

**UTERINE ARTERIES DOPPLER VELOCIMETRY IN A PREGNANT
WOMAN WITH GENETIC RISK FOR THROMBOPHILIA**

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ABSTRACT

The objective of this study was to follow the velocimetry changes in the uterine arteries and the fetal growth curves in a pregnant woman with a genetic risk for thrombophilia. The patient received aspirin until 25 weeks of gestation, when the hematologist decided on thromboembolism prophylaxis with heparin until 24 hours before delivery. The velocimetry indices in uterine arteries and the umbilical artery were within normal limits until the end of the pregnancy. During the follow-up, the coagulation tests remained within normal parameters for the pregnancy period and fetal growth was within normal limits. The birth was done by cesarean section at 38 weeks of gestation. The fetal weight at birth was 3190 grams and the Apgar score was 8/9.

INTRODUCTION

Pregnancy is associated with changes in blood circulation in the uterine vessels characterized by the decrease in impedance with advancing gestation. The uterine circulation can be assessed by Doppler velocimetry of the uterine arteries (Bhide et al. 2013).

Inherited thrombophilia is a genetic condition that increases the risk of thromboembolism. The risk of thrombotic events is influenced by many factors including inherited or acquired thrombophilia, personal medical history or family medical history of thrombophilia, multiparity, smoking, age over 35, obesity and trauma that causes immobilization (Silver & Airoidi 2019).

The venous thromboembolism is associated with Factor V Leiden and prothrombin gene mutations, antithrombin deficiency and low values of Protein C and Protein S (Chu Lam & Airoidi 2019).

Inherited thrombophilia has been associated to a small extent with poor pregnancy outcome, such as preterm birth, preeclampsia and intrauterine growth restriction (Silver & Airoidi 2019).

Venous thromboembolism is one of the main causes of maternal morbidity and mortality. The risk of thromboembolism is 5 times higher during pregnancy and 60 times higher postpartum (Pomp et al. 2008).

About 50% of patients with thrombosis have a genetic risk, but 50%-60% of them develop thrombosis only if another risk factor is also associated (Chu Lam & Airoidi 2019).

Antiphospholipid syndrome is the most important cause of acquired thrombophilia associated with pregnancy. It is associated with venous thromboembolism, intrauterine growth restriction, early pregnancy loss, preterm birth and fetal death (Manuck 2019).

MATERIAL AND METHODS

The objective of this study was to evaluate the blood flow through the uterine arteries in a pregnant woman with a genetic risk for thrombophilia and who was treated with antithrombotics and anticoagulants.

Serial measurements of the velocimetric indices were made at 13w1d, 17w0d, 23w0d, 28w2d and 33w6d of gestation.

The ultrasound examination was performed with an Aloka-5-alfa-proultrasound, transvaginally in the first trimester using a transducer with a frequency of 6.5 MHz and transabdominally in the second and third trimesters, using a 3.5 MHz transducer.

Using the pulsed Doppler, the following parameters were evaluated: the resistance index (RI), the pulsatility index (PI), the ratio between systole and diastole (S/D), the peak systolic velocity (PSV), the end-diastolic velocity (EDV), the mean velocity (MnV) (Bhide et al. 2019).

At each ultrasound examination the fetal weight was evaluated and the growth curves were followed.

RESULTS AND DISCUSSIONS

The patient came to the first medical consultation at 11 weeks of gestation. She had a history of pregnancy loss at 5-6 weeks of gestation.

At the time of the first presentation she weighed 59 kilograms, blood pressure was 124/79 mm Hg and heart rate 68 beats per minute. The tests that evaluate blood coagulation were within normal limits.

In the first trimester of pregnancy the patient received treatment with prenatal vitamins, folic acid, progesterone 100-200 mg per day and aspirin 75 mg per day. In the second trimester of pregnancy she received treatment with prenatal vitamins, progesterone, antispasmodics and an injectable solution of enoxaparin sodium 0.4 mg per day administered subcutaneously.

The patient had quarterly check-ups with the hematologist who monitored blood coagulation tests and prescribed antithrombotic and anticoagulant prophylaxis.

