Venous thromboembolism in pregnancy. A case report of deep venous thrombosis (DVT) in puerperium

L. Di Stefano[1], C. Di Berardino[1], L. Marsili[2], G. Coppola[1], F. Patacchiola[1], G. Mascaretti[1]

[1]Department of Obstetrics and Gynaecology, [2]Department of Radiology and Radiotherapy, University of L'Aquila (Italy)

Summary

The authors describe a case of DVT during pregnancy in a 41-year-old woman who had a normal haemocoagulative picture during pregnancy and in puerperium (PT, PTT, S protein, C protein, ATIII, xdp and fibrinogenous). All the haemocoagulative dosages were within the norm and compatible with the gestation period. Both homocysteine and antiphospholipid antibodies (mostly in puerperium) were always within normal limits. The authors believe that DVT occurs infrequently but it is also unforeseeable. Systematic heparin prophylaxis for seven to ten days, ante- and postpartum, can prevent this problem.

Key words: Deep venous thrombosis; Anticoagulant prophylaxis; Pregnancy.

Introduction

Deep venous thrombosis (DVT) is a leading cause of maternal morbidity and mortality [1] during pregnancy and puerperium because of the maternal endocrine and vascular changes happening in these periods [2].

The incidence of thromboembolic disease has been estimated to vary from 0.71 to 1.3% in 1,000 women and the risk is higher during puerperium [3]. In the literature it is clear that the risk of venous thromboembolism is higher during the third trimester of gestation because of compression of the pregnant uterus on the pelvic veins. In 90% of the cases the lower left limb is the most common site of venous thromboembolism during pregnancy [4] because of compression of the right ovarian artery and the iliac artery on the common iliac vein [5]. Thus, during pregnancy the most common site of DVT is in the iliac-femoral vessels, with an increased risk of pulmonary embolism. The risk of venous thromboembolism is five times higher in a pregnant woman than in a non pregnant woman of similar age [6]. The causes of this higher risk are:

1) venous stasis due to compression of the pregnant uterus on the iliac veins and to the prolonged immobilization of pregnant women;

2) coagulation changes during pregnancy towards a hypercoagulation status involving coagulation and fibrinolitic factors.

Clotting normally results from a balance between procoagulant and anticoagulant mechanisms. The "procoagulant" proteins, after a signal, put in to action a "cascade-like" mechanism to produce fibrin. The third antithrombin and the C and S proteins are the natural anticoagulant mechanisms [7]. Figure 1 shows the coagulation cascade and the role of the natural anticoagulant proteins. During pregnancy there is venous stasis (pelvic and peripheral stasis) due to the decreased tone and haematic flow to the lower limbs and because of the compression of the pregnant uterus on the lower venous cava and on the left iliac vein. Placental circulation with its slow flow and staunching represents another important thrombosis risk factor. The damaged endothelial cells release the Von Willebrand factor that leads to an aggregation of platelets, thus the placenta becomes a site of initial coagulation activation [11].

The major abnormalities of clotting are increased plasmatic levels of fibrinogenesis, prothrombin, V, VII, VIII, IX and X factors during the second trimester of gestation [8], an increase of fibrin factors [9] and a decrease of the S protein levels without changes in the C protein [10]. The S protein, K-vitamin dependent, is the C protein cofactor which is the natural inhibitor of coagulation. There are two forms of the S protein: the first is a free and anticoagulant protein, while the second one is reversibly tied to fraction 4 of the complement system (C4).

Delivery is a thrombotic risk factor as an operation, especially if the delivery is a cesarean section; in the latter case the risk of venous thromboembolism is ten times higher than in vaginal delivery [13]. DVT risk increases in pregnant women when there are other risk factors such as smoking, older age, family history of thrombosis, high body mass index, use of oral contraceptives, high parity, hereditary thrombophilia factors (decrease of antithrombia III (ATIII), C and S proteins, factor V Leiden, hyperhomocysteine) cardiopathies, previous DVT, diabetes and/or preeclampsia, and prolonged immobilization [14]. The diagnosis is based on clinical signs (swelling, discomfort and warmth in the legs are common) and instrumental examinations such us Doppler imaging, magnetic resonance (MR) and vascular MR. These examinations are very useful to localize the site of DVT and to perform an operation on the vessels using radiological tecniques such as filters [16]. The therapeutic management consists of heparin, FANS drugs, proteolitic enzymes [17] and immobilization of the limb. As venous thromboembolism is a

