Significance, aetiology and prevention of venous thromboembolism in pregnancy and puerperium

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Introduction

Venous thromboembolism (VTE) complicates only 0.05–0.2% of all pregnancies, yet it is a leading cause of maternal morbidity in the western world, while pulmonary embolism (PE) is the cause of about 10% of all maternal deaths during pregnancy and puerperium 1–11.

Deep vein thrombosis (DVT) and PE are distinct but related aspects of the disease process called VTE 6, 10. This is a dynamic process which can be presented as acute form, with all clinical symptoms and signs, and as a silent, sub-clinical, chronic form, with the recurrence rate of 17.5% during the first two years, and 30.3% within eight years after the first episode 12. More than 60% of women develop chronic venous insufficiency due to postthrombotic syndrome, with leg swelling, pain, ulcerations and varices 11, 13, 14. The most significant consequence of VTE is massive PE, which may end by sudden death in 20% of cases, leaving no time for any medical intervention 10. Discovering such a state could be a diagnostic problem, but it was proven to be worth the effort, because appropriate diagnosis, prevention and treatment could reduce mortality rate from 20% to 0.7% 15.

Pregnancy itself is an independent risk factor for VTE (4–5 times higher risk than in non-pregnant women of similar age) and in puerperium the risk is even higher (from 15 up to 60 times) 1, 6, 8, 9, 11, 19–21. Pregnancy is associated with prothrombotic state, which is one of physiologic changes meant to protect pregnant women from peripartal haemorrhage, which is still the main cause of maternal mortality in the developing world 9, 16, 21. Beginning early in pregnancy, there is an increase of procoagulant factors and a decrease in the level of protein S, and a resistance to activated protein C 8, 9, 11, 18. Two other elements of Virchow’s triad are also present. Venous stasis is a consequence of mechanical obstruction of blood flow by gravid uterus, and of hormonally induced decrease in venous tone, resulting in slower blood flow in lower limbs. Endothelial damage is a result of tearing and distension during delivery 8, 9, 11, 18.

One of the characteristics of pregnancy-related DVT is 80–90% occurrence in the left leg (compared to 55% in non-pregnant patients), which is a consequence of the anatomy of the left common iliac vein 7, 9, 13, 22. More than 70% of gestational DVTs are located in the ileofemoral region (9% in non-pregnant patients), again predominantly on the left side; they are more likely to embolise (in 40–50% of cases), and are associated with low abdominal pain, mild fever and leukocytosis 23, 24.
Risk factors for venous thromboembolism

It is believed today that VTE is a convergence of underlying genetic predisposition – thrombophilia, and of acquired precipitating causes.12

Inherited thrombophilias

Factor V Leiden (FVL) is thrombophilia with high prevalence in general population; in 20–46% of pregnant women with VTE the heterozygous for FVL is found.1, 11 FVL is a single base pair mutation on a factor V gene that makes it resistant to inactivation by the activated protein C complex. This results in a loss of one of the normal protective antithrombotic mechanisms and increases the risk of VTE 41 times in homozygous and 2–16 times in heterozygous patients.5, 11. In the non-pregnant state, FVL deficiency makes it resistant to inactivation by the activated protein C complex. This results in a loss of one of the normal protective antithrombotic mechanisms25 and increases the risk of VTE 41 times in homozygous and 2–16 times in heterozygous patients.5, 11. In the non-pregnant state, FVL deficiency equally leads to DVT and PE; in pregnancy DVT dominates, probably because FVL is here associated with a more adherent and stable thrombus, due to increased local thrombin generation, which reduces the probability of embolisation.11

Mutation on a 20210 nucleotide on a prothrombin gene (G20210A) increases plasma prothrombin concentration, with consequent increased risk of myocardial infarct, cerebral venous thrombosis and VTE.25 In pregnancy it increases the risk of VTE 3–10 times, and it is found in 20% of gestational VTE.5

