pH 7.4 (SCB) during 30 min each, and permeated with 2% glutaraldehyde in SCB. Clots were left in glutaraldehyde overnight at 4°C and removed from the tips with a syringe inside small beakers filled with SCB and rinsed three times during 30 min, then dehydrated with a series of graded concentrations (30%–100%) ethanol. A solution of 100% hexamethyldisilazane (HMDS) was added to the last dehydration step with 100% ethanol to have a 50% HMDS-ethanol and left for 15 min, this last step was repeated until to reach 100% HMDS. The samples were left overnight. A film of 20 nm gold was added using sputter coating HHV and imaged in a Sigma 300 VP FE-SEM (Field-emission SEM) from Zeiss (Oberkochen. Germany). The fibrin fiber diameters were measured using the plugins DiameterJ of Image J 1.49v (Fiji, National Institute of Health, Bethesda, Maryland, USA). Plasma sample from a healthy subject was used as control.

2.4 | Whole blood clot contraction

Whole blood clot contraction (BC) was performed essentially as described in Ref.[17] Briefly, whole blood (WB, 930 μL) was poured in a 10 × 75 mm borosilicate tube filled with 20 μL of Tyrode-Hepes buffer (TH). The WB was recalcified adding 25 μL $CaCl_2$ (10 mM, final) and then 25 μL of human thrombin (Merck, Germany; 1.25 U/mL, final). Finally, a sealed glass pipette was introduced inside the tubes and incubated during 2 h a 37°C. After the incubation time, the clots were removed and weighed and the serum extruded from the contracted clots was measured. BC was expressed as the ratio of the clot weight (g) divided by the volume of serum extruded (mL). The quantity of red blood cells (RBCs) extruded from the retracted clots was counted in a Sysmex XN-9000 (Kobe, Japan) and expressed in % (the ratio of the number of RBCs in the serum divided by the count of RBCs in WB). Whole blood clot from a healthy subject was used as control.

2.5 | Thrombin generation

Thrombin generation (TG) was measured with the reference method calibrated automated thrombogram (CAT) (Stago, Asnières-sur-Seine, France), using an automated fluorimeter (Fluoroscan Ascent, ThermoLab Systems. Franklin, USA).[18] TG was initiated with PPP-reagent (TF 5 pM and phospholipids 4 μM, final concentration; Thrombinoscope BV, Maastricht, Netherlands) or PPP-reagent low (TF 1 pM and phospholipids 4 μM, final concentration; Thrombinoscope BV, Maastricht,

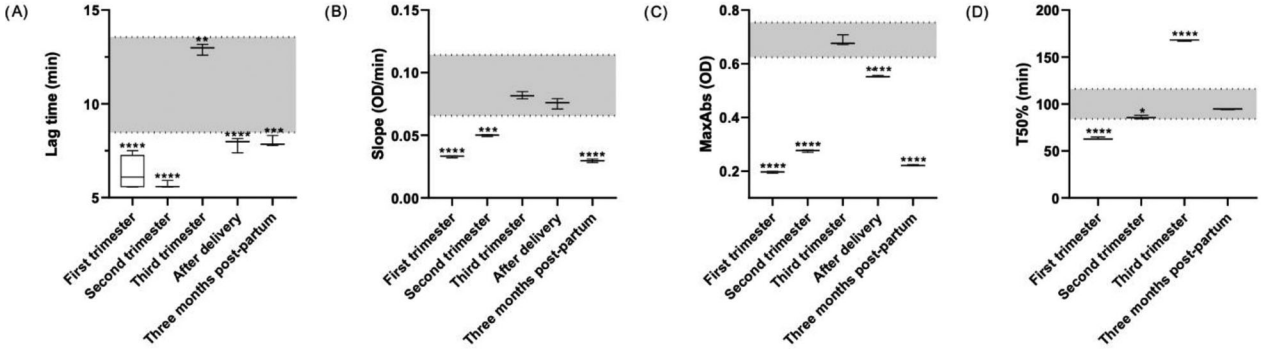

FIGURE 2 Turbidimetry parameters during pregnancy, early after the delivery and at 3 months of post-partum. The box plot spans from 25th to 75th quartiles (interquartile range, IQR) and the line inside the box indicates the median value. The dotted grey lines and shaded area indicates normal control 2.5th and 97.5th percentiles, respectively. *P*-value of comparison between patient and control: *, significant (.01 to <.05); **, very significant (.01 to <.001); *** and ****, extremely significant (.001 to .0001).

