Pregnancy and venous thrombosis

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GUALTIERO PALARETI

Dept. Angiology & Blood Coagulation "Marino Golinelli" University Hospital S. Orsola-Malpighi, Bologna, Italy
E-mail: palareti@tin.it

Epidemiology and pathophysiology

The risk of venous thromboembolism (VTE) during pregnancy and puerperium is markedly higher than in non-pregnant women of comparable age. In developed countries, where the mortality for other causes has been reduced, VTE is currently one of the most common cause of maternal mortality.[1,2] The incidence of VTE events is about 1/1000 women-y of pregnancy and more 7 out of 1000 women-y post partum; this represents a 2.5-fold increase in the risk of VTE during pregnancy and 20-fold increase during puerperium compared to non-pregnant women of comparable age.[3] The incidence of VTE in the United States has been estimated between 0.5 and 0.7 events/1000 deliveries for deep vein thrombosis (DVT), and between 1:2500 to 1:10,000 deliveries for pulmonary embolism (PE).[4] In the Swedish population the incidence of pregnancy-related VTE events was 13 per 10,000 deliveries.[5] In a recent study 6 that analyzed 21-year diagnostic trends for pregnancy-associated VTE in the United States, the rate of diagnosis of pregnancy-associated DVT was reported to be increased in the period between 1979 to 1999. Women who were pregnant had a 2.33-fold greater rate of diagnosis compared with non-pregnant women. Older age, being black, and delivery by cesarean section were associated with higher rates of DVT. This upward trend for pregnancy-associated DVT during the two last decades contrasted markedly with the declining trend observed in non-pregnant women in the general population.[7] The authors suggest this increasing trend in cases of pregnancy- associated DVT may be attributed to an increased clinician awareness and diagnostic surveillance, or to an increasing comorbidity during this period, which previously precluded conception.[6] A similar trend to an increasing incidence of DVT in pregnant women has also been observed in Denmark.[8]

Known risk factors for VTE can be found in many though not all patients. Previous history of VTE, age > 35 y, overweight, parity > 3, presence of medical complications or of congenital/acquired thrombophilic conditions and delivery by caesarean section are reported as risk factors for pregnancy-associated VTE.[9-11] A list of pre-existing and new or transient risk factors (drawn with modification from the Guideline No. 37 of Royal College of Obstetricians and Gynaecologists 12) is shown in Table 1.

DVT events during pregnancy occur with similar frequency in the three trimesters, though a higher portion of events has been reported to occur during the first 15 weeks' gestation 10. There is an almost general agreement that the incidence of VTE, and especially PE and death, is higher during the post- than pre-partum period. Delivery by caesarean section seems to be a particularly important risk factor. Bonnar, in an analysis of maternal deaths recorded between 1982 and 1993, found that more than a half of deaths (57/113) occurred after delivery, 40 of whom after caesarean delivery and 17 after vaginal delivery. More than three quarters of the post-partum maternal deaths caused by VTE recorded between 1991 and 1993 in the United Kingdom were associated with caesarean section.[13] In the Swedish population 5 the prevalence of significant thrombotic events after caesarean delivery was 0.9%, which was fivefold greater than among those who delivered vaginally. Furthermore, 41% of all post-partum VTE were associated with caesarean section and 76% of women who died for post-partum PE had had a caesarean delivery. Gherman et al. found that most of the PE occurred in the post-partum period (23 of 38, 60.5%) and were strongly associated with caesarean delivery (19 of 36,470 compared with 4 of 232,032, $p<.001$).[10]

Several studies have reported that the left leg is more commonly affected by venous thrombi during pregnancy than the right

leg 10, 14, likely due to compression of the left iliac vein by the right iliac artery when they cross.