Hyperhomocysteinemia is rare in pregnancy, because of pregnancy-related physiological reduction in homocysteine3, 26. Protein S, protein C and antithrombin (AT III) deficiency are less common. The prevalence of AT III deficiency in women with pregnancy-associated VTE is 1–19%, the prevalence of protein C deficiency 2–14%, and for protein S deficiency 1–12%11. The risk of pregnancy-associated VTE in cases of AT III deficiency type I (quantitative) was found to be 1:2.8, and for type II (qualitative) 1:42 patients with no previous history of VTE. This leads to more aggressive thrombophrophylaxis in pregnancy for AT III deficient patients.37 AT III deficiency mainly leads to DVT, often in uncommon regions: kidney, retina, mesenterium, upper limbs, vena cava. In cases of protein C and protein S deficiency the risk of VTE is increased 2–4 and 3 fold respectively.5 One should keep in mind that there are numerous conditions that influence thrombophilia screen: liver disease, as well as pregnancy itself, lower protein C and S levels; severe infection, nephrotic syndrome, massive thrombosis lower AT III level, so laboratory results should be carefully interpreted.28

4G/5G sequence polymorphism in PAI 1 (plasminogen activator inhibitor 1) gene promoter: PAI 1 is produced by endothelial, smooth muscle, liver cells and platelets and represents a principal inhibitor of fibrinolysis. Its plasma level steadily increases during pregnancy and at term it is 3 fold higher than in the non-pregnancy state; there is also PAI 2, produced by placenta.29, 50 They both contribute to hypercoagulable state seen in every pregnancy. DVT risk could be augmented by the presence of mutation changes on 4G/5G base-pair region on PAI 1 gene, that modulate PAI 1 synthesis.4G allele is too small to bind gene transcriptional repressors, so 4G/4G allele homozygosity leads to 3–5 fold higher level of circulating PAI 1, and was associated with metabolic syndrome and a greater risk for cardiovascular and thrombotic disease.30–35 Sartori et al. report a greater risk of thrombosis both in symptomatic thrombophilic patients (OR 2.85, 95% CI 1.26–4.46) and idiopathic DVT patients (OR 3.1, 95% CI 1.26–7.59) with 4G/4G phenotype. In pregnancy, this disorder is frequently associated with FVL mutation, or antiphospholipid syndrome, or protein S deficiency, further predisposing these women to thrombosis as well as implantation failure.30, 32, 35, 37, 38

It should be mentioned that the inherited thrombophilias are involved in development of other obstetrics complications associated with insufficient fetomaternal circulation and failure of implantation, such as early and late abortion, preeclampsia, placental abruption, fetal intrauterine growth restriction (IUGR).25, 39–41.

Inherited thrombophilias are proven to be the cause of gestational VTE in 20–50%25 and represent a danger that should not be underestimated.2, 3, 7, 10. On the other hand, thromboprophylaxis itself could be risky for both fetus and mother; so one should be rational, meaning that one should estimate the risk and identify patients who really need thromboprophylaxis. Estimated risk of pregnancy-associated VTE in thrombophilic women without prior VTE (odds ratio) is 34.4 for FVL homozygosity, 8.32 for heterozygosity; 26.6 for homozygous prothrombin gene mutation 6.8 for heterozygous; 4.76 for antithrombin, 4.76 for protein C and 2.19 for protein S deficiency9, 20, 26, 42, 43 (Table 1).

Table 1

<table>
<thead>
<tr>
<th>Type of pregnancy-associated venous thromboembolism (VTE) in women with thrombophilia and without previous VTE</th>
<th>Relative VTE risk OR (95% CI)</th>
<th>Estimated absolute VTE risk (per 1,000 patients)</th>
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</thead>
<tbody>
<tr>
<td>AT III deficiency</td>
<td>4.7 (1.5–17.0)</td>
<td>4/1000</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>4.8 (2.2–10.6)</td>
<td>4/1000</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>3.2 (1.5–6.9)</td>
<td>3/1000</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>homozygous</td>
<td>34.4 (9.9–121)</td>
<td>34/1000</td>
</tr>
<tr>
<td>heterozygous</td>
<td>8.3 (5.4–12.7)</td>
<td>8/1000</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>homozygous</td>
<td>26.4 (1.2–559.2)</td>
<td>26/1000</td>
</tr>
<tr>
<td>heterozygous</td>
<td>6.8 (2.5–18.8)</td>
<td>6/1000</td>
</tr>
<tr>
<td>MTHFR C677T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>homozygous</td>
<td>0.74 (0.22–2.48)</td>
<td>1/1000</td>
</tr>
</tbody>
</table>