Revised manuscript accepted for publication March 8, 2004

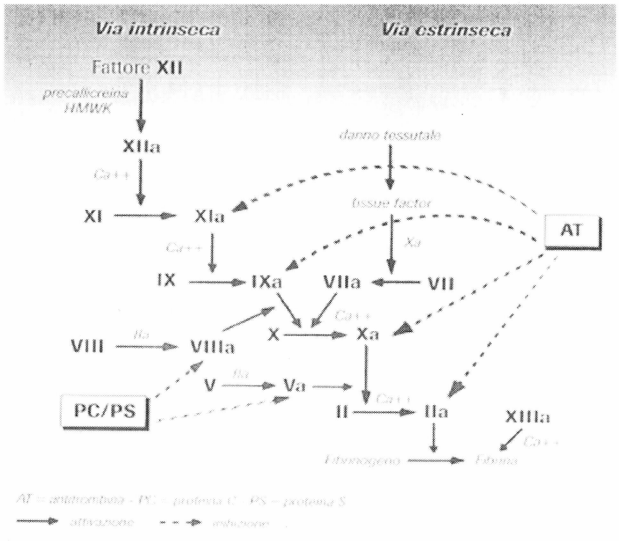


Figure 1. — Coagulation cascade.

leading cause of illness and death during pregnancy, the aim of this article was to estimate the role of systematic antepartum prophylaxis on DVT, describing a case report of DVT in puerperium of a 41-year-old woman who was hospitalized at the Department of Obstetrics and Gynaecology of the University of L'Aquila.

Case Report

We describe a case of a 41-year-old woman, gravida 5, para 1 at 37 weeks of gestation who was hospitalized for delivery at the Department of Obstetrics and Gynaecology of the University of L'Aquila.

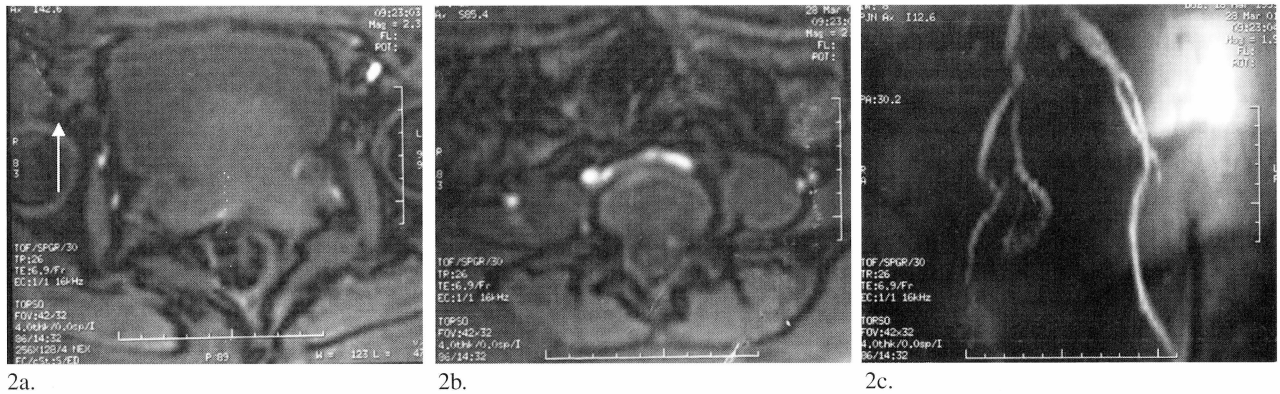
The pathological anamnesis showed a history of hepatitis A, appendix removal, tonsillectomy and uterine curettage for endometrial polyps. There was no venous thromboembolism in her familial and physiological history and she did not smoke or drink. Her menstrual cycle had always been regular. She had had three miscarriages, all in the first trimester of gestation. In 1999 she delivered at-term and following puerperium was regular. During the present pregnancy, because of the risk of miscarriage (in the first trimester), the patient underwent medical treatment (low-dose aspirin, 5 mg deltacortene, progesterone) and bedrest. Laboratory analyses and ultrasonographic examinations were in the norm. She weighed 75 k with a weight gain of 15 from the beginning of the pregnancy. The clinical examination did not show any oedema or varices. Since the beginning of her pregnancy, both uterine contractile activity and foetal cardiac frequency, and local obstetric conditions were taken into consideration.

