

## Case Report

# Morphological Survey of Placenta in Trombophilia Related Hypoperfusion of Maternal-Fetal Blood Flow

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**ABSTRACT:** Complex and modern obstetric medical care provides a constant improvement for the pregnancy prognosis. Thus, young women with an undiagnosed pathology become pregnant and, during pregnancy, the previously undiagnosed pathology, without any clinical signs and symptoms, becomes present during pregnancy, having an unfavorable impact on the fetus and the health state of the pregnant woman. The gestational syndromes during pregnancy influence the woman's health state over a long period of time and the quality of the conception product. The recommendation, performance of laboratory tests and imagistic investigations at the right time during pregnancy, as well as a correct interpretation of their results, may prevent the onset of catastrophic occurrences including fetal death in utero and/ or maternal death. We report the case of a 30-year old primigesta, primipara (IGIP) patient with a singleton, naturally obtained pregnancy, severe preeclampsia, severe IUGR and thrombophilia.

**KEYWORDS:** *intrauterine growth restriction (IUGR), small for gestational age (SGA), preeclampsia, thrombophilia, pathology.*

## Introduction

Placenta represents a gestational transitory structure essential for the transfer of nutrients and gases from mother to the fetus and for removing the fetal residual products [1]. In normal pregnancies, decidual and myometrial segments of the spiral arteries pass through changes that convert them into high caliber vessels and low resistance. The trophoblast invasion is a key process during human placentation. The change of spiral arteries and the poor trophoblast invasion lead to a reduced perfusion of the placenta and the fetus and to an inappropriate fetal oxygenation and nutrition. This condition is called utero-placental insufficiency, due to the fact that the metabolic needs of the fetus and the placenta exceed the capacity of utero-placental transport [1].

The trophoblast invasion has two stages, the first of trophoblast invasion converts the decidual segments of the spiral arteries between the 6th and 10th weeks of pregnancy, while the second, and converts the myometrial segments between the 14th and 16th weeks of pregnancy. In complicated pregnancies by preeclampsia and IUGR, trophoblast invasion is limited to the decidualized endometrium, and the spiral arteries do not become low resistance vessels.

By using the Doppler ultrasound (US), there may be evaluated the conversion of spiral uterine arteries into utero-placental vessels and there may be evaluated the placental development.

On term, the placenta has approximately 470g of weight, it is round or oval, with a diameter of about 22cm and a central thickness of 2.5cm [2,3].

The first stage of US maturation of the placenta is found at the beginning of the third trimester. It is characterized by small indentations in the villous chorion. Small calcifications (hyperechoic) may be found, with a diffuse distribution in the placenta thickness [4].

The second stage is found in the second part of the third trimester and generally, it is allowed at 30 gestation weeks (gw). The villous chorion presents deeper indentations, and the calcifications appear with a higher density [4].

The third stage is found after 39gw and in a prolonged pregnancy. The indentations of the villous chorion reach the basal chorion, thus forming the cotyledons. The calcifications are frequent in the placenta thickness, causing conic posterior shadows [4].

This aspect is more frequently met in IUGR, in smoking mothers, hypertensive, in lupus and in diabetes mellitus [5].

Thrombophilia are diseases in which there is a strong tendency of thrombosis onset. These may be inherited or acquired. The best known acquired thrombophilia is the antiphospholipidic syndrome [6-8].

Hereditary thrombophilia represent genetic abnormalities associated with homeostasis disorders that induce a high probability of thrombotic, venous and arterial events, which, together with the physiological pro coagulant status during pregnancy, increase the risk for thromboembolic events of pregnant women.

The screening for thrombophilia includes Protein S, Protein C, Antithrombin III, Activated Protein C Resistance (Factor V Leiden), lupic anticoagulant, homocysteine. The molecular tests for inherited thrombophilias are: factor V mutation, factor II mutation, methylentetrahydrofolate-reductase (MTHFR) gene mutation, plasminogen activator inhibitor gene mutation (PAI), factor XIII gene mutation. These tests identify the state of heterozygous (forms inherited from a single parent, with a lighter evolution) or homozygous (where there are affected the genes acquired from both parents, with a severe evolution).