OR = odds ratio; CI = confidence interval; AT III – antithrombin III; MTHFR – methylene tetrahydrofolate reductase.
Based on these estimates, in cases of thrombophilia with no prior VTE the American College of Chest Physicians (ACCP) recommends antepartum low-molecular weight heparin (LMWH) prophylaxis only for homozygous women with FVL or prothrombin gene mutations, who have a positive family history for VTE. Stratta et al. emphasized that a low dose LMWH might not be sufficient in 5.5% VTE recurrence, all in the high risk group and concluded that antepartum prophylaxis in women with intermediate risk for VTE (during six weeks postpartum) and with high risk (during entire pregnancy and six weeks postpartum). They had experienced VTE related to a temporary risk factor. This study challenged the assumption that all women with the history of VTE should receive antepartal thromboprophylaxis. In their retrospective cohort study Roeters Van Lennep et al. tried to evaluate effectiveness of low doses of LMWH prophylaxis in women with intermediate risk for VTE (during six weeks postpartum) and with high risk (during entire pregnancy and six weeks postpartum). They had 5.5% VTE recurrence, all in the high risk group and concluded that a low dose LMWH might not be sufficient in the high risk pregnant patients. Stratta et al. emphasize that it is important to estimate the risk properly and determine the appropriate LMWH dose and dosing regimen (once/twice daily) for each risk level. Thus, although available data from clinical trials are not completely uniform, it can be concluded that even though pregnancy increases the risk of VTE recurrence, antepartal prophylaxis is not routinely recommended. It should be applied in patients with idiopathic first VTE episode, in the presence of an underlying thrombophilia, in women who used oral contraceptives. Puerperium is by all means a period that demands prophylaxis and, in cases of higher risk, even augmentation of the usual doses. Phabinger et al. studied the risk of VTE recurrence in pregnancy without antepartal thromboprophylaxis and found that antepartal risk was 6.2%, and postpartal 6.5%. Antiphospholipid-antibody syndrome (APLA) leads to recurrent arterial and venous thrombosis, as well as other pregnancy complications (spontaneous abortion, preeclampsia, IUGR). APLA presence affects almost all haemostatic factors, provoking thrombotic diathesis, complement activation, inflammation, disbalance of angiogenic factors and disturbance of normal fetoplacental development. Anticomplemental and vasomodulatory action of heparin make this drug irreplaceable in prevention of APLA complications in pregnancy. ACCP recommends antepartum administration of heparin combined with a low dose aspirin (75–100 mg/day).

After Caesarean section the prevalence of clinically significant VTE is 0.9%. We should consider thromboprophylaxis in women older than 35 years, with body mass over 90 kg, with present infection, varicous veins, gestational hypertension, multiparity, VTE in anamnesis, emergency Caesarean section or hysterectomy after Caesarean section.

Assisted reproductive treatment (ART) also represents a risk factor for VTE, especially when associated with ovarian hyperstimulation syndrome (OHSS). It is believed that this is a consequence of 10 fold increased estradiol levels by hormonal stimulation, increased coagulation factors concentration and decreased fibrinolysis. Thrombosis typically occurs between the 7th and 10th week of gestation, located in about 60% in upper limbs, neck and head veins. In cases of pregnancies after ART routine thromboprophylaxis is not recommended, but in cases of OHSS, LMWH prophylaxis is recommended after a resolution of the syndrome.

Preeclampsia was found to increase three fold the risk of VTE in the third trimester and postpartum. Preeclampsia is a consequence of maternal immunologic maladaptation to fetal and placental tissue, resulting in generalised endothelial insufficiency, disturbed eikosanoid metabolism, lipid peroxidation, inflammation, activation of complement system and coagulation cascade. There are numerous studies that connect inherited thrombophilias and preeclampsia. Heparin and low-dose aspirin are used to treat preeclampsia and inflammatory disorders in such situations.

