Deep vein thrombosis during pregnancy work up

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ABSTRACT

Background: Deep venous thrombosis (DVT) during pregnancy is a determining factor that contributes to increased maternal-fetal morbidity and mortality. It may occur when there is thrombophilia, due to compression of the inferior vena cava, venous stasis or hormonal changes.

Objectives: To assess patients who are pregnant or have just given birth and who have a DVT condition in the lower limbs, to search for possible causes of thrombophilia and to perform a review of the literature.

Methods: Pregnant and puerperal patients were assessed by gynecologists and obstetricians when there was suspicion of DVT, from January 2004 through November 2006, during which time there were 24,437 childbirths at Hospital e Maternidade São Luiz; of these, 89% were cesarean, 7.5% were normal births and 3.5% were forceps deliveries. Of the total number of patients referred with a clinical status suggesting DVT, 42 cases were clinically diagnosed as DVT, in pregnant women aged between 21-39 years, confirmed by venous duplex scan. Right before the introduction of anticoagulant therapy, samples were collected to investigate thrombophilia, which were repeated after the treatment.

Results: Of the 42 patients with DVT, 32 were primigravid (three twin pregnancies with no thrombophilic changes, two resulting from in vitro fecundation), eight were mothers at second birth and two were at third birth. In four patients, DVT occurred in the first trimester of pregnancy (9.5%), in 11 patients DVT was present in the second trimester (26.2%) and in 27 patients the disease developed in the third trimester of pregnancy (64.3%). Of the 42 patients diagnosed with DVT, 18 (42.8%) occurred in infrapatellar veins. There was a case of pulmonary thromboembolism in a 37-year-old patient, who had been submitted to in vitro fecundation, with twin pregnancy and a

diagnostic of DVT (no thrombophilia) after a cesarean section. Of the 42 patients, 16 (38.1%) had the cause of their DVT determined, with a prevalence of heterozygous mutation of factor V Leiden in six patients (14.2%), followed by phospholipid syndrome and other causes. Most patients were treated with low-molecular-weight heparin.

Conclusion: DVT during pregnancy, despite having low frequency, is a major cause of increased maternal-fetal morbidity. Investigation of thrombophilia should be conducted in selected cases, such as personal or family history of thrombotic phenomena and/or thrombophilia. Twin pregnancy, cesarean birth and artificial insemination were also found as factors leading to DVT.

Keywords: Deep venous thrombosis, thrombosis, pregnancy, anticoagulant, heparin.

RESUMO

Contexto: A trombose venosa profunda (TVP) na gravidez é fator determinante no aumento da morbidade e da mortalidade maternofetal. Pode ocorrer na presença de trombofilias, por compressão da veia cava inferior, estase venosa ou alterações hormonais.

Objetivos: Analisar pacientes grávidas e no pós-parto imediato portadoras de TVP em membros inferiores, pesquisar as possíveis causas de trombofilia e realizar revisão de literatura.

Métodos: Foram analisadas gestantes e puérperas encaminhadas por ginecologistas e obstetras com quadro clínico suspeito de TVP, de janeiro de 2004 a novembro de 2006, período em que foram realizados 24.437 partos no Hospital e Maternidade São Luiz (HMSL), sendo 89% cesarianas, 7,5% partos normais e 3,5% fórceps. Do total de pacientes encaminhadas com quadro clínico sugestivo, foram realizados 42 diagnósticos clínicos de TVP em gestantes com idade entre 21 e 39 anos, confirmados por duplex scan venoso. Imediatamente antes da introdução da terapia anticoagulante, foram colhidos exames para pesquisa de trombofilia, os quais foram repetidos após o período de tratamento.

