



Case Report

Congenital Thrombophilia Associated with Intrahepatic Cholestasis of Pregnancy. A Case Report

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Received: 14 Mar 2021 ♦ **Accepted:** 15 Apr 2021 ♦ **Published:** 31 Aug 2022

Citation: Iliadi-Tulbure C, Cemortan M, Bubulici C, Botnari-Gutu M, Cernetchi O. Congenital thrombophilia associated with intrahepatic cholestasis of pregnancy. A case report. *Folia Med (Plovdiv)* 2022;64(4):688-692. doi: 10.3897/folmed.64.e65939.

Abstract

Intrahepatic cholestasis of pregnancy is pregnancy-specific liver disorder, characterized by pruritus as the main clinical symptom, and fasting liver function tests. The term thrombophilia is used to describe a group of conditions characterized by blood coagulation disorder with increased risk of blood clot formation, which may be congenital or acquired. In general, population the incidence of thrombophilia and intrahepatic cholestasis of pregnancy varies widely, depending on the type of disorder (in case of congenital thrombophilia) and geographical distribution (in case of intrahepatic cholestasis of pregnancy). A high incidence of pregnancy complications makes both congenital thrombophilia and intrahepatic cholestasis of pregnancy very important in clinical practice. At the same time, association between these two disorders is extremely complicated in management, due to perinatal risks. The key-point for the management is cooperation among obstetricians, hematologists, and hepatologists, being crucial for better outcomes.

Keywords

congenital thrombophilia, intrahepatic cholestasis of pregnancy, pregnancy

INTRODUCTION

The term thrombophilia is used to describe a group of conditions characterized by blood coagulation disorder with increased risk of blood clot formation. It may be congenital (an inborn condition) or acquired (refers to all cases that present later in life). Congenital thrombophilia is more often associated with some hereditary abnormalities.^[1,2] In general population, incidence of congenital thrombophilia depends on the type of disorder. The appearance of antithrombin, C-protein and protein S (natural coagulation inhibitors) deficiency is about 1% in the general population. Factor V Leiden mutations (making anticoagulant protein secreted enable to bind to factor V) occur in approximately 7% of cases in Caucasian, and 1% in non-Caucasian. The incidence of high-level factor VIIIc is up to 11% in the

general population.^[1] Pregnancy complications such as recurrent miscarriage, preeclampsia, and HELLP syndrome may arise as a result of congenital thrombophilia.^[1,3] Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disorder characterized by elevated liver function tests (LFTs) and/or elevated serum bile acids and presence of pruritus.^[4] A rash may occur, but it is secondary of intense scratching. Recent studies suggest that the incidence of ICP is approximately 1% in the global population, although it varies with geographical distribution.^[5] ICP may develop as early as 11 weeks of gestation, but most commonly it develops in the third trimester of pregnancy.^[6] It should be mentioned, that ICP has a major recurrence rate in the following pregnancies, reaching up to 40-90%, according to some studies.^[7]

CASE REPORT

Patient G., age 25 years, 37 weeks of gestation (w.g.) was admitted to the hospital complaining of pruritus and pyrosis. The symptoms occurred one week before, due to its increase, patient G called for consult and lately was admitted to the hospital.

Before pregnancy, the patient and her partner were diagnosed with congenital thrombophilia with the mutation of several genes characterized with the increased risk for thrombosis and confirmed by laboratory examination. Furthermore, a hyperhomocysteinemia was determined (level of homocysteine – 14.5 mmol/l). Therefore, the tests were carried out and revealed the following gene mutations (**Table 1**).

Patient G. had one at term natural life-birth (in 2013)

cobalamin – 6 mcg). The doses were adjusted depending on the laboratory tests results and the medications were planned to be discontinued before the expected delivery. Besides that, patient G. was recommended to receive supp. progesterone 200 mg per vagina until 30 w.g., due to imminent preterm labour. At the same time, the patient decided by herself to continue the prescribed therapy until 32 w.g, because of periodic pain in the hypogastrium.

