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Screening for thrombophilia and antithrombotic prophylaxis in pregnancy: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET)

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ABSTRACT

The term thrombophilia describes an increased tendency to develop thrombosis and many laboratory markers with different strengths of association with thrombosis have been identified. The main causes of maternal mortality and morbidity in developed countries is venous thromboembolism (VTE) and obstetric complications. During pregnancy and puerperium the risk for VTE increases due to hemostatic imbalance towards a prothrombotic state, and it is further increased in women carriers of thrombophilia; recent studies have also demonstrated an association between thrombophilia and obstetric complications. These complications are, therefore, considered potentially preventable with the prophylactic administration of anticoagulant drugs, although their efficacy is not proven by data from randomized controlled trials. After a systematic comprehensive literature review and using a rigorous methodology, the expert panel formulated recommendations regarding the usefulness of screening for thrombophilia in pregnancy to identify high-risk women and for the management of antithrombotic prophyalxis. When evidence is lacking, consensus-based recommendations are provided.

Introduction

Thrombophilia includes a heterogenous group of inherited or acquired disorders that cause a tendency towards venous or arterial thrombosis and it is associated with obstetric complications such as recurrent pregnancy loss (RPL) (≥3, or 2 in the presence of at least one normal fetal karyotype), unexplained intrauterine fetal death (IUFD), preeclampsia, HELLP syndrome, fetal growth restriction (FGR) and abruptio placentae. The pathophysiologic mechanisms underlying the association of inherited thrombophilia and pregnancy complications are not at all clear and are presumably related to vascular problems such as placenta thrombosis.

The association of thrombophilia and pregnancy complications is controversial and limited by the small sample size of some studies. Identification of high-risk women is crucial in order to institute the appropriate prophylaxis of these complications. Drugs that prevent the formation of thrombosis are potentially useful and, based on the association between thrombophilia and venous thrombosis and the placenta-mediated pregnancy complications, women with a positive history are advised about the indication for anticoagulant treatment although the efficacy of heparins in this setting is not supported by data from randomized controlled trials.

The objectives of these guidelines are to critically evaluate: i) the usefulness of performing screening for thrombophilia to identify high-risk women; ii) the tests to be included in thrombophilia screening for pregnant women; iii) the optimal pharmacological management in order to prevent venous thromboembolism (VTE) and obstetric complications.

Materials and Methods

The methodology used for developing SISET guidelines has been previously reported [1]. The working group was composed of two

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methodologists, nine experts in this field and one specialized in legal medicine. The literature search to support the recommendations was performed using the following sources: literature databases (MEDLINE, EMBASE, Cochrane Library), reference lists of selected papers and narrative reviews, editorials, guidelines and direct consultation with field experts. The list of papers was updated in December 2008. The Scottish Intercollegiate Guideline Network (SIGN) level of evidence system was adopted for treatment issues [2] and that proposed by the National Institute for Clinical Excellence (NICE) for diagnostic issues [3]. In accordance with outstanding international organizations, the SISET guidelines used the grading system proposed by SIGN/NICE to formulate some evidence-based recommendations and expertise-based recommendations when relevant areas could not be addressed by the available evidence. The full body of recommendations was discussed and approved during 3 meetings held in Bologna between June 2006 and May 2008.

Definitions

The present guidelines adapted the following definitions: 1) Recurrent pregnancy loss: ≥3, or 2 in the presence of at least one normal fetal karyotype; 2) Ante-partum: as soon as possible during pregnancy.

Screening for Thrombophilia in Pregnancy

Maternal mortality due to hemorrage has been reduced in developed countries, while VTE together with obstetric complications, such as RPL, unexplained IUFD, preeclampsia, HELLP syndrome, FGR and abruptio placentae are the main causes of maternal mortality and morbidity. During pregnancy and puerperium the risk for VTE increases due to hemostatic imbalance towards a prothrombotic state and it is further increased in women carriers of thrombophilia [4]. The incidence of VTE during pregnancy is 1 per 1.000 deliveries [5–7], with a 5 fold increase during puerperium [5]. Pregnant women carriers of thrombophilia have an increased risk of VTE by 3 to 52 fold depending on the type of thrombophilic defect [4,8–11]. Thrombophilia is also associated with pregnancy complications and the strength of this association is controversial depending on the type of obstetric complication and of specific thrombophilia [12,13].

Due to the low prevalence of some types of thrombophilic genotype and to the objective difficulty to perform research involving pregnant women, the available literature is generally of poor quality. In this section we describe the results of a systematic literature review and the recommendations for an appropriate use of thrombophilia screening.