Resultados: Das 42 pacientes portadoras de TVP, 32 eram primigestas (três gemelares sem alterações trombofílicas, duas por fecundação in vitro), oito secundigestas e duas tercigestas. Em quatro pacientes, a TVP ocorreu no primeiro trimestre da gestação (9,5%); em 11, no segundo trimestre (26,2%); em 27, no terceiro trimestre (64,3%). Dos 42 casos de diagnóstico de TVP, 18 (42,8%) ocorreram nas veias infrapatelares. Houve um caso de tromboembolismo pulmonar (TEP) em paciente de 37 anos que havia realizado fecundação in vitro, com gestação gemelar, e TVP (ausência de trombofilia) diagnosticada após a cesariana. Das 42 pacientes, 16 (38,1%) tiveram a causa da TVP estabelecida, com prevalência de mutação heterozigótica do fator V de Leiden (FVL) em seis pacientes (14,2%), seguida pela síndrome antifosfolípide e outras. A maioria das pacientes foi tratada com heparina de baixo peso molecular.

Conclusão: A TVP na gravidez, apesar de sua baixa freqüência, aumenta consideravelmente a morbidade maternofetal. A pesquisa de trombofilia deve ser realizada em casos selecionados, tais como antecedentes pessoais ou familiares de fenômenos trombóticos e/ou trombofilia. A gestação gemelar, a cesariana e a inseminação artificial também foram fatores predisponentes para a ocorrência de TVP.

Palavras-chave: Trombose venosa profunda, trombose, gestação, gravidez, anticoagulante, heparina.

Introduction

Pregnancy toxemia is the most frequent cause of maternal mortality, followed by pulmonary

embolism.[1-4] High number of cesarean deliveries has significantly contributed to increase in incidence of thromboembolic phenomena. Pulmonary thromboembolism (PTE), deep venous thrombosis (DVT) in pregnancy and in the puerperium are determining factors for increase in maternal-fetal morbidity and mortality. There are reports between 0.5 and three cases of DVT for each 1,000 pregnancies. Some authors have estimated that DVT in pregnant women is five times more frequent than in nonpregnant women in the same age group.

Pregnancy is a state of preparatory hypercoagulability for delivery, by production of plasminogen inhibitors 1 and 2 through the placenta, reducing fibrinolytic activity and increasing platelet aggregation. There are also reduction in protein S levels, increase in factors I, VII, VIII and X and progressive resistance to protein C activity.[2,3] Concomitantly, compression of the inferior vena cava by the pregnant uterus contributed to venous stasis, thus favoring thrombotic phenomena.[5]

Thrombophilia, described as a tendency to development of thrombosis, can be hereditary or acquired. It is polymorphic as to genetic condition for platelets or proteins of coagulation factors. When present, it favors the previously described thrombotic phenomena in pregnancy. Hyperhomocysteinemia is an example of both hereditary and acquired thrombophilia (defect in homocysteine metabolism or folate-deficient diet). Both cause increase in plasma homocysteine and higher possibility of thrombosis.[3]

DVT in pregnancy and in the postpartum period substantially increases maternal-fetal morbidity and mortality, placing two lives at risk. These factors, associated with our hospital-maternity experience, motivated us to perform this research study.

This article analyzes the causes of thrombosis during pregnancy and immediate postpartum period in patients with lower limb DVT at Hospital e Maternidade São Luiz (HMSL), in São Paulo, Brazil, from January 2004 through November 2006, and performs a literature review.

Methods

Forty-two pregnant women were analyzed, aged between 21-39 years, referred by HMSL obstetricians and gynecologists to be assessed by our team, with clinical suspicion of DVT from January 2004 through November 2006, when there was a record of 24,437 deliveries (Table 1). Diagnosis was based on clinical signs and symptoms. Personal and family history of thrombophilia and thromboses were exhaustively investigated. Pain, edema and calf tenderness were present in more than 80% of patients; Homans' sign, superficial venous dilatation and cyanosis were present at a lower proportion. Of all referred patients, 42 had clinical diagnosis of DVT confirmed by venous *duplex scan* .