Netherlands). For each assay, lag time, thrombin peak height (in short, 'peak'), endogenous thrombin potential (ETP), and time to peak (in short, 'tt peak') were calculated. Raw data were analyzed with Thrombinoscope V5. Plasma sample from a healthy subject was used as control.

2.6 | Prothrombin fragments 1 + 2 and thrombin-antithrombin complex

Prothrombin fragments 1 + 2 (F1+2) were measured by the Enzygnost® F 1+2 (monoclonal) Kit and thrombin-antithrombin complex (TAT) by Enzygnost® TAT micro (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany).

2.7 | Statistics

Results are presented as mean ± standard deviation (SD) or median ± interquartile range (IQR), after assessing normality by Shapiro-Wilk test. Comparisons were performed by one-way ANOVA test with Dunnett's correction for multiple comparisons or Kruskal-Wallis test with Dunn's correction for multiple comparisons, with 95% confidence level ($p < .05$). Statistical analyses were carried out with GraphPad Prism version 8.01.

3 | RESULTS

3.1 | Turbidity

During pregnancy the patient's fibrinogen concentration increased, improving, as expected, the fibrin formation and the resistance to lysis (all parameters are summarized in Table S1). The lag time, the slope and the MaxAbs increased from the first trimester, reaching the control's value at the third trimester (Figure 2A–C). Similarly, the T50% increased and reached the control's value at the second trimester (Figure 2D). Of note, at the delivery no lysis was measurable due to the administration of tranexamic acid.

3.2 | Scanning electron microscopy

Fibrin network of the patient varied during pregnancy, reflecting the increase of fibrinogen level (Figure 3A,D). At the first and second trimesters, patient's clots were dense with reduced pores and fibrin fibers size (89 ± 9 and 88 ± 6 nm). At the third trimester, patient's fibrin clot structure was similar to that of control (Figure 3E,F), with fibrin fibers diameter of 134 ± 23 nm (control: 123 ± 13 nm, $p = .68$). Patient's fibrin fibers diameter of the first and second trimesters were significantly decreased compared to that of the third trimester ($p = .001$ and .0009, respectively). After delivery and at 3 months post-partum, patient clot structure returned to that of the first trimester (Figure 4A). Fibrin fibers diameter decreased gradually from 113 ± 21 nm to 93 ± 9 nm and were statistically thinner compared to those of the third trimester ($p = .003$). Instead, when compared to the control, only fibrin fibers diameter of the first and second trimesters, and of the 3 months after delivery were significantly thinner than control ($p = .015$, .010, and .032, respectively).

3.3 | Clot contraction

Patient's BC values were around 0.4 g/mL at the first and second trimesters of pregnancy, and 3 months after the delivery (Figure 4B, Table S2), significantly lower than control ($p = .006$, .004 and .001, respectively). They reached control's values at the third trimester of pregnancy (.74 ± 0.04 g/mL; control: .88 ± .09). When patient's BC values were compared with each other, in the third trimester they were higher than in the first trimester, second trimester and 3 months post-partum ($p = .007$, .002 and .003, respectively). When BC values were adjusted to fibrinogen activity, patient's BC of first trimester remained statistically different compared to that of the second and