On the grounds of favourable obstetric conditions, after seven hours of hospitalization the patient underwent amniocentesis with clear amniotic fluid. After two hours of labour, the patient delivered vaginally with a lateral episiotomy; the following afterbirth was spontaneous. Then she underwent the standard medical treatment (20 IU of oxitocin and 2 metilergometrin phials). Ten hours later the patient complained of a sensation of heaviness in her right leg together with a slight swelling. Clinical examination showed a blushed, hot, aching limb together with light oedema. Deep venous thrombosis (DVT) was immediately diagnosed so the patient underwent laboratory analyses to study the haemocoagulative parameters, all previously in the norm, and venous echocolor Doppler of the lower limbs. The echocolor Doppler report was "femoral venous thrombosis, external iliac venous thrombosis, recently arising and involving the internal saphenous vein for 2-3 cm and the common iliac vein with a continent and open deep venous circle on the left and an opening in the lower vena cava. Therefore the patient underwent venous MR and the report was "stoppage of the external iliac veins together with the common femoral vein". The caliber of the common iliac vein in its lower third part was smaller than the one on the opposite side. The inferior vena cava and the left femoral and common iliac veins were open (Figures 2a, b, c).

The patient underwent medical treatment consisting of low molecular weight heparin (12,500 IU u.c every 12 hours), betametasone disodium phosphate (1 mg every 12 hours) and nimesulide (50 mg every 12 hours) together with bedrest.

Eight days later, venous MR showed advancement of the iliac thrombosis going from the lower vena cava to the outlet of the renal veins but the thrombus was stuck to the vascular walls. Due to the continuation of the thrombosis, in spite of heparin therapy, nimesulide was suspended and the patient underwent treatment consisting of warfarin (5 mg every 12 hours) on the grounds of prothrombin (PT) and timed PT examinations together with heparin (5,000 IU every 12 hours).

Thirteen days after the last venous MR and 21 days after the delivery, the limb was very oedematous. Another venous MR confirmed common iliac vein thrombosis and inferior subrenal vena cava thrombosis. There were also paravertebral and genital collateral circles. The renal and inferior suprarenal cava veins were open. There were no floating thrombi. Thus anticoagula-



2a. 2b. 2c.

Figure 2a. — Veint-RM. Femoral common right vein thrombosis (signature)

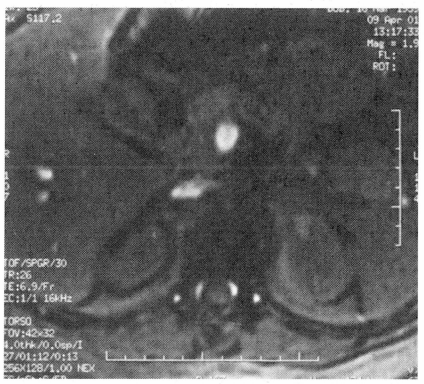


Figure 3a. — Vein-RM 8 days after.

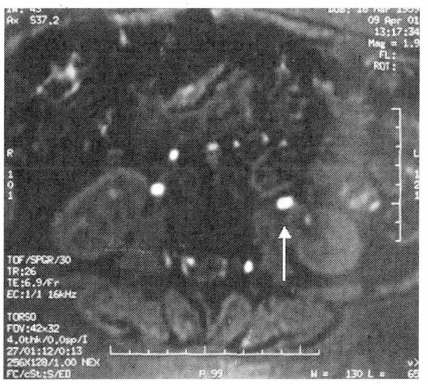


Figure 3b. — Inferior vein cava thrombosis and paravertebral and genital collateral circles (signature).

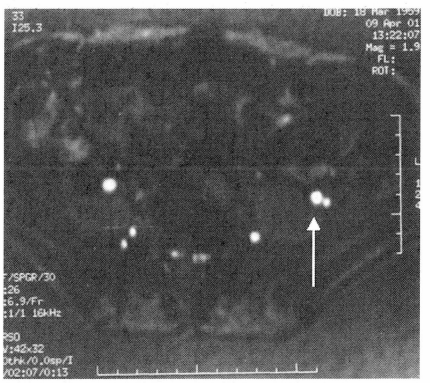


Figure 3c. — Collateral circles.