Table 1 - Type of procedure performed in delivery and number of births

Types of deliveries and births	n
Total deliveries	24.437
Cesarean	21.748
Normal	1.832
Forceps	857
Total births	25.055
Primiparous	14.110

Immediately before introduction of anticoagulant therapy and 1 month after its end, the following examinations were performed for investigation of thrombophilia: dosage of antithrombin and protein C (functional method with chromogenic substrate), determination of protein C (coagulometric method), factor V Leiden (FVL) mutation (R506Q mutation by PCR-RFLP) in the factor V gene, IgG anticardiolipin (immunoenzymatic), IgM anticardiolipin (immunoenzymatic method), lupus anticoagulant (automated BCS method), prothrombin mutation (PCR method to detect G20210A mutation of the prothrombin gene) and homocysteine dosage (high-performance liquid chromatography or HPLC method). Inclusion criteria for thrombophilia were established after clinical and ultrasound confirmation of DVT, and especially after confirmation of thrombophilia before and after the treatment. Blood count, coagulogram, echocardiogram and D-dimer were also performed to evaluate the treatment and comorbid conditions.

Low-molecular-weight heparin (LMWH) was the first-choice drug, being careful to control dosage to avoid levels of activated partial thromboplastin (APTT) higher than 1.5-2 times the normal value. Limiting factor for its use was the drug's high cost. Not all patients had financial conditions to maintain LMWH treatment. In these cases, we chose subcutaneous unfractionated heparin (UFH), also adjusted according to APTT levels between 1.5-2 times the normal level. Platelet control was monitored by coagulogram.

Minimal anticoagulation time was 3 months. In the group of patients with thrombosis in the first and second pregnancy trimesters, it reached the puerperal period in cases of thrombophilia. Treatment was suspended 24 hours before delivery and resumed 6 hours after anesthesia. In suspicion of thrombophilia, treatment was suspended 2 months after delivery, when thrombophilia results were confirmed in 12 cases. Three patients who were initially considered positive for thrombophilia during pregnancy did not have laboratory confirmation after the therapy. Patients with thrombophilia were then referred to a hematologist.

In cases of great saphenous thrombosis, surgical treatment was chosen through aortic arch ligation using local anesthesia, with no sedation.

Oral anticoagulation was not used in any case, neither fibrinolytic drugs or implantation of inferior vena cava filter.

The literature is controversial regarding maternal-fetal side effects of heparin. Some authors report fetal complications in approximately 30% of cases, whereas others report that heparin is safe for the fetus.[1] In our study, there were no teratogenic complications. Two patients treated with UFH had small metrorrhagia, but treatment did not have to be suspended. Aspirin was maintained in patients with antiphospholipid syndrome, with the aim of avoiding fetal loss.

Results

From January 2004 through November 2006, 24,437 deliveries were performed at HMSL and 25,055 births were recorded; of these 21,748 were cesarean (89%), 1,832 were normal (7.5%) and 857 forceps deliveries (3.5%) (Table 1). Decision as to procedure was made according to clinical indication or patient's choice, excluding any interference by the HMSL, which recommends normal delivery as the first option. Of all pregnant women, 14,110 were primiparous (57.7%). Patients with clinical suspicion of DVT were referred, and 42 diagnoses were confirmed by our vascular surgery team. Total occurrence of thrombosis must be higher, since the HMSL is a private hospital, open to all specialists in São Paulo, and other DVT have certainly been treated by other angiologists. Of the 42 patients with DVT, 32 were primigravid (76%), of whom three had twin pregnancy without thrombophilic changes and two had *in vitro* fecundation, eight were mothers at second birth (19%) and two were at third birth (5%) (Table 2). The patients' age ranged between 21-39 years. Two were smokers.