Deep vein thrombosis: diagnosis

An objective VTE diagnosis is absolutely needed in suspected pregnant women to avoid an unnecessary, potentially harmful treatment. The diagnostic strategies for DVT are less well studied in pregnant women than in other patient populations. Clinical assessment, though less diagnostic in pregnant women than in the general population, due to the common presence of signs and symptoms in these subjects (such as leg swelling and pain) that can mimic a DVT, should however be the first approach in pregnant women with suspected DVT, with particular emphasis on their thrombotic history and on that of their family. The role of D-dimer assay is markedly limited by the fact that its levels rise with gestational age even in uncomplicated pregnancies;[15] the specificity of this assay is therefore very low. Notwithstanding this, the test can be performed and if the result is negative and associated with a low clinical probability a thrombotic process can be excluded. Ultrasonography (US) by an echocolordoppler instrument is the method of choice, mainly based on compression. The main aim is to assess the presence/absence of a proximal DVT. A normal compression US does not exclude calf DVT; the test should therefore be repeated several times if persistently normal (after 1-2 days and again after 4-5 days and in the following week) to exclude the possibility of a proximal extension of a calf DVT. Alternatively, an immediate and complete US examination of proximal and distal veins can be performed; however, if the result is negative but the clinical probability is moderate or high it is advisable to repeat examinations in the following days. It is well known that US has a limited ability in diagnosing a thrombotic process in the iliac vein, though its diagnostic ability can be improved by assessing with the doppler probe the absence of the phasic changes in the blood flow associated with the breath movements. When an isolated iliac DVT is suspected (back pain and swelling of the entire leg) and US is non-diagnostic or negative, a conclusive test is necessary, by using MRI or venography without lead shielding (the risks to the fetus caused by the radiation used in venography are negligible[16]).

Peculiar aspects of anticoagulant treatments in pregnancy

Both UFH and LMWH do not cross the placenta and therefore do not give risk of teratogenesis or fetal hemorrhage. On the contrary, warfarin crosses the placenta and an embryopathy may occur in 4-5% of fetuses exposed to the drug between 6 and 12 weeks of gestation.[17,18] Abnormalities in the central nervous system can occur after exposure to coumarin drugs during any trimester.[16] Coumarins add their anticoagulant effect to the lower concentrations of vitamin k-dependent coagulation factors normally present in the fetus, with a subsequent higher risk of bleeding, especially during delivery for the associated effect of trauma.[19] Coumarin drugs should therefore be avoided at least after 36 weeks gestation to not give an excessive risk of bleeding to both mother and fetus during the peripartum period.

Warfarin, UFH and LMWH are not secreted in breastmilk and can safely be given during lactation.

The rate of major bleedings during UFH treatment in pregnant women was reported to be of 2%.[20] In a recent systematic review this kind of complication was reported to be uncommon during LMWH treatment in pregnancy.[21] Besides the risk of bleeding, the disadvantages of a prolonged treatment with UFH or LMWH during pregnancy are osteoporosis, heparin-induced thrombocytopenia and allergy. LMWH appear to carry a lower risk of osteoporosis than UFH[22, 23,] of heparin-induced thrombocytopenia,[24] and on the whole to be safe in pregnancy.[25]

During pregnancy the woman weight changes and consequently also the volume of distribution of LMWH. The changes in renal function may also affect the pharmacokinetics of LMWH.[26] Different options have been proposed regarding the management of LMWH treatment for VTE during pregnancy:[27] a) to maintain the same LMWH dose throughout the pregnancy, b) to progressively adjust the dose in relation to the weight gain, and c) to monthly assess the heparin levels by performing the anti-Xa assay. In this case blood samples are taken 4-6 h after the morning dose and the LMWH dose is adjusted to maintain an anti-Xa level of 0.5-1.2 U/mL when the drug is administered twice-daily, or 1.0-2.0 U/mL if administered once-daily.[28] Some authors prefer the last option,[27] though no experimental evidences are available on this issue.