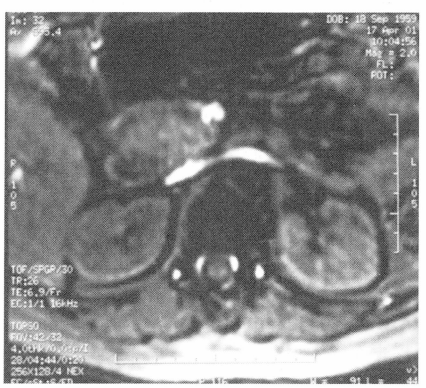


Figure 4a. — Clinical picture 21 days after.

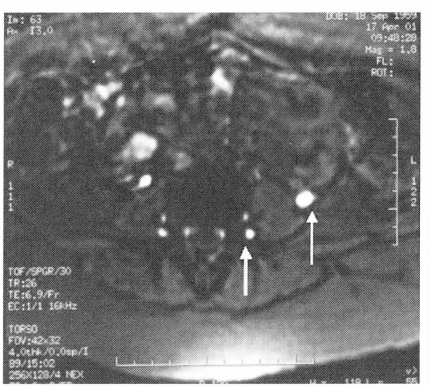


Figure 4b. — The some thrombosis with an increasing of the collateral circles (signature).

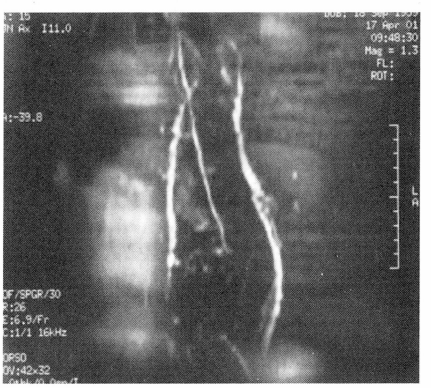


Figure 4c.

tion therapy was not stopped on the grounds of PT and the limb was wrapped with a compressive bandage. Thirty-seven days after the first diagnosis the inferior right limb was only a little greater than the one on the opposite side, especially the thigh. The patient was discharged from hospital with anticoagulative therapy. She underwent the therapy for 6-8 months and a venous MR within 30 days. This venous MR showed an unchanged clinical situation (Figure 5a, 5b). Three MR examinations every eight months showed the same clinical picture.

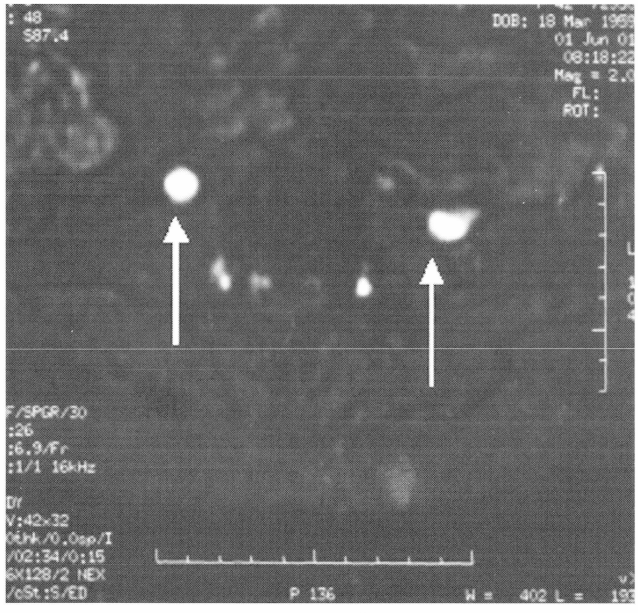
Discussion

Certainly, a significant risk factor for DVT is pregnancy. Several authors report that thromboembolic risk is higher during the puerperium period, whereas the incidence of pregnancy associated-DVT is no different for non pregnant women of similar age. Our case report should confirm this hypothesis. It is a particular case mostly with regard to the swiftness of the clinical evolution and the slow resolution, considering that the age (41 years old) was the only risk factor other than minor ones, and other thrombosis risk factors were lacking. There is ongoing debate as to whether pregnant women should routinely receive antepartum prophylactic anticoagulation therapy with heparin, considering the heparin-induced disadvantages, the high costs and its very little manageable use. Considering the recent data, should unfractionated heparin (twice daily at variable doses) or a single standard dose (0.3 ml/daily) of low-molecular weight heparin be used [19].