Table 2 - Characteristics of patients with DVT

Characteristic	n	%
Number of pregnancies		
Primigravid	32	76
Second birth	8	19
Third birth	2	5
Gestation period in which DVT occurred		
Third trimester	27	64,3
Second trimester	11	26,2
First trimester	04	9,5
After cesarean delivery	04	9,5
DVT location		
Left lower limb	23	54,8
Right lower limb	19	45,2
Affected vessels		
Infrapatellar	18	42,9
Popliteal	10	23,8
Femoral	07	16,6
Iliac	05	11,9
Great saphenous veins	02	4,8

DVT = deep venous thrombosis.

In four patients, DVT occurred in the first pregnancy trimester (9.5%); in 11 in the second trimester (26.2%); in 27 in the third trimester (64.3%), including four post-cesarean sections (Table 2). There was one case of PTE on the first post-cesarean day in a 37-year-old patient who had performed *in vitro* fecundation, with twin pregnancy (no thrombophilic change), whose diagnosis of infrapatellar DVT was performed after PTE.

Thirty-eight patients developed DVT between the ninth and 36th week. Four thromboses (9.5%) occurred between the first and third postoperative day. There was no DVT in normal or forceps

deliveries.

The left lower limb was prevalent compared to the right lower limb: 23 (54.9%) and 19 (42.2%), respectively; the infrapatellar territory was the most frequently affected, with 18 cases (42.8%), followed by 10 cases in the popliteal veins (23.8%), seven in the femoral veins (16.6%), five in the iliac veins (11.9%) and two in the great saphenous veins (4.7%) (Table 2) in non-thrombophilic patients who had no chronic venous insufficiency (Figures 1 and 2).

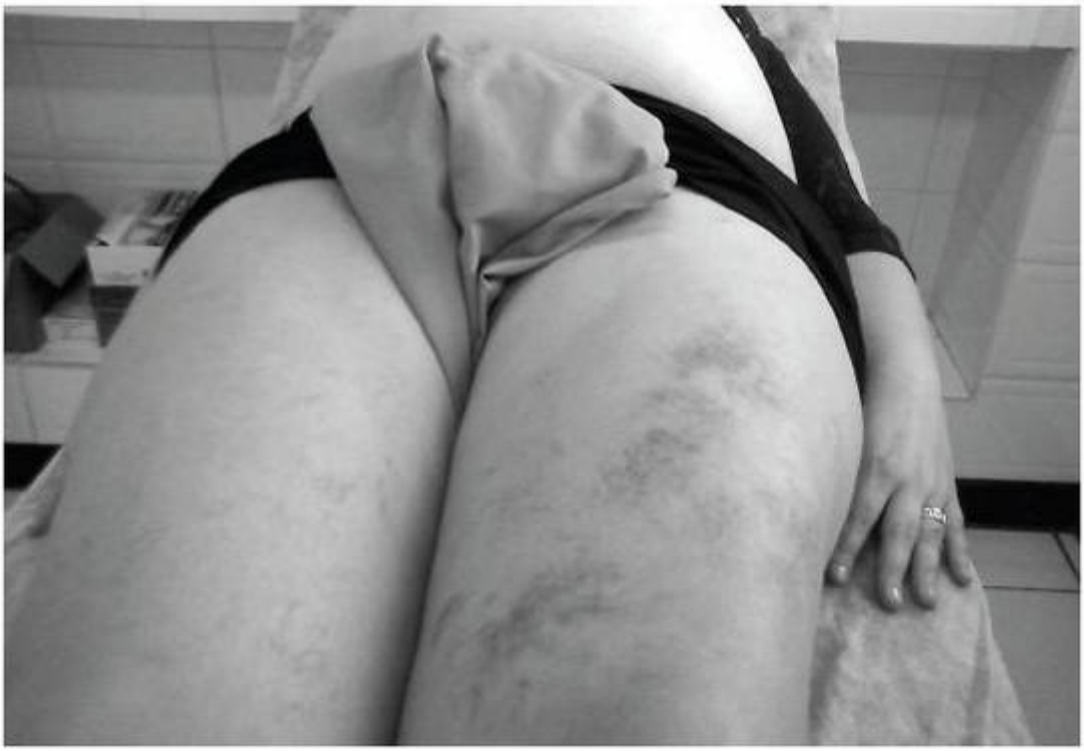

Figure 1 - Left iliac deep venous thrombosis in a patient during her 30th gestational week; presence of good collateral circulation