IUGR, in theory, refers to any process that is capable of intrinsically limit the potential of *in utero* growth of the fetus, but it is used mainly for defining those cases where a placental insufficiency is responsible for the growth deficit. It is defined as a situation resulted from a newborn weight lower than the tenth percentile for its gestational age [1].

In general, IUGR is caused by utero-placental insufficiency and shares some common ways with preeclampsia, thus leading to a poor trophoblast invasion and, as a result, IUGR was associated with a high resistance in uterine arteries [9-11].

The potential risk factors for IUGR include toxic substances (tobacco, alcohol and other drugs), antecedents of SGA or still birth, fetal infections (cytomegalovirus and Rubella are the most frequent infections that may cause IUGR), maternal factors (mainly vascular and renal diseases) [1,12].

The main risk factors are the ones connected to preeclampsia, thrombophilia and chronic hypertension [13]. But an accurate anamnesis, the preconceptional consult and complex obstetric care represent key steps for selecting a

high risk population group, where a thorough evaluation is quite necessary.

Preeclampsia is an important obstetric complication and represents the second cause of maternal death all over the world (after obstetric hemorrhage) [10]. In developed countries, preeclampsia represents the most frequently quoted cause of premature birth [14,15].

The etiology is complex, pluri-factorial, incompletely elucidated, more and more frequently being postulated the idea that preeclampsia should not be seen as a single disease, but more as a heterogeneous syndrome with a multitude of clinical signs and symptoms, which generate overall various phenotypes.

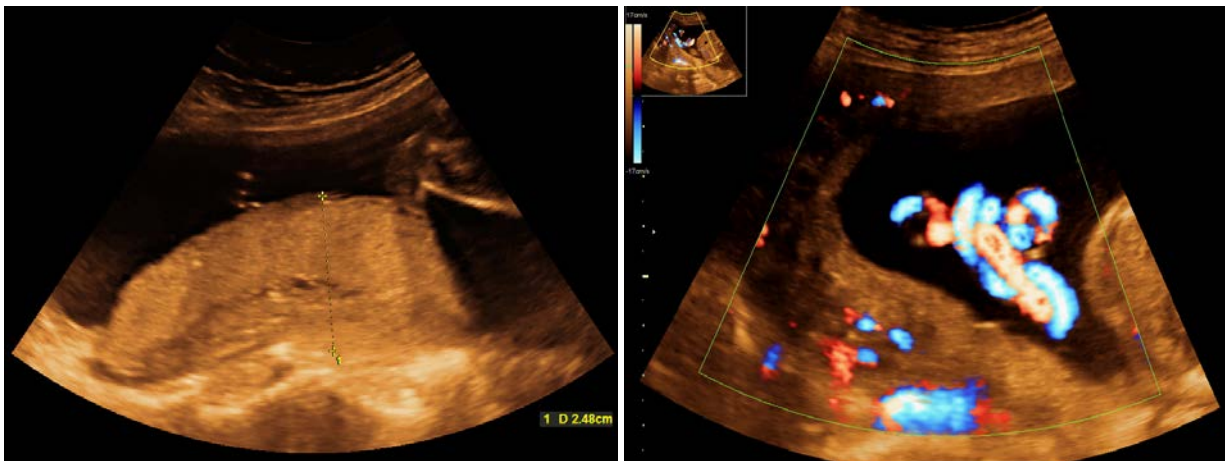
## Case presentation

We present the case of a 30-year old patient who obtained pregnancy spontaneously, transferred to the Clinical County Emergency Hospital of Craiova, and managed in accordance with current practice in maternal-fetal medicine.

The study was performed according to the tenets of the Declaration of Helsinki and was approved by the University Ethics Committee. The patient was fully informed about the possible consequences of the present study, and she filled in an informed consent form to participate.

The patient presented to the territorial hospital for a minimal vaginal bleeding. The anamnesis did not provide any valuable data that may quantify the condition etiology, familial and personal medical history being quite irrelevant, biological or imagistic explorations being absent.