Genetic tests that evaluate the risk for thrombophilia showed:

Factor V Leiden G1691A – without mutation

Factor V H1299R (haplotip R2) – without mutation

Factor II G20210A – without mutation

MTHFR C677T (methylentetrahydrofolate reductase) - heterozygous genotype

MTHFR A1298C – without mutation

PAI-1 (Plasminogen Activator Inhibitor 1) – 4G/5G heterozygous genotype

EPCR (Endothelial Protein C Receptor) – alleles A1/A2 are present

Factor V Leiden is a moderate risk factor for thrombosis and increases cardiovascular risk. Factor XIII V34L provides protection against thromboembolism.

EPCR binds Protein C and inhibits its anticoagulant activity. Carriers of the allele A3 have increased levels of EPCR in plasma and have a predisposition to develop deep venous thrombosis.

The heterozygous mutation of the MTHFR is associated with a decrease in enzyme activity and an increase in the plasma level of homocysteine in association with folate deficiency.

The homozygous 4G/4G genotype and the heterozygous 4G/5G genotype in position 675 of the PAI-1 gene are associated with an increase in the plasma level of PAI-1, the consequence being a decrease in fibrinolytic activity.

The risk of thrombosis increases in the case of association of PAI-1 gene mutations with mutations of the Factor V Leiden gene, the prothrombin gene or the MTHFR gene (Silver & Airoidi 2019).

Clinical guidelines do not recommend anticoagulant treatment in pregnant women without a history of venous thromboembolism, even if the tests show a genetic risk for thrombophilia (Chu Lam & Airoidi 2019).

Clinical guidelines do not recommend routine screening for the genetic risk of thrombophilia in pregnant women without a history of venous thromboembolism (Silver & Airoidi 2019).

In the case of antiphospholipid syndrome, anticoagulant treatment is recommended. The diagnosis of antiphospholipid syndrome requires the association a clinical criterion and a paraclinical criterion. The clinical criterion refers to the existence of three or more pregnancy losses in the medical history, which did not happen in the present case. The tests performed did not show the existence of antiphospholipid syndrome (Manuck 2019).

The velocimetric indices on the uterine arteries have different values depending on the gestational age (Merz 2005).

At 14w2d of amenorrhea the size of the fetus measured by ultrasound corresponded to 13w1d, so this it was the real gestational age. The values of the velocimetry indices in the right uterine artery were: PI=1.47, RI=0.71, S/D=3.40, PSV=77.2 cm/s, EDV=22.7 cm/s, MnV=37.1 cm/s (Figure 1).

The values of the velocimetry indices in the left uterine artery were: PI=1.06, RI=0.62, S/D=2.64, PSV=98.7 cm/s, EDV=37.4 cm/s, MnV=57.6 cm/s (Figure 2). The notch was observed in the waveforms of the blood flow in both uterine arteries, more significantly in the right uterine artery.

At 17w0d of gestation the values of the velocimetry indices in the right uterine artery were: PI=1.00, RI=0.59, S/D=2.44, PSV=91 cm/s, EDV=37.4 cm/s, MnV=53.5 cm/s (Figure 3).

The values of the velocimetry indices in the left uterine artery were: PI=0.97, RI=0.57, S/D=2.33, PSV=144.7 cm/s, EDV=62.3 cm/s, MnV=84.7 cm/s (Figure 4).

At 23w0d of gestation the values of the velocimetry indices in the right uterine artery were: PI=0.84, RI=0.53, S/D=2.11, PSV=51 cm/s, EDV=24.1 cm/s, MnV=32.1 cm/s (Figure 5).

The values of the velocimetry indices in the left uterine artery were: PI=0.65, RI=0.44, S/D=1.78, PSV=105.2 cm/s, EDV=59.1 cm/s, MnV=70.6 cm/s (Figure 6).