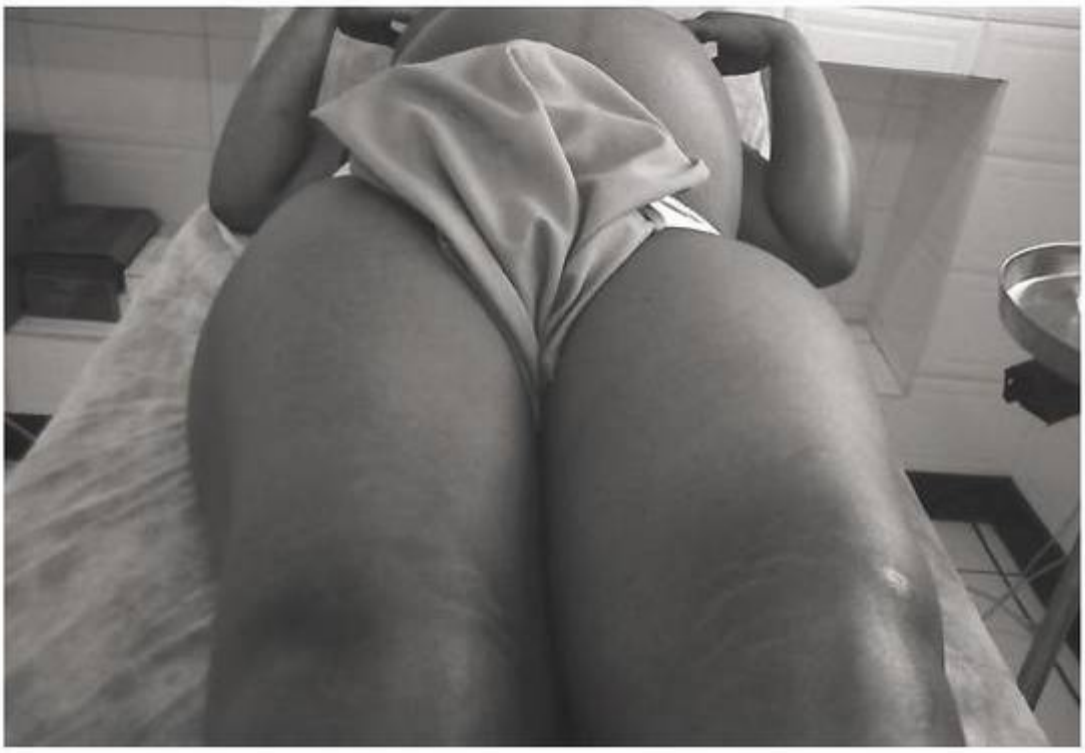

Figure 2 - Intense edema in left limb due to deep venous thrombosis during the 28th gestacional week

In 16 patients (38%), DVT etiology was defined (Table 3); 12 patients (28.5%) had positive results for thrombophilia in pre- and post-coagulation exams; six patients (14.3%) had FVL heterozygotic mutation; three (7.1%) had antiphospholipid syndrome (two had systemic erythematous lupus), antithrombin deficiency, protein C deficiency and protein S deficiency (one patient each). Four non-thrombophilic women had the following factors as determined cause: polycythemia vera (one case); long plane trip (one case); and great saphenous thrombophlebitis in proximal third of the thigh (two cases). We credited the other 26 cases (61.9%) to alterations that are typical of pregnancy (Table 3). Three of these patients had examinations suggestive of thrombophilia in DVT diagnosis, but we had no post-treatment confirmation, therefore these patients were excluded from the thrombophilia group.