However, a week before admission, the patient developed pruritus which intensified causing insomnia and fatigue. Physical examination on admission revealed scratching signs on the patient's back, abdomen, and legs. As the patient was asked to note the intensity of pruritus at the onset of complaints and at admission, she reported that the prurition increased

Table 1. Gene mutations found in patient G. and her partner

	Gene	Protein	Polymorphism by mutant allele	
Patient G	FXIII	Fibrin	G103T	Homozygote
	MTHFR	Methylenetetrahydrofolate reductase	C677T	Homozygote
	MTHFR	Methylenetetrahydrofolate reductase	A1298C	Homozygote
	PAI-1	Plasminogen activator inhibitor 1	4G/5G	Homozygote
	MTRR	Methionine synthase reductase	A66G	Homozygote
Partner	PAI-1	Plasminogen activator inhibitor 1	4G/5G	Homozygote
	MTHFR	Methylenetetrahydrofolate reductase	A1298C	Homozygote
	FXIII	Fibrin	G103T	Heterozygote
	MTHFR	Methylenetetrahydrofolate reductase	C677T	Heterozygote
	MTRR	Methionine synthase reductase	A66G	Heterozygote
	CBS	Cystathionin β -synthase	844ins68pb	Heterozygote

in anamnesis. The obstetrical history was complicated by an emergency cesarean section at 30 w.g. (in 2017), performed due to severe preeclampsia, the fetus being diagnosed with diaphragmatic hernia, with the clinical outcome of neonatal death at the first day of life. The patient also had a miscarriage in the first trimester (in 2017). After the second pregnancy (in 2017), a laparoscopic cholecystectomy was performed at 3 months after delivery due to pronounced symptomatology (subcostal pain, jaundice, increased values of LFTs) with the onset in pregnancy, becoming worthier in post-partum. At the same time, her somatic anamnesis was complicated with grade II hydronephrosis of the right kidney and grade I iron-deficiency anemia.

In the current pregnancy, an interdisciplinary management of the patient was performed, with involvement of geneticist, hematologist and hepatologist during the perinatal period. The levels of prothrombin, fibrinogen, INR, D-dimer were assessed every 2 weeks, with the onset at 6 w.g. However, at 22 w.g., the levels of fibrinogen and D-dimer were observed to increase (**Fig. 1**).

In view of the presented laboratory tests, starting with the 24 w.g., the following medications were recommended to be administered: Sol. enoxaparin 0.4/day and vitamins of group B (pyridoxine hydrochloride – 4 mg, folic acid – 5 mg, cyano-

in intensity from 3 to 9 points on the visual analogue scale. The liver function tests showed increased concentrations of alanine aminotransferase (ALT) – 123.8 U/l (reference range 0–33 U/l), aspartate aminotransferase (AST) – 66.8 U/l (reference range 0–32 U/l), and alkaline phosphatase 589 U/l (reference range 100–240 U/l). Hepatitis B and C markers were tested, showing absence of acute or chronic viral hepatitis.

In view of the gestational age, it was decided to begin symptomatic treatment and to monitor this pregnancy and the patient status. Clinical management was performed according to the international recommendations. During the admission to the hospital, patient G was prescribed caps. ursodeoxycholic acid (UDCA) – 900 mg/day, divided into thrice-daily dosing, and enterosorbents: polymethylsiloxane polyhydrate and activated charcoal.

Elective caesarean section was planned at 37 w.g. But the patient went into spontaneous labour and gave birth to a female fetus weighing 2984 g, with Apgar score of 8/8 points. Total blood loss was estimated at 300 ml. Two days after delivery, the LFTs were re-assessed. They showed a tendency of decrease in the ALT and AST values (91.5 U/l and 42.5 U/l, respectively). The patient and her baby were discharged from the hospital 3 days post-delivery. There were no re-admissions in the hospital for her baby during the first year of life.

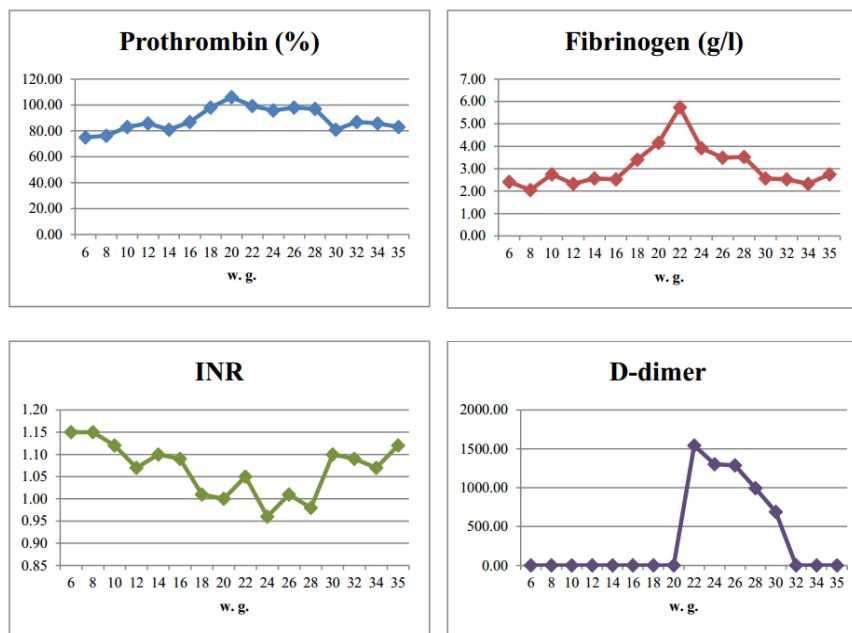


Figure 1. Levels of prothrombin, fibrinogen, INR, D-dimer during pregnancy.