Thus, at 34 gestational weeks, with a good health state, the pregnant woman presents minimal vaginal bleeding and, during hospitalization, on US examination, there was observed severe IUGR, the fetus US age being of 29 weeks and two days (biparietal diameter-7.72cm, head circumference-25.98cm, abdominal circumference-22.79cm, femur length-5.06cm) with the presence of a subchorial hematoma (4.5cm in diameter), and at the level of uterine arteries, there were observed a high pulse index, a notch aspect and a high resistance index, the cerebroplacental ratio being still in normal limits (Fig.1).



**Fig.1. A. Transabdominal US scan demonstrating thin and inhomogeneous placenta, Grannum 3 at 34gw. B. Transabdominal US scan demonstrating umbilical cord knot**

After the diagnosis of severe IUGR, there are recommended clinical and paraclinical investigations, which may conclude upon the incriminated pathological factors, upon the maternal fetal management and the treatment conduct. The patient was monitored clinically, being observed the value of blood pressure, active fetal movements and fetal heart frequency. There were recommended the cardiological, ophthalmological and neurological consults. The recommended paraclinical investigations were: full blood count, investigation of maternal liver function, TORCH (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex) complex, thrombophilia screening, investigation of maternal kidney function and repeated imagistic investigations.

The systolic blood pressure was 160mmHg and the diastolic blood pressure was 110mmHg, and were maintained at the determination performed every 4 hours, while the patient was at rest in bed and received oral medication for high blood pressure (Methyldopa 250mg). The cardiological consult recommended therapy for high blood pressure. The neurological and ophthalmological consults did not detect any neurological or eye changes.

The full blood count highlighted mild anemia (Hb 9.8mg/dl) and medium thrombocytopenia (98.000 thrombocytes), alteration of liver function was indicated by high values of the hepatic enzymes (Glutamic Oxaloacetic Transaminase/GOT-180U/L, Glutamic-Pyruvic Transaminase/GPT-211U/L).

The TORCH complex did not bring any information regarding any possible chronic or acute infection, yet the thrombophilia screening

highlighted hypercoagulation, being present heterozygous mutations of MTHFR genes (C677T, A1298C) and PAI-1 (PAI 1 675, PAI 1 844). We also noticed the existence of proteinuria 4380mg/dl.

The diagnosis established after the evaluation was IGIP, singleton 34 weeks pregnancy, alive fetus, severe preeclampsia, severe IUGR and thrombophilia.

There was recommended physical rest, low sodium diet, anticoagulant treatment (Enoxaparin 60mg/0.6ml subcutaneous once a day), corticotherapy (Dexamethasone 8mg/2ml every 8 hours, three doses), oral martial treatment, monitorization of blood pressure every hour, fetal US monitorization every 12 hours and cardiotocographic monitoring every 6 hours. There was continued the high blood pressure treatment, the dose of 250mg Methyldopa being administered every 4 hours in order to maintain the blood pressure values in normal limits. Vaginal bleeding diminished and disappeared after 48 hours.

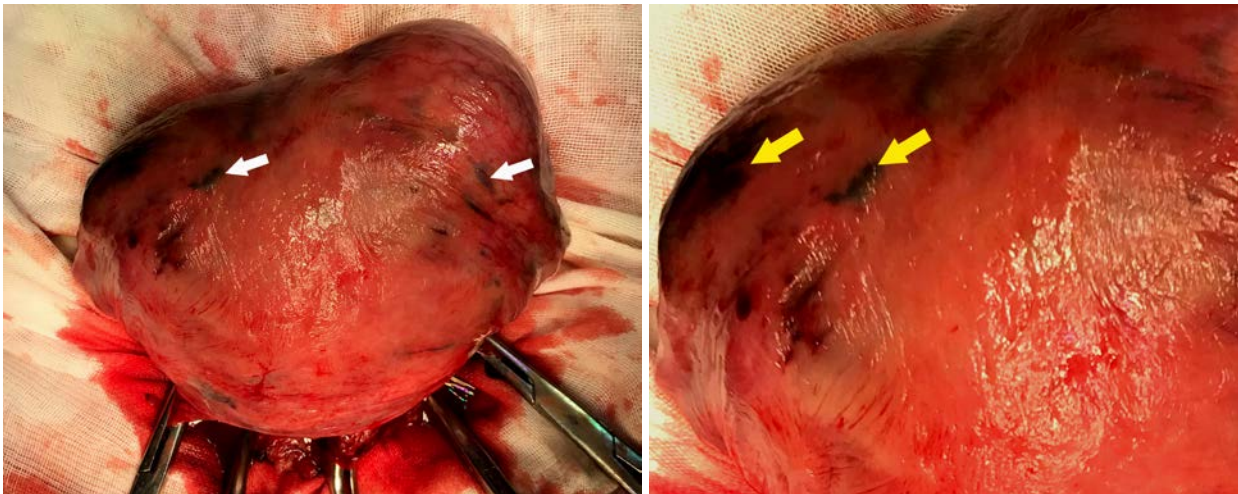
A thorough repeated maternal-fetal evaluation detects a severe alteration of the maternal-fetal Doppler hemodynamic profile, in uterine arteries and changes of the cerebro umbilical ratio going towards a unitary value, and in the 8th day of monitorization, the active fetal movements started do diminish and the non-stress test became non-reactive.