Most patients were treated with LMWH or UFH.

Table 3 - Causes of DVT in 42 patients

Alteration	n	%
Alterations typical of pregnancy	26	61,9
Thrombophilias		
Factor V Leiden mutation	06	14,2
Antiphospholipid syndrome	03	7,1
Antithrombin deficiency	01	2,4
Protein C deficiency	01	2,4
Protein S deficiency	01	2,4
Other causes		
Great saphenous vein thrombosis	02	4,8
Polycythemia vera	01	2,4
Plane trip	01	2,4
Total	42	100

DVT = deep venous thrombosis.

Discussion

Many changes occur in pregnancy and contribute to hypercoagulability.[6] Pregnancy can be considered a form of disseminated intravascular coagulation due to reduced fibrinolytic activity and increased platelet aggregation. During pregnancy there are alterations such as reduced protein S and antithrombin, resistance to protein C activity, elevation of factors I (fibrinogen), VII, VIII (hemophilic), X and von Willebrand.[3] These changes of a thrombogenic nature are preparatory resources for delivery, reducing risks of bleeding for the mother. Twenty-six patients (61.9%), out of a total of 42, had DVT due to changes exclusive of pregnancy (Table 2), whereas in other 16 women they were attributed to thrombophilias, polycythemia vera, great saphenous vein thrombophlebitis and long trips. In addition to the above mentioned, there may be other causes of acquired thrombophilias, such as nephrotic syndrome, hepatic diseases, surgeries (including cesarean sections), oral contraceptive, estrogens and progestagens used in artificial inseminations.

During the first trimester of pregnancy, there is increased venous pressure due to hyperflow in the hypogastric and common iliac arteries, resulting from relaxation of vessel smooth muscles and opening of arteriovenous anastomoses due to progestogen activity. During the second and third trimesters, in addition to these factors, there is inferior vena cava compression due to pregnant uterus, resulting in reduced venous flow.[5] In the present study, we observed that DVT occurred more frequently in the third trimester of pregnancy, in 27 cases (64.3%), probably due to equivalence of procoagulating factors and stasis, followed by the second and third trimesters, respectively. Four patients (9.5%) had DVT in the immediate post-cesarean period. This is mainly due to pelvic trauma of femoral, iliac and tributary veins, in addition to an equally thrombogenic surgical procedure, according to Virchow's triad, described in 1860.

Ginsberg[7] and Shannon[8] reported that incidence of venous thromboembolism is probably two to four

times higher after cesarean sections when compared to normal and forceps deliveries. Risk of thrombosis in pregnancy is considered higher during the third trimester of pregnancy, and especially in the puerperium (up to 6 weeks after delivery); however, prospective studies using objective diagnostic tests did not show any difference between frequency of DVT and pregnancy trimesters.[2] Similarly, recent analyses have shown that DVT in pregnancy is at least as common as postpartum DVT.[9]

Incidence of DVT is similar in men and women, and it is more frequent in Caucasian women when compared to Asians.[10] It is not common to occur before 20 years of age, but after 40 years incidence doubles at each decade. Since maternity occurs at increasingly later ages and due to increase in number of *in vitro* inseminations and cesarean sections, there will be a higher tendency of DVT[11] in pregnancies. It is also important to observe that more than half of PTE episodes result from DVT, and 75% of these occur in the first episode.[12] Risk factors for a first DVT event may usually be present for recurrence. A detailed anamnesis, especially in patients with previous and family history of thromboembolic phenomena, should lead to laboratory investigation in selected pregnant women.