Treatment of DVT in pregnancy

In the case of high clinical suspicion of an acute VTE in a pregnant woman and a diagnostic test is not immediately available it is recommended to start the anticoagulant treatment even before having obtained objective diagnosis and to prolong it until the diagnosis has been confirmed or excluded. For the treatment of acute DVT in a pregnant woman a fixed-dose, weight-adjusted (according to the manufacturer's rec-

Table 1. Risk factors for venous thromboembolism in pregnancy and puerperium (modified from Royal College of Obstetricians and Gynaecologists.[12])

Pre-existing	*New onset or transient*
· Previous VTE	· Surgical procedure in pregnancy or puerperium
· Thrombophilia congenital or acquired	· Hyperemesis
· Age over 35 years	· Dehydration
· Obesity (BMI > 30 kg/m^2) either pre-pregnancy or in early pregnancy	· Ovarian hyperstimulation syndrome
· Parity > 4	· Severe infection
· Gross varicose veins	· Immobility (> 4 days bed rest)
· Paraplegia	· Pre-eclampsia
· Sickle cell disease	· Excessive blood loss
· Inflammatory disorders	· Long-haul travel
· Some medical disorders (e.g. nephrotic syndrome)	· Prolonged labour
· Myeloproliferative disorders (e.g. essential thrombocythaemia, polycythaemia vera)	· Midcavity instrumental delivery · Immobility after delivery

ommendations) subcutaneous LMWH administration is recommended, preferred over UFH and maintained throughout pregnancy.[27, 29] UFH can also be used for treatment. Initially an i.v. bolus is necessary followed by continuous infusion for at least 5 days to maintain the aPTT in the therapeutic range. Subsequently, adjusted-dose UFH can be administered s.c. and aPTT monitored every 1-2 weeks.

With DVT, the affected leg is elevated and a graduated elastic compression stocking is applied, worn throughout pregnancy and recommended for two years after the event to reduce the risk of post-thrombotic syndrome.

To reduce the risk of bleeding complications peripartum heparin treatment should be discontinued 24 hours before induction of labor or caesarean section. In case of very high risk of recurrent VTE (e.g. a VTE occurred in the previous 4 weeks) UFH can be administered i.v. till 4-6 h before the expected time of delivery or, alternatively, a temporal cava filter can be positioned. If spontaneous labor occurs in a woman receiving: a) adjusted-dose s.c. UFH, an aPTT determination is necessary and protamine administration should be evaluated, or b) fixed, weight-adjusted s.c. LMWH, the distance from the last administration should be considered and management regulated accordingly: if the interval period is very short an anti-Xa assay is recommendable (if available); epidural analgesia is avoided, protamine administration is considered, the obstetrician is alerted of the potential increased risk of bleeding. Postpartum, LMWH therapy is recommenced after the hemostatic conditions have been verified (usually within 12 h). Overlapping with OAT is started on the same day or a few days after. LMWH treatment is stopped when INR is > 2 for two consecutive days and OAT is given for not less than 6 weeks at 2.0-3.0 INR therapeutic range.

Thromboprophylaxis

All women should be assessed as soon as possible, ideally before pregnancy, for their VTE risk. It has been discussed before that pregnancy is a risk factor for VTE. Some women are at even higher risk during pregnancy because they have one or more additional risk factors (see Table 1). Women with previous VTE may be at an increased risk of recurrence in pregnancy.[30] In a prospective study performed in women with a previous VTE the rate of recurrent antepartum events was 2.4%, though it was higher (5.9%) in those women with abnormal laboratory results and/or whose previous thrombotic episode was idiopathic.[31] In a recent, large, retrospective cohort study, that included women who had at least one pregnancy after a VTE, the rate of VTE during pregnancy without thrombosis prophylaxis was 6.2%, whereas no VTE occurred in the women who had received prophylaxis.[32] The authors conclude that without thrombosis prophylaxis the risk for recurrent symptomatic VTE is substantial during the whole period of pregnancy and especially high in the postpartum period. It is recommended that women with a previous VTE have a careful history documented and undergo screening (before pregnancy) for inherited and acquired thrombophilia. Women with previous VTE and no thrombophilia should receive LMWH prophylaxis for six weeks after delivery. It still remains controversial whether they should also receive antenatal thromboprophylaxis; this procedure seems at the moment more recommendable in those whose

Table 2. Risk assessment profile for thromboembolic complications after caesarean section (from Bonnar[13] modified).