Therefore, for severe intrauterine growth restriction and imminence of fetal status deterioration in utero, there was required the medical indication of premature delivery, involving the extraction by Caesarian section of a female fetus, 1340g, with an Apgar Score 8,

taken over by the neonatology resuscitation department.

During surgery, in the uterus, under the visceral peritoneum, there were observed

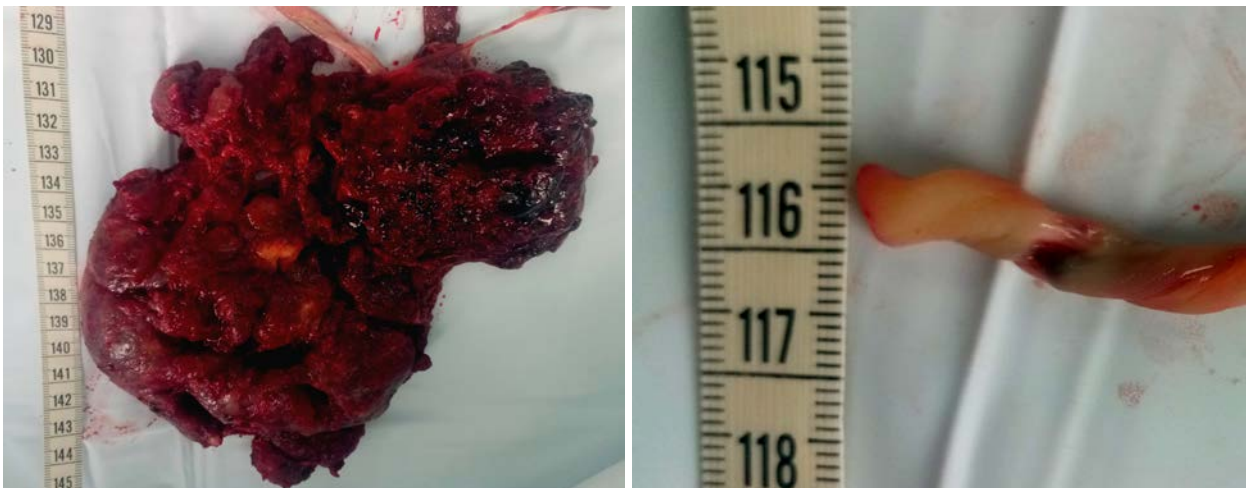
multiple areas of thrombosis-a characteristic aspect of hypercoagulation in thrombophilia (Fig.2).