Figure 1. Right uterine artery flow velocity waveforms at 13w1d of gestation

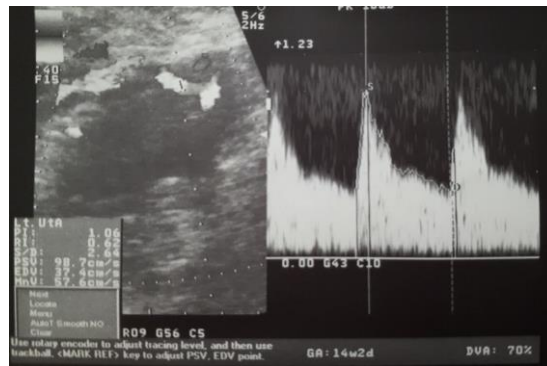


Figure 2. Left uterine artery flow velocity waveforms at 13w1d of gestation

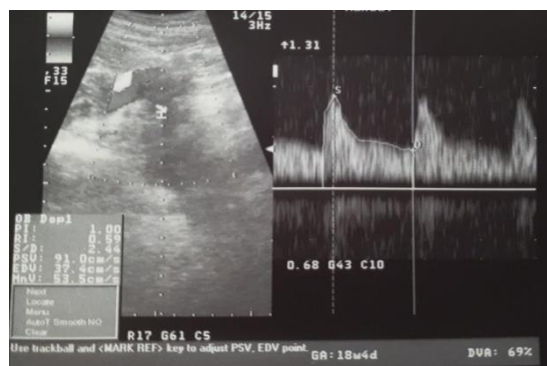


Figure 3. Right uterine artery flow velocity waveforms at 17w0d of gestation

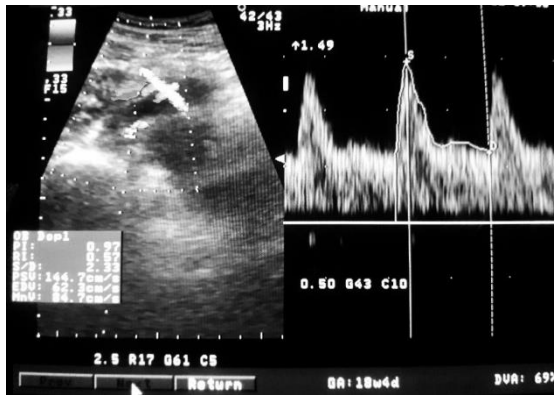


Figure 4. Left uterine artery flow velocity waveforms at 17w0d of gestation

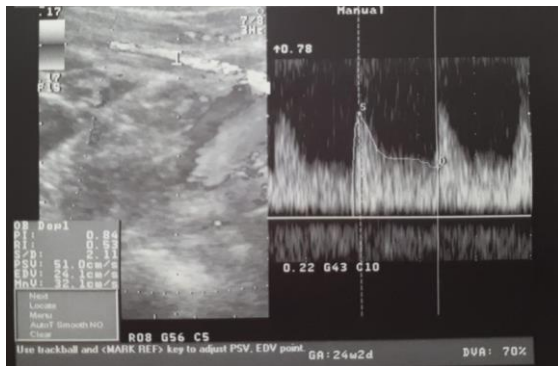


Figure 5. Right uterine artery flow velocity waveforms at 23w0 of gestation

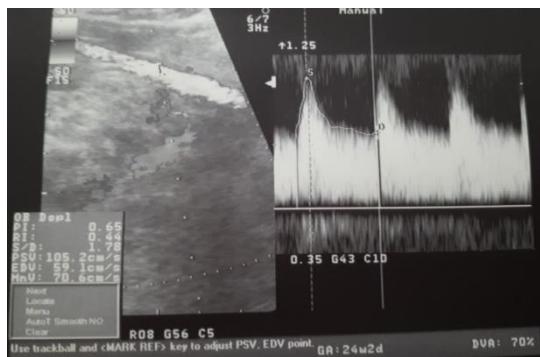


Figure 6. Left uterine artery flow velocity waveforms at 23w0d of gestation

The velocimetry indices in the uterine arteries and the umbilical artery were within normal limits until the end of the pregnancy.