DISCUSSION

According to the literature, pregnancy is a state of hypercoagulation which may cause an increase in the coagulation factors Vc, VIIIc, Xc, and von Willebrand factor antigen and reduction in the S protein levels.^[1,2,8] At the same time, coagulation activation markers are increased, especially in the third trimester of pregnancy.^[1] This prothrombotic condition lasts up to 12 weeks after delivery.^[9] The association between inherited thrombophilia and pregnancy, being procoagulant conditions, has an important impact for the mother and fetus. The most common forms of hereditary thrombophilia are associated with mutations in factor V Leiden, prothrombin (both inherited in an autosomal dominant way) and methylenetetrahydrofolate reductase (MTHFR) (inherited in an autosomal recessive way).^[1] In the presented clinical case, two important mutations, C677T and A1298C, have been implicated in the deficiency of MTHFR, which leads to elevated levels of homocysteine. In addition, the C677T mutation is an important predictor of severe arterial and venous deep vein thrombosis and infertility in men and women.^[1]

According to the American College of Obstetricians and Gynecologists recommendations, all pregnant women with a history of thrombosis should be tested for thrombophilia.^[1] At the same time, screening for thrombophilia should be performed on women with more than three miscarriages, late miscarriage, and fetal death.^[3] It is well known that almost in half of the cases, congenital thrombophilia during pregnancy can be associated with venous thromboembolic events.^[1] The known thrombotic nature of the placental vascular lesions and the increased thrombotic risk associated with the existence of thrombophilias strongly suggest a cause-and-effect relationship between inherit-

ed and acquired thrombophilias and the severe obstetric complications.^[10] A high incidence of pregnancy loss at all trimesters of pregnancy and several complications can occur. Preeclampsia, placental abruption and fetal growth restriction seem to be associated with factor V mutation. Hyperhomocysteinemia and prothrombin mutation may lead to higher risk of placental abruption.^[1] Prothrombin G20210A heterozygotes have a stronger association with second-trimester loss.

Despite the fact that there is no curative treatment for hereditary thrombophilia, thromboprophylaxis in pregnancy is recommended.^[3] Regarding the management, the low-molecular-weight heparin is a first-line medication in thromboprophylaxis in case of hereditary thrombophilia because it is safe for the fetus as it does not pass through the placenta.^[1] It is recommended to stop prophylactic administration at 37 weeks of gestation, suggesting then induction of labour.^[1] However, postnatal thromboprophylaxis should be performed after assessing the risk factors.^[11] It could require up to 6 weeks of low-molecular-weight heparin administration in the postnatal period.^[11] On the other hand, administration of vitamin B12 and folate may be suggested, due to the fact that this low-risk medication reduces homocysteine levels in most cases.^[1] The management of thrombophilia during pregnancy include primary thromboprophylaxis in asymptomatic women and secondary prophylaxis of recurrences in case of previously developed thrombosis. Anticoagulation is used also as treatment of acute thrombotic episodes and/or pregnancy complications.^[10]

At the same time, according to the clinical case, we were interested in intrahepatic cholestasis of pregnancy and its presentation in our patient. Pruritus, being the main symptom of ICP, is defined as a subjective unpleasant sensation,

which causes the desire to scratch. This symptom becomes worthier with the progression of pregnancy and severe in the absence of treatment. Pruritus often passes over shortly after delivery. Most patients report intensified pruritus at night, becoming excruciating, which often causes insomnia.^[12] At the same time, presence of the skin itching in any intensity affects the quality of life of the pregnant woman and leads to anxiety and depression.

Transaminases, including alanine aminotransferase and aspartate aminotransferase, refer to liver enzymes and are markers of hepatocyte damage; for this reason, ALT and AST are essential for assessing the functional state of the liver. According to the literature, ALT and AST values increase significantly in 85% of cases of ICP, in some cases reaching levels 25 times higher than its reference values.^[5,8] It should be mentioned that ALT is a more specific diagnostic marker in ICP; its values can increase by 2-10 times higher compared to AST.^[11] These data are confirmed by the results of our research. Alkaline phosphatase activity may increase in late pregnancy due to placental isoenzyme production and increased bone isoenzyme levels. Therefore, in intrahepatic cholestasis of pregnancy, it cannot be interpreted individually, but only along with other LFTs.^[13] In the post-partum period, it is recommended that measurement of LFTs should be performed 10 days after delivery to make sure that they have returned to normal.^[4] Hepatitis C virus seropositivity was reported as a risk factor for ICP and may be associated with early onset of the pathology.^[14] At the same time, in patient G. there was no acute or chronic viral hepatitis.