Performing *duplex scan* after the 20th week makes its interpretation more difficult, due to alteration in venous return; therefore, serial examinations at every 7 days should be performed in case of doubt.[2] *Duplex scan* should be the choice examination to investigate pregnant patients with suspicion of DVT.[1,6-8] D-dimer was not considered, since it can be high during pregnancy, progressively increasing throughout pregnancy and possibly reaching high levels (up to 30%), which makes routine assessment useless.[3]

In the present study, thromboses occurred more frequently in the left lower limb, 23 (54.8%) vs. 19 (45.2%) in the right lower limb. Despite that difference not being considered significant, the literature states that approximately 80% of cases occur in the left leg, due to abnormal compression of the left iliac vein by the right common iliac artery (Cocket syndrome).[2] Infrapatellar location in our population was more frequent, in agreement with the literature.

As to number of pregnancies and DVT, we observed a higher frequency in primigravid women (76%), followed by mothers at second birth (19%) and at third birth (5%). Perhaps these numbers reflect the great majority of primigravid women admitted to our hospital: 14,110 (57.7%) out of 24,437 deliveries.

We observed that in three primigravid patients with twin pregnancy DVT possibly occurred due to higher compression of the inferior vena cava as a result of large pregnant uterus.

Two parturient women had *in vitro fertilization*. This type of fecundation favors thrombogenic phenomena, due to hormone therapy with estrogen and progesterone in high doses. Korintoya reported that *in vitro* fertilization may cause ovarian hyperstimulation syndrome and favor thrombosis in little frequent locations, such as subclavian and jugular arteries.[13]

As to thrombophilias, we observed that there was a higher prevalence of FVL mutation (six cases) and antiphospholipid syndrome (three cases), followed by antithrombin, protein S and C deficiency (one case each).

Hereditary thrombophilia may lead to placental vessel thrombosis and recurrent abortions in patients with FVL and prothrombin mutation. FVL mutation is present in approximately 5% of the population and is the most frequent alteration. Persistence of that trait in the population has been attributed to reduced risk of bleeding during labor. Deficiencies in protein C and S are relatively uncommon. A recent study has shown that asymptomatic women with antithrombin, protein C or protein S deficiency have approximately eight times more chances of having DVT during pregnancy when compared to normal women.[3]

FVL mutation, which was the most present cause in our population, is more frequent in individuals from Northern Europe (3-8%), being rare in Asians and Africans. In the USA, prevalence is 4-6%.[3] Langan et al. reported that FVL mutation predisposes to pre-eclampsia due to marked fibrin deposition, resulting in endothelial lesion that may cause vasospasm, platelet activation and coagulation.[14,15] Similarly, mutation delays intrauterine fetal growth, can be the cause of recurrent abortions, favors fetal death and significantly raises incidence of thrombosis during pregnancy.[10,14,15] Analogously, it is responsible for recurrent venous thromboses. Becker reported that individuals can be heterozygote or homozygote for FVL mutation; thrombosis occurs more frequently in homozygotes. In heterozygotes, the first episode of thrombosis usually occurs when there are imposed risk factors, such as surgery, oral contraceptives or pregnancy.

Three patients had thrombosis with positive antiphospholipid antibody; two had erythematous lupus. Presence of antiphospholipid antibodies in pregnant women, besides causing DVT, increases incidence of abortions in the second trimester (due to DVT), favors pre-eclampsia, delays intrauterine fetal growth and may cause fetal death.[16]

Di Stefano described that protein C, protein S and antithrombin deficiencies reduce placental perfusion[15] (in the present study, we observed one patient in each group). When present, prothrombin mutation is also a triggering factor of DVT.