Tests to be included in the screening for thrombophilia, if testing is indicated

Several studies, including systematic reviews and meta-analyses, evaluated the association between thrombophilia and VTE or obstetric complications [12–22]. The meta-analyses of heterogenous case-control studies suggest an increased prevalence in women with pregnancy complications of the following thrombophilic defects: antithrombin deficiency, protein C deficiency, protein S deficiency, factor V Leiden mutation (FVL), prothrombin 20210A mutation (PTM), mild hyperhomocysteinemia and antiphospholipid antibodies (APLA). We used as definition of APLA the criteria established by the "International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome" published in 2006 [23]. There is not enough evidence of association between pregnancy complications and the following laboratory tests: levels of FVIII, FIX, FXI, and FXII; polymorphisms of the FXIII, MTHFR, and PAI-1 genes, and polymorphisms of the factor V or II genes different from FVL or PTM. Table 1 summarizes the association between inherited thrombophilia and pregnancy complications for the tests suggested, reporting data from the more complete meta-analyses.

Normal pregnancy is associated with major changes in hemostatic balance and laboratory markers, such as the fall in free protein S levels or the reduction in activated protein C (APC) sensitivity. For these reasons it is preferable to perform thrombophilia tests, when possible, before pregnancy.

Recommendation

We suggest including the following tests in the screening for thrombophilia in pregnancy: antithrombin, protein C, protein S, activated protein C resistance and/or FVL, PTM, homocysteine, APLA (Grade A). It is advisable to perform screening for thrombophilia before pregnancy. If the screening is performed during pregnancy the results should be interpreted with great caution and in some cases completed with a family study.

Testing asymptomatic women for thrombophilia

Universal screening for thrombophilia in pregnant women

A large number of studies in literature is available which includes cohort studies and systematic reviews on the association between thrombophilia and the risk of VTE and obstetric complications. Systematic reviews are limited by the underlying published studies, the majority of which are retrospective giving an estimate of the magnitude of the increased risk of pregnancy complications which is

Table 1
Association between inherited thrombophilia and pregnancy complications.

	Meta-analysis	VTE	Recurrent pregnancy loss	Unexplained intrauterine death	Pre-eclampsia	FGR	Abruptio
Factor V Leiden (heterozygous)	Robertson et al. [14]	8.3 (5.4-12.7)	1.9 (1.0-3.6)§	2.1 (1.1-3.9)	2.2 (1.5-3.3)	2.7 (0.6-12.1)	4.7 (1.1-19.6)
	Rey et al. [12]	N.A.	2.0 (1.1-3.6)*	3.3 (1.8-5.8)	N.A.	N.A.	N.A.
	Kovalevsky et al. [15]	N.A.	2.2 (1.4-3.3)	N.A.	N.A.	N.A.	N.A.
Factor V Leiden (homozygous)	Robertson et al. [14]	34.4 (9.8-120.1)	N.A.	2.0 (0.4-9.7)	1.9 (0.4-7.9)	4.6 (0.2-115.7)	8.4 (0.4-171.2)
Prothrombin mutation (heterozygous)	Robertson et al. [14]	6.8 (2.5-18.8)	2.7 (1.4-5.3)§	2.7 (1.3-5.5)	2.5 (1.5-4.2)	2.9 (0.6-13.7)	7.7 (3.0-19.8)
	Rey et al. [12]	N.A.	2.1 (1.2-3.5) *	2.3 (1.1-4.9)	N.A.	N.A.	N.A.
	Kovalevsky et al. [15]	N.A.	2.5 (1.3-4.7)	N.A.	N.A.	N.A.	N.A.
Prothrombin mutation (homozygous)	Robertson et al. [14]	26.4 (1.2-559.3)	N.A.	N.A.	N.A.	N.A.	N.A.
Antithrombin deficiency	Robertson et al. [14]	4.7 (1.3-17.0)	N.A.	7.6 (0.3-196.4)	3.9 (0.2-97.2)	N.A.	1.1 (0.1-18.1)
	Rey et al. [12]	N.A.	0.9 (0.2-4.5)	N.A.	N.A.	N.A.	N.A.
Protein C deficiency	Robertson et al. [14]	4.8 (2.2-10.6)	N.A.	3.1 (0.2-38.5)	5.2 (0.3-102.2)	N.A.	5.9 (0.2-152.0)
	Rey et al. [12]	N.A.	1.6 (0.2-10.5)	N.A.	N.A.	N.A.	N.A.
Protein S deficiency	Robertson et al. [14]	3.2 (1.5-6.9)	N.A.	20.1 (3.7-109.2)	2.8 (0.8-10.6)	N.A.	2.1 (0.5-9.3)
	Rey et al. [12]	N.A.	14.7 (1.0-218.0)	N.A.	N.A.	N.A.	N.A.