Among other risk factors (advanced age, parity, maternal morbidity etc) maternal obesity should not be forgotten, because it is a global epidemic nowadays. Hypercoagulability, venous stasis and endothelial dysfunction in pregnancy are exacerbated by obesity. Body mass index (BMI) over 30 kg/m² increases the risk for VTE 1.5–5.3 fold, so it is recommended that all women with morbid obesity (BMI over 40 kg/m²) receive seven days postpartal LMWH prophylaxis. In cases of increased body mass higher LMWH doses may be needed, but dose estimation according to actual body weight could lead to overdosing. In such cases it would be wiser to use lean body weight for appropriate dosing, with plasma anti-factor Xa level monitoring.

We thought it would be interesting to mention a study of Jakobsen et al. who investigated ante- and postpartal factors for development of VTE. To antepartal risk factors already mentioned in the literature (age older than 35 years, multiple pregnancy, blood group A, obesity, smoking), they added pregnancy after assisted reproductive treatment, gestational diabetes, nulliparity, weight gain in pregnancy less than 7 kg. The authors found that besides the age over 35 years, operative delivery, hypertension, blood group A, postpartal risk factors were emergency Caesarean section, haemorrhage or infection, preeclampsia, IUGR, assisted reproductive treatment, smoking. Immobilisation, especially in combination with higher BMI, represents an important risk factor ante- and postpartaly.

Medication options for thromboprophylaxis in pregnancy and puerperium

The goal of thromboprophylaxis is to provide VTE protection with minimal side effects for the mother and no effects on the fetus. Although today we have a huge choice of anticoagulant and antiplatelet agents, heparin is still the anticoagulant of choice for VTE prophylaxis and treatment in pregnancy. Effective anticoagulation can be achieved (based on anti-Xa level) or UFH used instead.

Heparin, neither unfractionated (UFH) nor LMVH, crosses the placenta; it is not secreted in breast milk, it is not teratogenic and there is no evidence of risk of fetal haemorrhage. Currently, LMWHs have replaced UFH as the first choice anticoagulant. LMWHs are at least as effective as UFH, but produce more predictable anticoagulant response due to better bioavailability (90–100% after subcutaneous administration), longer half life (4–6 h), dose-independent renal clearance, decreased affinity for heparin-binding proteins, endothelial cells and macrophages. Effective anticoagulation can be achieved by subcutaneous application of LMWH once daily, with no need for routine laboratory monitoring of anti-factor Xa activity in plasma.

Nevertheless, in certain situations LMWH dose adjustment is necessary and that demands anti-Xa level assessment. Pregnancy changes LMWH pharmacokinetics. Together with the increase of cardiac output and plasma volume, glomerular filtration rate progressively increases from the first trimester; at term it is 50–60% higher than in the non-pregnant state, with increased volume of distribution and drug clearance. This could result in subprophylactic anti-Xa level in 26% of patients. Anti-Xa activity is inversely related to body weight, so LMWH doses should be modified in cases of maternal obesity. On the other hand, in patients with renal disease and creatinine clearance below 30 mL/min, standard LMWH doses may lead to accumulation of heparin, higher anti-Xa level and increased risk of bleeding. In such cases LMWH dose should be reduced (based on anti-Xa level) or UFH used instead.