McCool published a multi-centered study involving superficial thrombophlebitis (STP) in pregnant women. He found an average of 0.68 STP/1,000 deliveries and concluded that thrombophilia can be the lowest STP etiology in pregnancy. More comprehensive studies are necessary to confirm that hypothesis.[17,18]

One patient with polycythemia vera had DVT in our population. Robinson[19] reported only 20 cases of polycythemia vera associated with pregnancy, which may be related to premature births and fetal death. For that reason, careful attention should be given to hematocrit.[19,20]

One patient had DVT after a long plane trip. Kingman[21] published an article suggesting that pregnant women should travel in the second trimester, which offers lower risk and more comfort (some airline companies do not allow pregnant women at more than 36 weeks to board their airplanes). Robin also warned that pregnant women are not always prepared to take long trips.[21] During that period, travelers, especially pregnant women, should adopt prophylactic measure for thrombosis, such as walking, performing foot and leg flexion and extension and wearing antithrombotic stockings; in case there is personal history of thrombophilia and/or thrombosis, LMWH can be indicated.[21,22]

One patient submitted to cesarean section, twin pregnancy, *in vitro* fertilization had PTE in the immediate postoperative period when retrospective DVT diagnosis was performed.

Anticoagulant therapy aims at preventing PTE, avoiding harm to the fetus (hemorrhage, teratogenesis, malignancy and genetic mutations) relieving acute and uncomfortable symptoms in women, minimizing postphlebitic sequelae of that disease,[3] besides preventing the thrombophilia complications mentioned above.[8] Thus, treatment onset should be as early as possible. LMWH and conventional heparin do not cross placental barrier, opposed to warfarin, which has risk of fetal malformation, especially between the sixth and 12th gestational week, besides providing more hemorrhagic complications. Therefore, warfarin should be avoided during the gestational period.[3,6,23] Fibrinolytics are included in the same category.[24]

LMWH is the anticoagulant of choice,[3,6,24-26] adjusted so that activated partial thromboplastin time (APTT) is not higher than 1.5-2 times the normal. We performed those examinations initially, weekly and at every 15 days thereafter. Substance should be suspended 24 hours before delivery and resumed 6 hours after anesthesia.[3,27] LMWH also causes less thrombocytopenia and osteoporosis.[3,25] Observation of bone density in pregnant women demonstrated lower occurrence of osteoporosis in

LMWH than in UFH. Some authors recommend control of blood heparin (by anti-factor Xa activity, especially in the last trimester). Some patients had no financial conditions to maintain LMWH treatment. In such cases, we chose to use UFH, adjusted with APTT. In both treatments, we also performed platelet count, since there may be low platelet count associated with heparin use. Two patients who had small metrorrhagia used UFH; drug suspension or use of protamine were not necessary. They remained under clinical observation and had their hematocrit and hemoglobin levels monitored.

In cases of antiphospholipid syndrome, LMWH associated with aspirin seems to have a significantly better result.[3]

Fokkin[28] published a study on 16 cases of temporary vena cava filter implantation in pregnant women in the third trimester of pregnancy. Other authors have reported that anticoagulation with permanent or temporary vena cava filter insertion did not have postpartum complications. These authors support the thesis that the filter can be an efficient prophylactic alternative or in the treatment of pregnancy with high risk of DVT in patients in whom there is contraindication for anticoagulation.[9] We did not use that procedure in any case.

Conclusions

-DVT in pregnancy has low occurrence, but it considerably increases maternal-fetal morbidity, bringing high risk to the pregnancy.

-Primigravid patients, twin pregnancies, cesarean sections and puerperium had higher risks for DVT.

- *In vitro* fertilization has more susceptibility to DVT, due to high doses of estrogen and progesterone required to that model of pregnancy.

-Clinical DVT investigation, using anamnesis, personal and family history of thrombophilia, clinical examination, being careful for age over 35 years and obesity, should be part of prenatal protocol and deserves relevant attention for risk of thrombosis in pregnancy. In suspected cases, laboratory examination is prudent.

-LMWH treatment seems to be the most indicated, since it had lower maternal-fetal complications; however, cost can be a limiting factor.

-Oral anticoagulants and fibrinolytics should not be used during pregnancy.

-Prophylactic doses of heparin are recommended during and after pregnancy for women who are confirmedly thrombophilic and with previous history of venous thromboembolism.

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