Low risk
- Elective caesarean delivery in woman with uncomplicated pregnancy and no other risk factors

Moderate risk
- Age > 35 years
- Obesity (> 80 kg)
- Parity =/> 4
- Presence of varicose veins
- Current infection
- Preeclampsia
- Immobility before surgery (> 4 days)
- Major current illness
- Emergency caesarean delivery during labor

High risk
- Presence of =/> 3 of the above risk factors
- Extended major pelvic or abdominal surgery
- Personal or family history of venous thromboembolism (longer period of prophylaxis)
- Congenital thrombophilia (longer period of prophylaxis)
- Acquired thrombophilia: lupus anticoagulant, antiphospholipid antibody (longer period of prophylaxis)
- Paralysis of lower limbs (longer period of prophylaxis)

previous episode was idiopathic or associated with persistent risk factors. Women with more than one previous VTE events or a previous VTE and a strong family history of VTE should receive thromboprophylaxis antepartum and for at least six weeks postpartum.

Women with thrombophilic alterations have an increased risk of VTE in pregnancy depending upon the specific thrombophilia and the presence of other risk factors. In women with asymptomatic inherited or acquired thrombophilia antenatal thromboprophylaxis can be evaluated case by case; however, since the postpartum period is that at the highest risk of VTE complications, it seems advisable to recommend them LMWH prophylaxis during 6 weeks after delivery.

A few data are available on VTE prophylaxis during pregnancy in women without previous VTE or thrombophilia. It has been suggested that women with three or more current or persisting risk factors (among those listed in Table 1) should be considered for prophylactic LMWH antenatally and for at least three to five days postpartum, while those with two factors be considered for prophylaxis only for three to five days after vaginal delivery.[12]

It has already been commented that the risk of VTE complications is highest in the postpartum and especially after caesarean section. However, the risk after caesarean section and the need for prophylaxis is not the same in all women. In line with Bonnar[13] the individual risk profile (see Table 2) should distinguish subjects at low, moderate and high risk. In cases with low risk, an early mobilization and hydration may be sufficient. Thromboprophylaxis should be considered for patients at moderate or high risk. In these cases LMWH prophylaxis should be administered for at least 5 days. The duration of prophylaxis should be longer in particularly high-risk women, such as women with a previous VTE or with ascertained thrombophilic alterations, involving all the puerperium period that is with the highest risk of thromboembolic complications. There may be a concern regarding a possible increase in the amount of bleeding after caesarean section, an operation which has a high operative blood loss, when prophylaxis with unfractionated heparin or LMWH is administered. No significant difference in the blood loss at elective caesarean section or in the puerperium has been reported when prophylaxis with low dose UFH was given.[33]

A recent retrospective study[34] has shown that administration of LMWH within 2 hours of caesarean section was associated with a higher rate of wound haematoma than when the interval was greater (12% vs 3%). A multivariate regression analysis indicated that administration of LMWH within 2 hours prior to delivery was the only statistically significant factor influencing the development of wound haematoma after caesarean section. It should be considered that peak activity of subcutaneous LMWH administration occurs after 3 to 4 hours. The adopted anaesthetic technique is also a factor influencing the timing of prophylaxis since it is well known that, due to the risk of spinal haematoma, an interval of at least 12 hours

is recommended between LMWH administration and regional anaesthetic manoeuvres. In line with these data, it is advisable to start thromboprohylaxis with LMWH at a sufficient time after surgery.

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