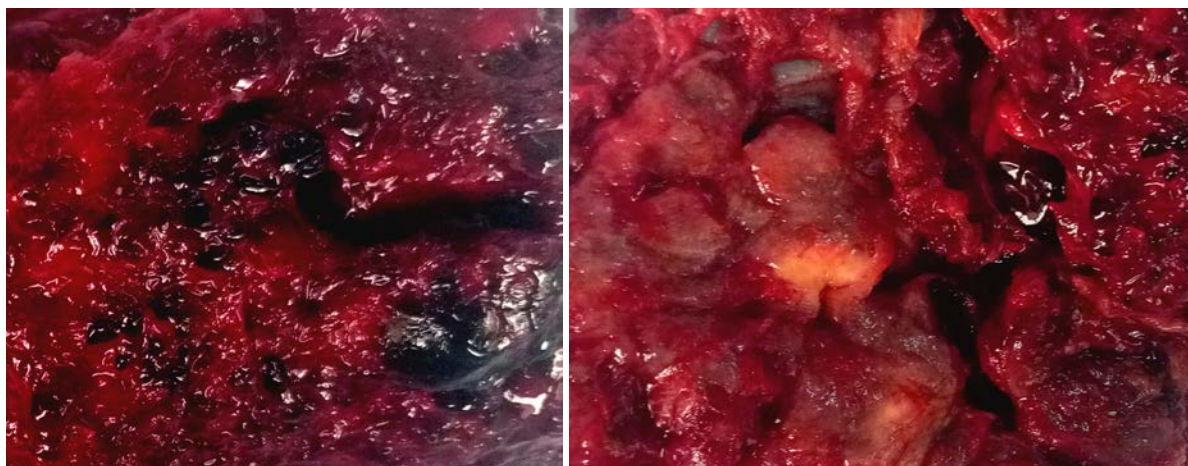
**Fig.2. A. Intraoperative appearance after delivery demonstrating multiple subserosal uterine thrombosis (white arrows). B. Intraoperative detail demonstrating the blue-blackish petechial appearance of the subserosal thrombosis (yellow arrows)**

Placenta with reduced placental disk (15cm diameter), crossed by deep grooves, with low thickness, weight of 220 grams, presenting an old, organized hematoma (Fig.3A), together with the umbilical cord (Fig.3B), without any

Wharton's jelly and reduced diameter, were sent for pathology examination. Macroscopically, the placenta presents multiple fibrin deposits and areas of calcic impregnation areas (Fig.4).



**Fig.3.A. Maternal surface of the placenta demonstrating asymmetric, reduced placental disk and deep grooves. B. Umbilical cord demonstrating lack of Wharton's jelly and low diameter**

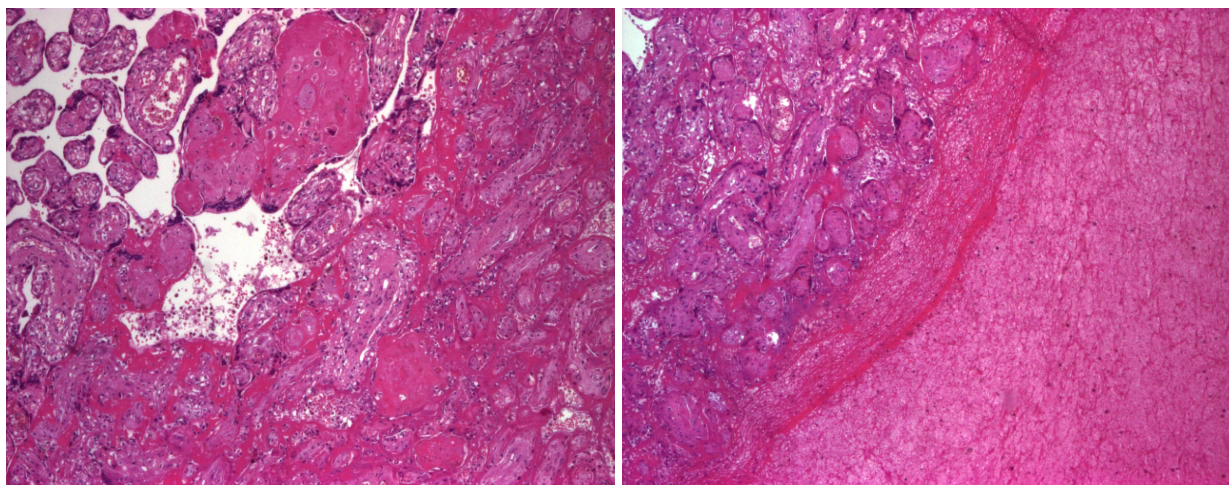


**Fig.4. A. Maternal surface of the placenta demonstrating intervillous thrombi with a soft, dark red appearance. B. Maternal surface of the placenta demonstrating placental infarction with a roughly triangular shape and a white-yellowish color**

Pathology of placenta and umbilical cord highlighted the chorial hematoma, microcalcifications, intervillous infarction, necrosis and intervillous hematic infiltrate secondary to changes induced by thrombophilia.