According to dose regimen, LMWH doses used for VTE prophylaxis in pregnancy could be prophylactic (for example dalteparin 5000 units or enoxaparine 40 mg, subcutaneously every 24), intermediate (dalteparin 5000 units or enoxaparine 40 mg, subcutaneously every 12) or adjusted (dalteparin 200 units/kg once daily or 100 units/kg/12 h; enoxaparin 1 mg/kg/12 h) (Table 2). More favorable anti-Xa/IIa ratio of LMWHs comparing to UFH (2–4 : 1), significantly lowers the risk of haemorrhage (1–2%, and mostly related to obstetric causes). Prolonged use of UFH increases risk of osteoporosis, with 2–3% incidence of osteoporotic fractures and significant reduction in bone density in up to 30% of patients. After LMWH therapy bone mass reduction equals physiological bone mass reduction in pregnancy. Heparin induced thrombocytopenia with or without thrombosis (HIT/HITT), carries 1–3% risk with UFH and is 10 fold less frequent after LMWH than after UFH therapy. The risk is indeed very low in obstetric patients receiving LMWH, so routine platelet monitoring is not recommended. Cutaneous allergic reactions (delayed type 4 hypersensitivity reaction) occur more frequently in pregnancy (1.8–29%) than in general population, but they are seldom severe. This problem may be resolved by switching to another LMWH preparation or danaparoid or fondaparinux. One further advantage of LMWH over UFH is significantly less procoagulant “rebound effect” after withdrawal of the therapy.

At the time of delivery LMWH advantages may become disadvantages: anticoagulant effect can persist more than 12 h after the last dose and protamin sulfate cannot neutralise its action completely in case of need (anti-Xa effect remains), so peripartal haemorrhage can occur. LMWH discontinuation is recommended 24 h before induction of labour or planned Caesarean section. High risk patients can be converted to intravenous UFH (aPTT monitoring required), which can than be stopped 4–6 h before the induction of labour. If haemostasis is adequate, thromboprophylaxis could be continued 12–12 h after vaginal and 12–24 h after Caesarean delivery.

With the increased use of neuraxial anesthesia in labor, we should be aware of its possible complication – spinal haemathoma with subsequent paraplegia. In order to reduce the risk of such event, epidural catheter can be safely inserted 12 h after prophylactic and 24 h after therapeutic LMWH dose; it can be removed 12 h after the last dose. Anticoagulation can be restarted 4–24 h after catheter removal.

Warfarin crosses the placenta and has proven teratogenicity. Coumarin embriopathy is dose-dependent (more than 5 mg/24 h) and occurs in 5% of cases exposed between the 6th and 12th gestational weeks, so in this period warfarin is contraindicated. The first trimester warfarin exposure leads to abortion; later exposure may be associated with fetal haemorrhage, CNS abnormalities, child’s mental

<table>
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<th>Table 2</th>
<th>Thromboprophylactic low-molecular weight heparin (LMWH) dose regimen in pregnancy/puerperium</th>
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<tbody>
<tr>
<td><strong>LMWH</strong></td>
<td><strong>Subcutaneous doses (for women weighting 50–90 kg)</strong></td>
</tr>
<tr>
<td></td>
<td>prophylactic (low)</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>40 mg/24 h</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>5000 U/24 h</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>4500 U/24 h</td>
</tr>
</tbody>
</table>
retardation and increased risk of placental abruption and postpartum haemorrhage. The use of warfarin in pregnancy can be justified in case of women with mechanical heart valves, where benefit outweighs the risk. In all the other cases it should be replaced by heparin as soon as patient finds that she is pregnant. Since it is not secreted in breast milk, warfarin is safe to use during breastfeeding, although it requires close monitoring.

Dextran is today practically abandoned in obstetrics, because of the risk of anaphylaxis associated with uterine hypertonus, profound fetal distress and even death.

Danaparoid – experience is limited with its use; crossing the placenta and secretion in breast milk were not found, but still its only indication in pregnancy for the time being is complication of heparin therapy. In the newest ACCP recommendations danaparoid is suggested over lepirudin or fondaparinux for treatment of HIT during pregnancy.

Fondaparinux – during its use 10% of anti-Xa activity in mother’s plasma was found in umbilical blood; although there were no fetal complications, it is still early to conclude that fondaparinux is safe for use in pregnancy. It has been used in pregnant patients with HIT.

Graduated elastic compression stockings (GCS) is recommended when LMWH is contraindicated, or in combination with LMWH after Caesarean section in the presence of several risk factors, or in pregnant women travelling by air longer than 4 h. Using GCS also reduces the risk of postthrombotic syndrome.

During lactation warfarin, LMWH, UFH, danaparoid and hirudin are allowed; pentasacharides (fondaparinux) are not recommended.

