Aims and objectives

Thrombophilia can be defined as a predisposition to thrombosis. Abnormalities in haemostasis that are associated with clinical thrombophilia include heritable defects, such as mutations in the genes encoding the natural anticoagulants antithrombin, protein C and protein S, or clotting factors prothrombin and factor V, and acquired factors defects, such as antiphospholipids. The most common acquired thrombophilia's are antiphospholipids, which comprise lupus inhibitors and anticardiolipin antibodies. Women with thrombophilic defects have been shown to be at increased risk, not only of pregnancy associated thromboembolism, but also of others vascular complications of pregnancy, including pre-eclampsia and fetal loss. Routine thrombophilia screening of all women attending antenatal clinics is not recommended. Because some thrombophilic defects - for example, type 1 antithrombin deficiency and antiphospholipids - are associated with high risk of recurrent thrombosis or other pregnancy complications, it is suggested that selected women (those with a personal or confirmed family history of venous thromboembolism or with a history of recurrent fetal loss) are screened for these defects to allow pregnancy management planning.

Pregnancy is hypercoagulable state. The field of thrombophilia; the tendency to thrombosis, has been developed rapidly and has been linked to many aspects of pregnancy.

Deficiencies of protein S C and antithrombin are rare and each of them is found in about 3% of patients with thrombosis. Recently, three important inherited thrombophilia's were discovered which are responsible of the majority of thromboembolic events in patients with otherwise no apparent risk of thrombosis. Resistance to activated protein C caused by an adenine 506 guanine (A506G) mutation in factor V (factor V Leiden) has been linked with an increased risk of venous thromboembolism. Heterozygosity for the factor V (FV) Leiden mutation is found in about 5% of the population and the mutation is responsible of 20-30% of venous thromboembolism events. A recently described guanine 20210 adenine mutation in prothrombin is associated with higher plasma prothrombin concentrations and increased risk for venous thromboembolism and cerebral vein thrombosis. Homozygosis for the cytosine 677 thymine (C677T) mutation in methylenetetrahydrofolate reductase (MTHFR) results in decreased synthesis of 5-methyltetrahydrofolate, the primary methyl donor in the conversion of homocysteine to methionine and the resulting increase in plasma homocysteine concentrations is a risk factor for thrombosis. The mutation is responsible for reduced MTHFR activity and is the most frequent cause of mild hyperhomocysteinaemia and can be found in 5-15% of the population.
There is growing evidence that women with thrombophilia are at increased risk, not only of pregnancy-related venous thromboembolism (VTE), but also other vascular pregnancy complications, including fetal loss, pre-eclampsia and intra-uterine growth restriction (RCIU).\textsuperscript{1} Many studies have now examined the association between thrombophilia and pregnancy complications, often with differing results.

In addition, clinical studies have been performed, using Doppler ultrasonography, to assess the uterine placental circulation in women with thrombophilia. Doppler studies of the umbilical artery in cases of intrauterine growth restriction have shown a high systolic to diastolic ratio (S/D) ratio, suggesting an increase in the resistance of the placental small vessels. When these placental vessels were examined after delivery, significant differences were found in comparison with placental vessels of normal pregnancies. Most of the Doppler studies of the umbilical and uterine arteries in pregnancies with thrombophilia were performed in women with antiphospholipid antibodies.\textsuperscript{10}

The purpose of this study is to analyze the association between inherited thrombophilia and obstetrics abnormalities and adverse fetal outcomes using Ultrasound and Doppler.
Methods and materials

During the period from June 2012 to August 2013, a prospective observational case-control study was carried out in the Section of Gynecology and Obstetrics of a private medical clinic in cooperation with the University State of São Paulo (USP), Brazil. Institutional review board approval was obtained for this study. Data were collected at entry to the study, by personal interview. Sonographic images of the obstetrical exams of patients in this study were obtained from B-mode and color Doppler amplitude.

Two groups of women were enrolled. We studied 60 pregnant women, between 20 and 38 weeks of gestation with history of recurrent pregnancy loss (RPL) may be in the 1\textsuperscript{st}, 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester and / or thrombotic placental damage. We analyzed these patients by using gray-scale ultrasound (US) and blood flow resistance in the uterine and umbilical arteries, assessed by multigate Doppler examinations. After we compared them to 70 healthy reproductive women, without pregnancy complications (intrauterine growth restriction, stillbirth, and abruption placentae). Cases and controls were tested for the mutations: factor V Leiden mutation (G1691A) (FVL), prothrombin mutation (G20210) (FII), methylenetetrahydrofolate reductase mutation (C677T) (MTHFR), and protein C, protein S and Antithrombin III deficiencies.