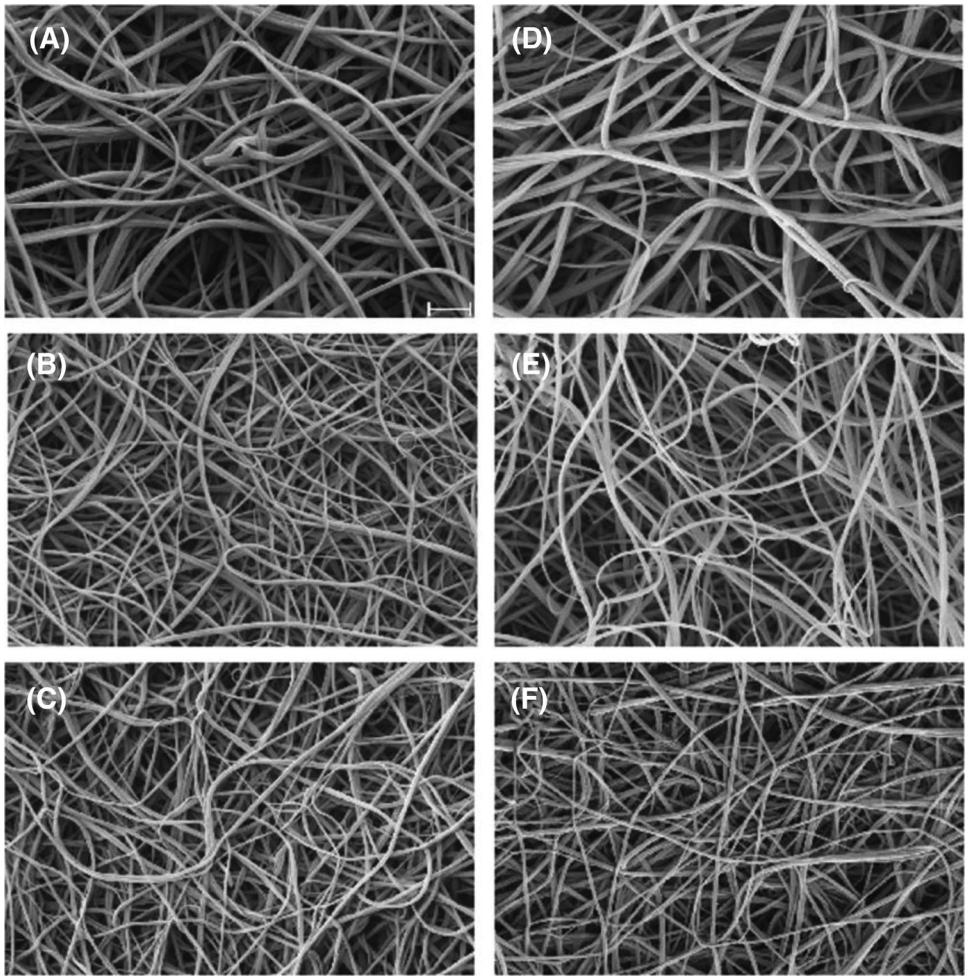

FIGURE 3 Scanning electron microscopy of fibrin clot. (A) Control. (B) Patient at the first trimester. (C) Patient at the second trimester. (D) Patient at the third trimester. (E) Patient early after the delivery. (F) Patient at 3 months of the post-partum. Tool magnification bar corresponds to 100 nm.

third trimesters ($p = .014$ both), while no longer different than those of control.

As a reflection of the increasing BC during pregnancy, the % of RBCs extruded from patient clots decreased steadily from the first to the third trimester, reaching values similar to the control at the third trimester ($p = .15$), and increasing again after delivery (Figure 4B–D and Table S2).

3.4 | Thrombin generation

The changes of TG parameters are summarized in Table 2 and the curves are reported in Figure S1A and B. Overall, patient's TG increased throughout the pregnancy, from the second trimester to the delivery, reaching the maximum values of ETP (2150 nM × min) and peak (321 nM) at the delivery. Since the second trimester, patient's TG was statistically higher than the control (ETP $p = .041$). At 3 months after delivery, TG parameters returned to the similar values measured in the first trimester. The pattern was similar regardless of the reagent, even though the differences were slightly more marked with PPP low compared to PPP.