**Recommendations for venous thromboembolism prophylaxis in pregnancy and puerperium**

In order to diminish the risk of VTE in pregnancy/ puerperium all women should undergo assessment of the risk factors for VTE in early pregnancy or, ideally, before pregnancy. This assessment should be repeated during pregnancy, before and after the labor. Based on this assessment an thromboprophylactic plan should be made with haematologist or other experts if needed.

Patients with very high VTE risk are those with previous VTE on the long term warfarin/AT III deficiency/APLA with previous VTE. For them, antepartal high dose LMWH and at least 6 weeks postpartal LMWH or warfarin are recommended.

Women with previous recurrent or unprovoked or estrogen provoked VTE, previous VTE with thrombophilia or with family history of VTE and those with asymptomatic thrombophilia (homozygous for FVL or prothrombin gene mutation) with positive VTE family history, are in high VTE risk. For them antepartal and 6 weeks postpartal LMWH prophylaxis is recommended.

Women with intermediate VTE risk are those with single previous VTE provoked by transient risk factor no longer present, without thrombophilia, family history, or other risk factors and those with mild asymptomatic thrombophilia or with medical comorbidities, or BMI over 40 kg/m². In this group consider antepartal LMWH prophylaxis and apply 7 days–6 weeks postpartal prophylaxis.

Lower-risk group consists of women older than 35 years, with BMI higher than 30 kg/m², or systemic infection, or OHSS, preeclampsia, ART, immobility, varicous veins, multiple pregnancies, operative delivery, postpartal blood loss more than 1,000 mL. If there is a combination of more than three of those risk factors antepartum and more than two postpartum, LMWH prophylaxis is given antepartum and at least 7 days postpartum. If there is less than three factors ante- and two postpartum, early mobilization and rehydration are sufficient.

Recommendations for thromboprophylaxis in pregnancy/ puerperium according to risk assessment are summarised in the Table 3.

We should emphasize that those recommendations are not meant to dictate the definite course of management; they should, of course, be adjusted to individual patient.

**Conclusion**

Venous thromboembolism although relatively rare in pregnancy, is a serious problem with hard consequences, so it deserves and demands medical attention. The fact that recognizing risk factors and performing adequate prophylaxis significantly reduces the incidence of venous thromboembolism, obligates us to an active relation towards this problem.

<table>
<thead>
<tr>
<th>Risk assessment</th>
<th>Antepartal</th>
<th>Postpartal</th>
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<tbody>
<tr>
<td><strong>Risk factors</strong></td>
<td>Risk factors</td>
<td>Thromboprophylaxis</td>
</tr>
<tr>
<td>Very high</td>
<td>AT III deficiency</td>
<td>high dose LMWH</td>
</tr>
<tr>
<td>- recurrent VTE</td>
<td>or APLA</td>
<td>at least 6 weeks high dose</td>
</tr>
<tr>
<td>High</td>
<td>documented thrombophilia</td>
<td>LMWH/warfarin</td>
</tr>
<tr>
<td>- previous VTE (unprovoked or idiopathic or estrogen-provoked)</td>
<td>positive family history of VTE</td>
<td>prophylactic 6 weeks</td>
</tr>
<tr>
<td>- asymptomatic thrombophilia (homozygous for FVL or homozygous for prothrombin gene mutation or combined defects)</td>
<td>positive family history of VTE</td>
<td>prophylactic dose or intermediate dose</td>
</tr>
</tbody>
</table>


Intermediate
- previous VTE (provoked by a transient risk factor no longer present, without other risk factors)
- asymptomatic thrombophilia (other than those mentioned above)
- medical comorbidities (heart/lung/sickle cell/inflammatory disease/SLE/cancer/nephrotic sy/surgical procedure/BMI > 40 kg/m²)

Lower risk
- age > 35 years
- BMI > 30 kg/m²
- parity > 3
- gross varicose veins
- immobility
- preeclampsia
- dehydration/hyperemesis
- OHSS / ART
- multiple pregnancy
- smoker
- current infection
- postnatal:
  - Caesarean section,
  - prolonged labour
  - postpartal haemorrhage > 1 L
  - or blood transfusion


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