§ recurrent first trimester; * before 13 weeks; N.A.= not applicable; APLA= antiphospholipid antibodies; VTE: venous thromboembolism; FGR= fetal growth restriction.

not reliable and based on the relative risk instead of the absolute risk. Therefore, the expert panel chose to base their evaluation on the results of cohort studies performed in relatives of patients with a particular thrombophilic defect [24–33]. The overall absolute risk of VTE or obstetric complications is generally low; therefore, there is no clear indication for performing mass screening for thrombophilia. Indeed, the absolute risk of VTE in a woman carrier of FVL mutation is about 0.8% and the absolute risk of obstetric complications is even lower [14]. These conclusions are also supported by a systematic review [13] in which a cost-effectiveness analysis was made and by an economic study [34] both of which did not show a good cost-effectiveness ratio of universal screening for thrombophilia. The former two studies refer to the British National Health Service system.

Recommendation

We do not suggest screening for thrombophilia in asymptomatic women without family history of VTE (Grade C).

Screening in asymptomatic women with family history of VTE or obstetric complications

Evidence is lacking to recommend testing women with family history of VTE or obstetric complications because there are no adequate studies to support this approach. However, considering the demonstrated association between thrombophilia and VTE, the expert panel considered it potentially useful to test women with a family history of VTE in order to identify individuals with severe thrombophilia, such as antithrombin deficiency, or multiple thrombophilic defects in which the risk of pregnancy-associated complications is relevant.

Concerning obstetric complications, a retrospective study evaluated the association between family history and the risk of pregnancy complications [35] showing an increased risk of unexplained IUFD, but the evidence of this study is limited by the retrospective design and the small sample size.

Recommendations

We suggest screening for inherited thrombophilia in asymptomatic women with family history of VTE (Grade D).

We do not suggest screening for thrombophilia in asymptomatic women with family history of obstetric complications (Grade D).

Screening for thrombophilia in pregnant women with relatives with inherited thrombophilia

Retrospective studies evaluated the risk of VTE in relatives of patients with a thrombophilic defect and found a significant increased risk in women carriers of a defect compared to non-carriers [9,10,28,36–39]. This association is considered particularly relevant for more severe thrombophilic defects, such as natural anticoagulant deficiency, or homozygous mutation or multiple thrombophilic defects [9,10,28,36–39], although two very recent Italian studies failed to confirm this association either in family members who are carriers of heterozygous PTM [40] and in double heterozygous carriers of FVL and PTM [41]. Concerning obstetric complications, the level of evidence is limited to FVL and to PTM [40,42,43]. It is difficult to establish if testing for thrombophilia was limited to the family defect or enlarged to a complete screening. Some authors suggested a possible advantage in performing a complete thrombophilia screening [44].

Recommendation

We suggest screening for inherited thrombophilia in asymptomatic women with family history of inherited thrombophilia (Grade C). It is suggested to search the family defect and at least the two most common mutations, FVL and PTM.

Testing symptomatic women for thrombophilia

Screening for thrombophilia in pregnant women with previous VTE

Women who have VTE are at high risk for recurrent events and whether the presence of a thrombophilic defect causes an additional risk is controversial. The results of studies that examined the relationship between hereditary thrombophilia and recurrent VTE are conflicting, and the characteristics of the first thromboembolic event seem to be the stronger predictor of recurrence than thrombophilia per se. Women with a previous idiopathic VTE, or pregnancy or estrogen-related event have a higher recurrence rate, and antenatal anticoagulant prophylaxis is suggested independently of the presence of thrombophilia [45–47]. Since the only available prospective study [45] showed an increased risk of recurrence in women who have thrombophilia and one study showed that standard antithrombotic prophylaxis could be inadequate in the presence of severe laboratory abnormality such as antithrombin deficiency [48], the expert panel considers it useful to test for thrombophilia women with a previous thromboembolic event for thrombophilia.

Recommendation

We suggest screening for thrombophilia in women with history of VTE (Grade C).