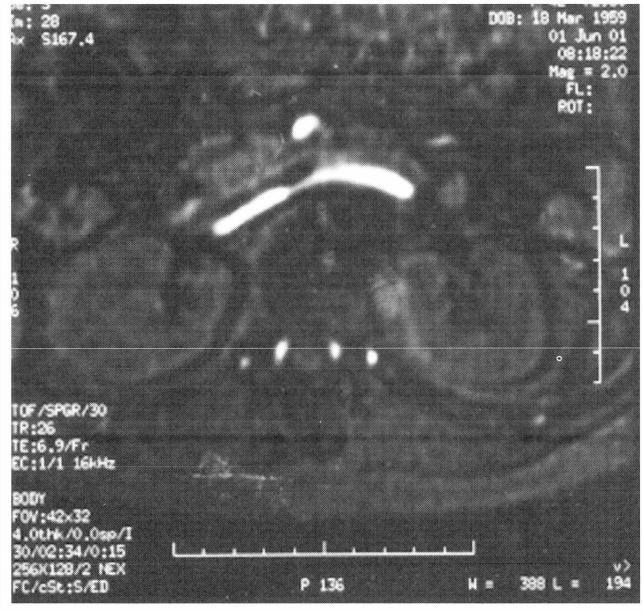
Today thromboprophylaxis centres largely use low-molecular weight heparin because it has substantial clinical and practical advantages compared with unfractionated heparin, particularly in terms of low haemorrhagic events, higher manageable use and a lower incidence of heparin-induced osteoporosis and thrombocytopenia [20, 21]. Heparin does not cross the placenta and is therefore the anticoagulant treatment of choice during pregnancy [22]. Based on our experience, considering patient risk, the costs and the disadvantages of clinical and instrumental examinations, the therapies and their negative effects, and mostly the very long patient convalescence without, up to now (3 years after) a *"real restitutio ad integrum"*, we believe that all women should routinely receive prophylactic heparin therapy during the postpartum period. This prophylaxis should be given, both after caesarean section and vaginal delivery, to all women with any thrombotic risk factor; the treatment should be made using the right therapeutic dose based on the different degrees of risk.

Consequently it should be useful to individualize different degrees of risk [23].