3.5 | Prothrombin F1+2 and TAT

Patient's prothrombin F1+2 and TAT increased throughout the pregnancy, from the second trimester to delivery, reaching the maximum value 12 h after the delivery (1091 pM and 16.58 μg/L, respectively). Since the second trimester, patient's F1+2 and TAT were higher than the control (270 ± 52 pM and 3.19 ± .18 μg/L, respectively).

4 | DISCUSSION

We report the evolution of fibrinogen levels and its effect on fibrin clot properties in a pregnant woman with mild hereditary hypofibrinogenemia. The fibrinogen levels increased from the first trimester to the delivery leading to a dense and stable fibrin clot. As expected, the TG

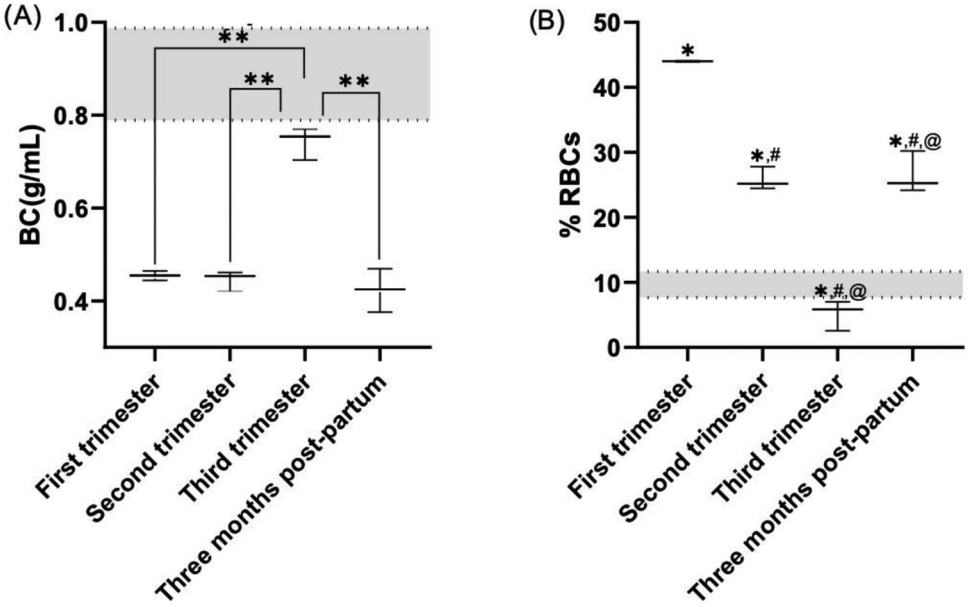

FIGURE 4 Whole blood clot contraction at different time points during and after pregnancy. The box plot span from 25th to 75th quartiles (interquartile range, IQR) and the line inside the box indicates the median value. Wiskers are calculated by Tukey method (lowest value close to the 25th percentile minus 1.5 IQR and higher values close to the 75th percentile plus 1.5 IQR). The dotted grey lines and shaded area indicated normal control 2.5th and 97.5th percentiles, respectively. Only the statistics amidst patient values are shown. (A) Clot contraction (B and C). ** Very significant ($p < .01$). (B) Red blood cells (RBCs) extruded from the clots. Statistically significant between first (*), second ($^{\#}$) and third trimester (@).

TABLE 2 Summary of thrombin generation parameters obtained with PPP reagent and PPP reagent low. Results are expressed as the median (IQR).