In the Hematoxylin-Eosin (HE) staining, the microscopic examination highlighted placental

infarction elements, perivillous fibrin depositions (Fig.5A), villous stasis and organized chorial thrombus (Fig.5B), aspects in accordance with utero-placental hypoperfusion leading to clinical and paraclinical signs highlighted during the maternal-fetal assessment.



**Fig.5. A. Placental infarction, peripheral fibrin depositions, HE staining, x40. B. Villous stasis, organized chorial thrombus, HE staining, x40**

The evolution was favorable after surgery, with a treatment including antibiotics, anticoagulant (Enoxaparin 40mg/0.4ml subcutaneous twice a day), antihypertensive (Methyldopa 250mg x 2/24h), pain relievers, local antiseptic, hydroelectrolyte rebalance and oral martial treatment. At 10 days after surgery, the patient is afebrile, the uterus is contracted, normal aspect vaginal bleeding. There was suppressed the suture line at post operative plaque, anticoagulant treatment (Enoxaparin

40mg/0.4ml subcutaneous once a day), antihypertensive therapy for blood pressure values higher than 140/70mmHg. Lactation was present, with mechanic milk evacuation. The new born was discharged together with her mother, with a 2500 grams weight.

## Discussion

Normal pregnancy is accompanied by a state of physiological hypercoagulability, where there are involved complex changes and natural

anticoagulant mechanisms. These changes have the role of protecting the delivery process when the placenta is delivered, as a natural phenomenon in eutocic birth and spontaneous abortion, still born antepartum or in any other obstetric complication. The existence of a maternal hematological pathology that amplifies these mechanisms may lead to placental ischemia, this phenomenon being a source of anti-angiogenic factors that damage the maternal endothelium with the onset of a generalized thrombotic risk [16].

Apart from the increase of maternal thrombotic risk, there are data supporting the hypothesis regarding the association of hereditary thrombophilia with the onset of obstetric complications, such as IUGR, preeclampsia and prematurity [16-18]. IUGR is, undoubtedly, one of the most challenging research areas of modern obstetric [1,5].

The high resistance of the uteroplacental flux is visible long before the clinical onset of high blood pressure and proteinuria [19-23]. Nowadays, there is no treatment way of preeclampsia, except for giving birth. Due to the devastating consequences for the mother and for the fetus, as well, preeclampsia is the prenatal diagnosis that requires the medical indication of premature birth [14,15]. Premature birth medically indicated represents the category that constantly increased the frequency of premature deliveries in the last two decades.

The association of thrombophilia and preeclampsia in the absence of treatment puts at high risk both the mother and the fetus; efficient monitoring, immediate medication and surgical intervention increase a favorable long-term prognosis for the mother and the fetus. There should be known that pregnant patients, who suffer from thrombophilia, have a greater risk of developing obstetric complications, even in the situation of a correctly managed treatment [23-26].

Preeclampsia and IUGR have a higher probability of being diagnosed in pregnant women with hereditary thrombophilia, the mutation of genes PAI 1, 2 and MHFR being the most frequently found in obstetric pathology [21,22,24].

Suboptimal prenatal management is incriminated as the most frequent observation in the unexplainable cases of intrauterine death [14].

## Conclusions

Preeclampsia and other associated pathological states, such as thrombophilia, are responsible for premature birth in a significant number of cases. There should be taken into account thrombophilias, either the inherited or the acquired ones that do not have any clinical signs and may be detected occasionally. Usually, these forms of thrombophilias are diagnosed either before pregnancy, or during pregnancy, when its evolution has different aspects than the normal ones. Prenatal detecting of IUGR and its causes is of maximum importance for modern obstetrics. The evaluation of the risk for thrombotic events should be performed in all pregnant women even from the beginning of the first trimester of pregnancy. It is recommended an anticoagulant treatment in pregnant women with thrombophilia during the whole pregnancy period and six weeks postpartum.

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