Odds ratio (OR) at confidence interval (CI) of 95% was used as a measure of association between the mutations and RLP and thrombotic placental damage (gray-scale US and resistance blood flow Doppler in uterine and umbilical arteries). However, the major limitation common to most studies was the failure to identify additional risk factors in the populations studied.
Fig. 3: 29 weeks of gestation. Increased end-diastolic flow in the middle cerebral artery (IP= 1.34). Umbilical artery IP= 1.53. Homozygous Factor V Leiden.

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Fig. 1: Femur length 56mm (29 weeks gestation). Placental adverse outcome. Classification of placental maturity grade 3 - Grannum)

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Fig. 2: Abnormal umbilical artery Doppler at 29 weeks of gestation. Decreased end-diastolic flow in the umbilical artery (higher IR, IP= 1.53, S/D= 5.20). Homozygous Factor V Leiden

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Results

Our statistical analysis showed a slightly increased association, which was not significant between Factor V Leiden, RPL and thrombotic placental damage. Analysis RPL subgroups revealed an association between FVL and first trimester loss. Due to the limitations of the available data, the analysis on factor V Leiden incorporates both homozygous and heterozygous carriers. These women were found to be at higher risk of pregnancy loss in the second compared with the first trimester (OR 5.0; 95% CI 2.2-8.9 and 2.0; 95% CI 1.02-03.80, respectively).\textsuperscript{11,12,13}

There was a significant association between the combination of FVL and MTHRF (two polymorphisms) and placental adverse outcomes (thrombotic placental damage) analyzed by abnormal placental texture gray-scale ultrasound and blood flow resistance uterine and umbilical arteries Doppler. Thrombophilia as associated with an increased risk of placenta abruption, but significant associations were only observed with heterozygous factor V Leiden (OR 4.80; 95% CI1.15- 19.62) and heterozygous prothrombin (OR 7.80; 95% CI 3.03-19.79).\textsuperscript{14,15}

There was a significant association between prothrombin and early pregnancy loss (OR 2.5; 95% CI 1.25-5.00).

There was a significant association between the combination of protein S and C deficiency\textsuperscript{16,17} and placental adverse outcomes (thrombotic placental damage), showed high blood flow resistance in the uterine and umbilical arteries, assessed by multigate Doppler examinations.

Acquired activated protein C resistance was associated with a higher risk of recurrent pregnancy loss in the first trimester (OR 2.70; 95% CI 1.25-5.63) than non-recurrent loss.\textsuperscript{18,19,20}

Acquired activated protein C resistance and the combination of FVL and MTHRF shown a high systolic to diastolic ratio (S/D) in umbilical arteries.\textsuperscript{10,21}
Fig. 4: Abnormal umbilical artery Doppler at 28 weeks of gestation demonstrates absent umbilical artery end-diastolic flow. Oligohydramnios, IUGR, and MTHFR mutation (homozygous)

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Fig. 6: Normal Uterine Artery Doppler. Absence of notch. In the same patient of figure 4 and 5.

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Fig. 7: Right Uterine Artery Doppler with notching in a patient at 28 weeks of gestation. IUCR, early maturing placenta (Grannum classification). Deficiency protein C and S.

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**Fig. 5:** Normal Middle Cerebral Artery Flow with abnormal umbilical artery flow (figure 4). Oligohydramnios, IUGR, and MTHFR mutation (homozygous)

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Fig. 8: Left Uterine Artery Doppler (bilateral - figure 7) with notching in a patient at 28 weeks of gestation. IUCR, early maturing placenta (Grannum classification). Deficiency protein C and S.

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CONCLUSION

The management of thrombophilia during pregnancy encompasses primary thromboprophylaxis in asymptomatic women, secondary prophylaxis of recurrences in women who have previously developed thrombosis, and the treatment of acute thrombotic episodes.

This study observed strong association of thrombophilia with thrombotic placental damage and adverse perinatal outcomes. Our findings have important implications for therapy and provide a rationale for clinical trials of thromboprophylaxis for affected women followed by serial placental gray-scale ultrasound and resistance blood flow Doppler.

The diagnosis has serious implications not only for the immediate management of the pregnancy, but also for the management of future pregnancies.

Integrated biochemical and ultrasound testing of placental function, followed by serial placental gray-scale ultrasound and blood flow resistance of uterine and umbilical arteries, may be an effective method of identifying of pregnancies at high risk of adverse pregnancy outcome.
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References