The first-line pharmacological treatment in the management of ICP is ursodeoxycholic acid (UDCA) - administration of this drug improves maternal symptoms and improves LFTs in approximately 75% of cases.^[8] Ursodeoxycholic acid improves the biliary transport of bile acids, has anti-apoptotic effects and is considered to have beneficial effects in the context of excretion of pruritogenic substances, for example progesterone sulfates.^[5] In vitro and in vivo studies show that UDCA improves the trans-placental transport of biliary acids from fetus to mother and reduces placental damage caused by ICP. A meta-analysis and in vitro studies suggest that the administration of UDCA may have a positive impact on the rate of premature labour and the admissions to neonatal intensive care units.^[8] The mechanism of action of UDCA is not fully understood, but some researches have shown a reduction in maternal serum bile acids levels as well as the bile acids levels in the umbilical cord blood.

According to different guidelines regarding the intrahepatic pregnancy cholestasis, it can be mentioned that most management strategies recommend delivery between 37 and 38 weeks in ICP cases; however, the obstetric anamnesis, laboratory test data, and gestational age should be considered. The American College of Obstetricians and Gynecologists, in the opinion of the committee detailing the medical indications for pre- and post-term births, recommends delivery at 36 to 37 weeks of gestation for cases complicated by intrahepatic cholestasis of pregnancy.^[15]

However, we have found no other studies in the literature studying the association of hereditary thrombophilia and intrahepatic cholestasis of pregnancy.

CONCLUSIONS

Intrahepatic cholestasis of pregnancy is a severe complication of pregnancy being frequently evaluated without pre-existing medical conditions. Due to maternal and fetal impact, ICP needs an active clinical management. Women should be informed of the inability to predict stillbirth in case of ICP. Besides that, many stillbirths occur in later gestational age. At the same time, thrombophilia can lead to pregnancy complications, including miscarriage and stillbirth. The early diagnosis of thrombophilia is important, having implications for the management of the ongoing pregnancy and of the future reproductive state of the couple. It makes the combination of mentioned conditions in one clinical case especially important in relation to perinatal outcomes. The key-point in the management of these patients is the cooperation between obstetricians, hematologists, and hepatologists, which can be crucial for achieving better results.

Ethics

Written informed consent was obtained from the patient for publication of the present study.

Funding

The authors have no funding to report.

Competing interests

The authors have declared that no competing interests exist.

Acknowledgements

The authors have no support to report.

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Врождённая тромбофилия, связанная с внутрипечёночным холестаазом беременных. Отчёт о случае

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Дата получения: 14 марта 2021 ♦ **Дата приемки:** 15 апреля 2021 ♦ **Дата публикации:** 31 августа 2022

Образец цитирования: Iliadi-Tulbure C, Cemortan M, Bubulici C, Botnari-Gutu M, Cernetchi O. Congenital thrombophilia associated with intrahepatic cholestasis of pregnancy. A case report. *Folia Med (Plovdiv)* 2022;64(4):688–692. doi: 10.3897/folmed.64.e65939.

Резюме

Внутрипечёночный холестаз беременных представляет собой специфическое для беременных заболевание печени, характеризующееся зудом в качестве основного клинического симптома и нарушением функции печени натошак. Термин тромбофилия используется для описания группы состояний, характеризующихся нарушением свертывания крови с повышенным риском образования тромбов, которые могут быть врождёнными или приобретёнными. В целом популяционная заболеваемость тромбофилией и внутрипечёночным холестаазом беременных широко варьирует в зависимости от вида патологии (при врождённой тромбофилии) и географического распространения (при внутрипечёночном холестаазе беременных). Высокая частота осложнений беременности делает очень важным в клинической практике как врождённую тромбофилию, так и внутрипечёночный холестаз беременных. В то же время связь между этими двумя расстройствами чрезвычайно сложна в лечении из-за перинатальных рисков. Ключевым моментом в управлении является сотрудничество между акушерами, гематологами и гепатологами, что имеет решающее значение для достижения лучших результатов.

Ключевые слова

врождённая тромбофилия, внутрипечёночный холестаз беременных, беременность