	Lag time (min)	ETP (nM × min)	Peak (nM)	ttPeak (min)
Control PPP	3.7 (.3)	1328 (141)	195 (12)	7.7 (.8)
Control PPP low	6.3 (.3)	875 (121)	77 (21)	12.2 (.7)
Patient PPP				
First trimester	2.7 (0)	1490 (18)	289 (1)	5.3 (0)
Second trimester	2.3(0)	1839 (46)	354 (15)	5.3 (0)
Third trimester	3.7 (0)	1955 (245)	271 (28)	8.3 (.3)
After delivery	3.7 (0)	2213 (365)	335 (47)	8.0 (.3)
3 months post-partum	3.0 (0)	1419 (93)	258 (16)	6.0 (0)
Patient PPP Low				
First trimester	4.3 (.3)	1341 (200)	224 (32)	8.0 (.3)
Second trimester	4.0 (0)	1572 (41)	276 (16)	7.3 (0)
Third trimester	5.3 (.4)	1629 (235)	186 (18)	11.0 (.3)
After delivery	5.3 (.3)	1997 (275)	283 (20)	10.0 (1.0)
3 months post-partum	5.3 (.3)	1132 (96)	143 (8)	9.7 (.3)

Abbreviations: ETP, endogenous thrombin potential; PPP, 5 pM TF; PPP low 1 pM TF; ttPeak, time to peak.

also increased contributing to the hemostasis balance in the setting of hypofibrinogenemia.

Hereditary hypofibrinogenemia is caused by mutations in one of the three fibrinogen chain-encoding genes. Causative mutations can be divided into two main classes: null mutations with no protein production at all and mutations producing abnormal protein chains which are retained inside the cell.[7] As is the case for our patient, hereditary hypofibrinogenemia is generally caused by heterozygosity for these mutations, which means that patients still have a normal fibrinogen gene allele. Thus, in specific clinical settings, e.g. trauma or pregnancy, patients are able to increase to some degrees the synthesis and secretion of fibrinogen into the circulation.[19] In the late preg-

nancy, fibrinogen concentrations increase to approximately twice the non-pregnant levels in healthy pregnant woman.[20] Therefore, in hereditary mild hypofibrinogenemia it can be expected that fibrinogen level would be in the normal range at the end of the pregnancy, though still lower than physiological levels (3.4–6.4 g/L).[20] In this study, we observed a significant increase of fibrinogen level in third trimester, reaching 3.3 g/L. Different results were reported in a recent series of 11 pregnant women with hypofibrinogenemia. Cai et al. reported a slight increase of the fibrinogen concentration from .75 ± .43 to .80 ± .29 g/L.[6] As neither the fibrinogen antigen nor the genotype were described, one possible explanation is that some women in this series were dysfibrinogenemic, which typically is not associated with a significant increase of the fibrinogen activity during the gestation, rather than hypofibrinogenemic.

Physiological modifications of the hemostatic system during pregnancy result in a procoagulant state. The increase of biomarkers such as factor VIII, TG and D-dimers, reflects the shift in balance between the hemostatic and the fibrinolytic systems.[21,22] Our patient showed a rise of TG and factor VIII similar to that reported in healthy pregnant women.[22] We can speculate that in pregnant women with mild hypofibrinogenemia the increased TG may compensate, at least in part, the bleeding risk related to the relative low levels of fibrinogen. Thrombin and fibrinogen concentrations are the most important determinants of the fibrin clot structure. As expected, throughout the pregnancy we observed that the fibrin clot became denser and more resistant to the lysis, i.e. a clot with a thrombotic phenotype. To our knowledge only one other study reported the fibrin clot structure in a pregnant woman with a fibrinogen disorder. Pretorius et al. compared the fibrin network between a nonpregnant woman, a healthy pregnant woman, and a pregnant woman with dysfibrinogenemia (Fibrinogen Pretoria, *FGG* Cys139Arg).[23] Interestingly, fibrin clots from patient at the third trimester and healthy woman presented a similar dense fibrin network suggesting that the modifications of fibrin clot were more related to the pregnancy than the fibrinogen disorder.

Clot retraction is an essential support of haemostasis, promoted by platelet and fibrin mechanics,[24] but knowledge is limited in the setting of decreased fibrinogen. In our experimental conditions, clot weight was correlated to the fibrinogen concentration. Low fibrinogen levels resulted in the formation of lighter clots, while concomitant to the increasing of fibrinogen concentration the clot weight normalized in the third trimester. It has been shown that clot strength increases linearly with fibrinogen concentration, with a minimum level of 2.0 g/L required in vitro for the optimal rate of clot formation to be achieved.[25] Again, we can speculate that lighter clots in early pregnancy may not afford an optimal seal to support hemostasis.