The presence of a diastolic notch in the waveform and an increase in the impedance index after 22 weeks of gestation characterizes an abnormal circulation (Bhide et al. 2013, Mlynarczyk et al. 2017).

The patient was treated with aspirin until 25 weeks of gestation, when the hematologist decided on thromboembolism prophylaxis with heparin until 24 hours before delivery.

During the follow-up the coagulation tests remained within normal parameters for the pregnancy period, the growth curves were positive and fetal growth was within normal limits. The birth was done by cesarean section at 38 weeks of gestation. The fetal weight at birth was 3190 grams and the Apgar score 8/9.

Several studies have followed the changes in blood flow in the uterine arteries in pregnant women with thrombophilia and the consequences on fetal growth. One study included 139 women with inheritable thrombophilia treated with daily low molecular weight heparin (LMWH) and aspirin, or aspirin only.

Ultrasound measurements were performed at 22-24, 28-39 and 34-36 weeks of gestation. The monitored parameters were the flow velocity of the umbilical and uterine arteries, fetal growth and birth weight.

The conclusion was that the addition of LMWH to aspirin did not influence the fetal growth or umbilical and uterine flow velocity (Abheiden et al. 2016).

The aim of another study was to evaluate the uterine arteries blood flow in 64 pregnant women with thrombophilia who received prophylaxis with low-dose of enoxaparin (40 mg) from the beginning of the pregnancy until 36 weeks of gestation. Fifty control subjects were also included in this study.

Transabdominal ultrasound examination and uterine arteries Doppler measurements were performed between 18 and 22 weeks of gestation. Women with thrombophilia had increased mean PI and RI indices even if they used heparin.

The mean PI was 1.07 ± 0.46 for the LMWH group and 0.91 ± 0.31 for the control group. The mean RI was 0.59 ± 0.12 . The values were significantly higher in women with thrombophilia (Cok et al. 2021).

A retrospective study was conducted in 139 pregnant women with 3 or more recurrent pregnancy losses and thrombophilia. Patients received aspirin, LMWH and prednisone. The measurement of the RI was done every two weeks until 32 weeks of gestation. The RI at 8 weeks of gestation was significantly higher in women who have lost pregnancy (0.51 ± 0.08 versus 0.42 ± 0.03) (Bao et al. 2019).

The objective of another study was the assessment of uterine artery blood flow in 20 women with congenital thrombophilia and antiphospholipid syndrome at 12 and 20 weeks of pregnancy. All patients received enoxaparin or aspirin and enoxaparin.

Mean PI values in the uterine arteries at 12 weeks in patient with thrombophilia were 1.82(1.00-3.13) and 1.52(1.30-1.88) in the control group. Mean PI values in the uterine arteries were 1.27(0.61-2.48) in women with thrombophilia at 20 weeks, significantly higher than in the control group 1.07(0.8-1.24).

The bilateral distolic notch was found at 12 weeks of gestation in 40% of patients with thrombophilia versus 0% in the control group. There was no significant difference regarding this parameter between the two groups at 20 weeks of gestation (Kornacki et al. 2012).

A study evaluated 41 pregnant women with bilateral uterine artery notches and found that women with inherited thrombophilia showed a six fold higher risk to have an adverse outcome (Grandone et al. 2006).

CONCLUSIONS

In pregnant women with a medical history of recurrent miscarriages tests are required to assess the genetic risk for thrombophilia and antiphospholipid syndrome. In the case of a history of venous thromboembolism and a genetic risk for thrombophilia, anticoagulant prophylaxis is recommended during pregnancy and postpartum.

The follow-up is necessary during the pregnancy by performing blood coagulation tests, ultrasound evaluation of fetal growth and Doppler analysis of blood flows through the uterine arteries, umbilical artery and middle cerebral artery. The occurrence of deep venous thrombosis requires the replacement of prophylaxis with anticoagulant treatment with low molecular weight heparin in doses depending on the patient's weight.

In the present case the clinical evolution was favorable, the blood coagulation tests had normal values and the velocimetric indices in the uterine arteries and the umbilical artery remained within normal limits. The fetal growth was appropriate and the birth was carried out at term.

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