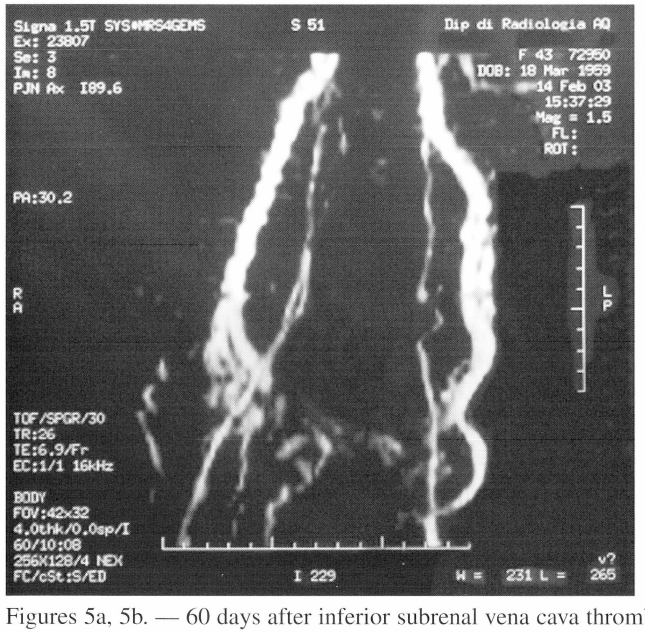
5a



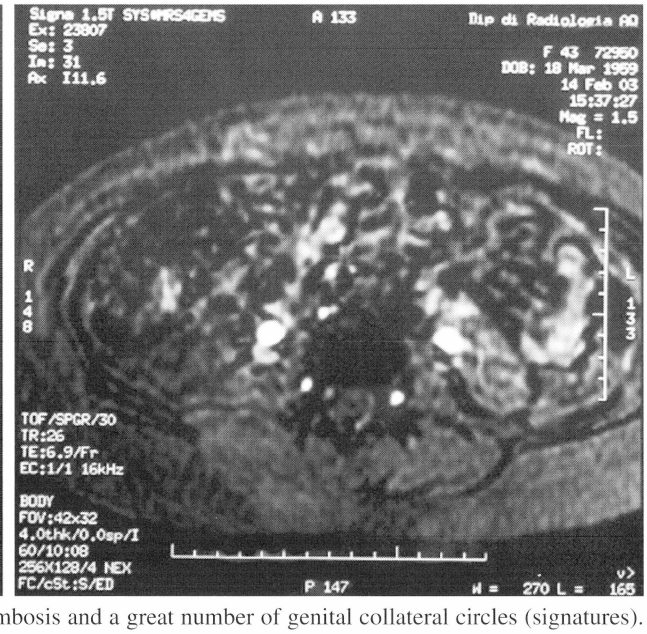
5b



6a



6b



Figures 5a, 5b. — 60 days after inferior subrenal vena cava thrombosis and a great number of genital collateral circles (signatures). Figures 6a, 6b.

– *High thrombotic risk:* patients who already received anticoagulant treatment before pregnancy; these women should be treated to obtain a modification of the coagulation time.

– *Medium thrombotic risk:* patients with a previous history of thromboembolism using unfractionated heparin (7,500-10,000 IU twice/daily).

– *Low thrombotic risk:* over 35 years, multiparous patients, suffering from varicose veins and chronic stasis of the lower limbs. In this group heparin prophylaxis should be given antepartum up to two weeks postpartum.

Pregnancy can reveal a primitive hypercoagulative status, generally replaced by other antithrombotic mechanisms [24]. We refer to congenital and familiar defects of coagulation proteins or the fibrinolitic system according to genetic mutations. Among these the most important are the the factor V mutation and the G20210A variation of the prothrombin gene. It has been estimated that the two mutations are relatively frequent in the general population.

Evaluation of the individual female thrombotic risk is very important to decide whether or not pregnant women should routinely receive prophylactic anticoagulation. Many authors have estimated this risk but they refer to too few case series to draw any conclusions. During pregnancy, prophylactic heparin should be given to all women after an accurate individual study (personal and familiar history, patient compliance) and after an estimate of the

risks/benefits of a very long pharmacological treatment. There are three possible clinical approaches: a watchful approach, without any therapy but with continuous patient examinations consisting of frequent Doppler every 4-6 weeks; antithrombotic prophylaxis mostly in the period of the highest thrombotic risk, which is 4-6 weeks postpartum; and lastly anticoagulant treatment throughout the pregnancy, starting during the first trimester up to 4-6 weeks postpartum. The watchful approach or the puerperium heparin prophylaxis should only be given to women with factor V Leiden or prothrombin gene G20210A mutations without symptoms. In case of previous venous thromboembolism during pregnancy, prophylactic heparin should be used starting during the first gestational weeks. Women with a high risk of DVT, such us patients with antithrombin deficiency, should routinely receive prophylactic anticoagulation starting the first trimester, apart from their personal history.

Today there are no indications with regard to routine screening of congenital thrombophilia because of the impossibility to understand the natural history of this problem and to give specific therapy. Furthermore, the cost of the screening is still too high with regard to the benefits of an early diagnosis [25].

Conclusions

Venous thromboembolism is a leading cause of illness and death during pregnancy and puerperium. Anticoagulant prophylaxis could reduce the incidence of this dangerous complication. There is ongoing debate regarding which women should routinely receive the anticoagulant treatment and regarding the modality of use. We should reflect upon the clinical and therapeutical management of venous thromboembolism, which occurs infrequently but, if underestimated, can produce severe complications and considerably increase health costs. A careful evalutation of thrombotic risk and presence of any risk factor (patient history) in our experience can indicate whether routine heparin prophylaxis is useful to avoid DVT and its consequences. A systematic examination during pregnancy of all the factors interfering with Virchow's triad and early heparin treatment for seven days (5,000 IU twice/daily) pre- and postpartum could prevent DVT and the consequences and problems such us radiological operations using Kim-Ray-Greenfield's filter, pulmonary embolism, high cost and finally the patient's quality of life.