It has been reported that women with hereditary hypofibrinogenemia are at elevated risk of adverse obstetrical outcomes.[26] In a recent systematic literature review including 77 pregnancies from 22 women with hereditary hypofibrinogenemia, 46.8% had a miscarriage, 20.8% a vaginal bleeding and 5.2% a placenta abruption. However, these data probably overestimate the prevalence of obstetrical complications in fibrinogen disorders due to publication and selection bias (i.e., inclusion of more severe symptomatic women).[5] There is no evidence-based recommendation for the minimal fibrinogen level required to avoid obstetrical complication in fibrinogen disorders. Reports on women with afibrinogenemia indicates that trough levels ≥1.0–1.5 g/L during pregnancy may reduce the risk of complications, including miscarriages.[27] In mild hypofibrinogenemia, as observed in our patient, the physiological increase of fibrinogen should be sufficient to maintain adequate hemostasis throughout the pregnancy. Expert recommendations for management of pregnancies in dysfibrinogenemia could also apply to hypofibrinogenemia. These include an accurate preconception counselling, a quarterly assessment of fibrinogen activity, a systematic monitoring of foetal growth, a fibrinogen supplementation targeting a fibrinogen trough level >1 g/L (1.5 g/L at labour for the neuraxial analgesia), avoiding of invasive foetal procedures and forceps delivery, early fibrinogen supplementation and antifibrinolytic drug in case of post-partum haemorrhage, accurate thromboprophylaxis if needed.[28]

Our study has some limitations. The first is that we did not compare the patient to a healthy pregnant control. However, the aim of our study was to determine the variation of the overall hemostasis throughout the pregnancy in hypofibrinogenemia. As women with hypofibrinogenemia will not reach the fibrinogen levels observed in healthy pregnant women, even in case of fibrinogen supplementation, we consider that a control with fibrinogen levels in the normal range is adequate for assessing fibrin clot structure in this setting. Also, our observations are based on a single patient with a mild hypofibrinogenemia. Unfortunately, as hereditary fibrinogen disorders are rare, it is unlikely to have a prospective follow-up of many concomitant pregnant women with hypofibrinogenemia. Care must be taken on extrapolation of the results to all patients with hypofibrinogenemia. Nevertheless, exhaustive coagulation exploration in pregnant woman with fibrinogen disorders are extremely scarce and, even if limited, our findings can help physicians, for instance in preconception counselling of women with mild hypofibrinogenemia. Of note, as no fibrinogen variant is usually present in the circulation, we do not expect any difference in the phenotypes of patients with similar fibrinogen levels due to the causative mutation.

5 | CONCLUSIONS

In conclusion, our study presents several novel observations in the field of fibrinogen disorders: (i) we describe for the first time the variation of fibrinogen levels and the subsequent modification of fibrin clot properties in a pregnant woman with hypofibrinogenemia; (ii) we report the fibrinogen variation throughout the pregnancy confirming that in mild hypofibrinogenemia patients are able to significantly increase the fibrinogen concentration; (iii) we investigate how other aspects of coagulation contribute to the hemostasis balance in a pregnant woman with hypofibrinogenemia.

Future studies should focus on moderate and severe hypofibrinogenemia, to assess fibrinogen variation and the overall impact of increased TG on the hemostasis balance in case of persistent hypofibrinogenemia at term.

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CONFLICT OF INTEREST STATEMENT

Alessandro Casini reports grants, and fees paid to his institution from CSL Behring, Octapharma, Sobi, Shire, Takeda, Pentapharma, Biotest and Novo Nordisk.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Institutional review board approval and written consent was obtained from the patient in accordance with the Declaration of Helsinki.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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