References

[1] Letsky E.A.: "Peripartum prophylaxy of thromboembolism". *Billers Clin. Obstet. Gynecol.*, 1997, *11* (3), 523.
[2] Pavel J.L. *et al.*: "Hypercoaguable states as on evolving risk for spontaneous venous and arterial thrombosis". *J. Am. Coll. Surg.*, 1994, *178*, 266.
[3] Ray, Chan. *Obstet. Gynecol. Surv.*, 1999, *54*, 265.
[4] Ginsberg J.S *et al.*: "Venous thrombosis during pregnancy: Leg and trimester of presentation". *Thromb. Haemost.*, 1992, *67*, 519.
[5] Cockett F.B. *et al.*: "Iliac vein compression: its relations to ileofemoral thrombosis and the post-thrombotic syndrome". *Br. Med. J.*, 1967, *2*, 14.
[6] Martinelli I.: "Le mutazioni del fattore V e del fattore II della coagulazione". Rivista di attualità diagnostiche "ESA DIA", 2001, 20.
[7] National institute of Health Consensus Development Conference: "Preventuion of venous thrombosis and pulmonary embolism". *JAMA*, 1986, *256*, 744.
[8] Colman R.W. *et al.*: "Mechanism of platelet aggregation". In: "Haemostasis and Thrombosis: Basic Principles and Clinical Practice" (3rd edition), Philadelphia, J.B. Lippincott Company, 1994, 508.
[9] Weiner W. *et al.*: "Fibrin generation in normal pregnancy". *Obstet. Gynecol.*, 1984, 64, 46.
[10] Faught W. *et al.*: "Changes in protein C and protein S in normal pregnancy". *Am. J. Obstet. Gynecol.*, 1995, *172*, 147.
[11] Bremme K. *et al.*: "Enhanced thrombin generation and fibrinolitic activity in normal pregnancy and puerperium". *Obstet. Gynecol.*, 1992, *80*, 132.
[12] Greer I.A.: "Haemostasis and thrombosis in pregnancy. Haemostasis and Thrombosis". Edinburg: Churchill Livingstone, 1994, 987.
[13] Berquist D. *et al.*: "Pregnancy and venous thromboembolism". *Acta Obstet. Gynecol. Scand.*, 1983, *62*, 449.
[14] Ginsberg J.S *et al.*: "Use of antithrombotic agents during pregnancy embolism". *Chest.*, 1995, *108*, 305.
[15] Rick W.M.: "Amniotic fluid embolism". *Clin. Obstet. Gynecol.*, 1996, *39*, 101.
[16] Toglia M.R. *et al.*: "Venous thromboembolism during pregnancy". *N. Eng. J. Med.*, 1996, *335*, 108.
[17] Pescetto G. *et al.*: "Manuale di Ginecologia ed Ostetricia". Società Editoriale Universo, Roma, 1990, 30, 860.
[18] Cotroneo A.R. *et al.*: "Venous interuption as prophylaxis of pulmonary embolism: vena cava filters". *Rays*, 1996, *21*, 461.
[19] Patterson D.E. *et al.*: "Thrombolytic and endovascular treatment of peripartum iliac vein thrombosis: a case report". *J. Vasc. Surg.*, 1996, *24*, 1030.
[20] Department of Obstetrics and Gynecology, Glasgow Royal Infirmary; University of Glasgow: "The special case of venous thromboembolism in pregnancy". *Haemostasis*, 1998, *28* (suppl.), 22.
[21] Lindhoff Last E. *et al.*: "Current managment of thromboembolism in pregnancy and puerperium". *Zentrabl. Gynaecol.*, 2000, *122*, 4.
[22] Ketta N.I. *et al.*: "Postpartum cerebral thrombophlebitis. A case secondary to acquired antithrombin III deficency". *J. Obstet. Biol-reprod.*, 1998, *27*, 197.
[23] Roseberg R.D. *et al.*: "New insights into hypercoagulable states". *Hosp. Pract.*, 1986, *21*, 31.
[24] Greer I.A.: "Thrombosis series: thrombosis in pregnancy: maternal and fetal issue". *Lancet*, 1999, *353*, 1258.

Address reprint requests to:
L. DI STEFANO, M.D.
Ginecologia e Ostetricia
Div. Univ. - Dip. Disc. Chirurgiche
Blocco 11/A - Via Vetoio
67010 Coppito (AQ) Italy