Screening for thrombophilia in pregnant women with previous obstetric complications

Several studies have demonstrated an association between thrombophilia and obstetric complications, such as RPL, unexplained IUFD, preeclampsia, HELLP syndrome, FGR and abruptio placentae [12,13,16,20]. A possible association between thrombophilia and a first pregnancy loss has also been shown [49]. Although in the absence of robust studies it is difficult to establish the exact strength of these associations, a stronger asssociation has been found between thrombophilia and recurrent pregnancy loss or unexplained intrauterine death. Testing for thrombophilia may be considered useful to evaluate the option for anticoagulant prophylaxis, even if based on limited available studies of intervention [50,51] and until data from ongoing controlled trials are published. Moreover, the expert panel suggests considering two different grades of recommendation based on the type of obstetric complication and specific thrombophilia.

Antiphoshpolipid antibodies are associated with recurrent pregnancy loss [22] and a recent Cochrane review showed the efficacy and safety of thromboprophylaxis with aspirin and heparin in these women [52]. Hence, testing women with recurrent pregnancy loss for APLA is suggested with a higher level of evidence.

Recommendations

We suggest screening for thrombophilia in women with recurrent pregnancy loss or prior unexplained IUFD (Grade C).

We suggest screening for thrombophilia in women with prior preeclampsia, HELLP syndrome, abruptio placentae, FGR (Grade D).

We suggest screening for APLA in women with recurrent pregnancy loss (Grade B). Testing for antiphoshpolipid antibodies is strongly suggested by the expert panel.

Role of Antithrombotic Prophylaxis

Pharmacological prophylaxis

The anticoagulant drugs normally used as antithrombotic prophylaxis are vitamin K antagonists and heparins. The former pass through the placenta and are controindicated in pregnancy because of known teratogenesis risk until the end of the first trimester of pregnancy and because of cerebral haemorrhage risk for the foetus at the delivery due

to trauma [53]. They can be safely used during puerperium, but considering the shortness of the prophylaxis and the necessity to obtain a therapeutic range, they are not particularly suitable. Heparins do not pass through the placenta so they can be given during pregnancy and puerperium. There are two systematic reviews regarding the safety and efficacy of low molecular weight heparin (LMWH) in pregnancy [54,55] and one Cochrane review [56] on the prophylaxis of VTE in pregnancy which includes studies both on LMWH and on unfractionated heparin (UFH). The quality of these reviews is limited by the lack of randomized clinical trials and they include above all small observational studies. Moreover, the studies assessing risk and efficacy-safety ratio of antithrombotic prophylaxis are heterogenous in terms of heparin dosage and type of molecule. Only one randomized clinical study directly compared LMWH vs UFH as prophylaxis in pregnancy [57]. The results of the aforementioned systematic reviews showed a similar efficacy of both heparins, but LMWH resulted in a safer profile compared to unfractioned heparin. Unfractioned heparin seems to be associated with a mild increased risk of haemorrhage and of symptomatic osteoporosis [58]. The risk of heparin-induced thrombocytopenia (HIT) in pregnant women receiving LMWH is very low; however, it is advisable to monitor platelet count after beginning of prophylaxis.

There are no studies assessing the efficacy-safety ratio of new anticoagulants in pregnancy.

Recommendation

LMWH should be preferred to UFH (Grade B). Monitoring platelet count during prophylaxis with LMWH is advisable. LMWH is preferable to vitamin K antagonists as antithrombotic prophylaxis during puerperium. There is no evidence to suggest adjusting the dosage of LMWH based on the levels of anti-Xa activity.

Dosages

The mentioned dosages of LMWH in the text are the following:

Prophylactic doses: dalteparin 5.000 IU sc od, or enoxaparin 40 mg sc od, or nadroparin 3.800 IU sc od
Moderate doses: dalteparin 5.000 IU sc bd, or enoxaparin 40 mg sc bd, or nadroparin 3.800 IU sc bd
Therapeutic doses: dalteparin 100 IU/kg sc bd, or enoxaparin 1 mg/kg sc bd, or nadroparin 92.7 IU/kg sc bd
The dosage of aspirin is 100 mg daily

Indication for antithrombotic prophylaxis in asymptomatic women with thrombophilia

Management studies in asymptomatic women who have thrombophilia are rare, and therefore it is difficult to balance the absolute risks of complications due to thrombophilia against the absolute risks of the considered prophylactic measures. From retrospective family studies the estimated risk of VTE in pregnancy is about 1/1000 [7,29,59] with a higher risk in the puerperium [7,59] and with a further increase of the risk from 3 to 41 fold depending on the type of thrombophilic defect present [8–11,24,28,37,60]. However, it is worth noting that a recent Italian study did not find an increased risk of first VTE during pregnancy and puerperium in double heterozygous carriers of FVL and PTM compared to the risk of single carriers [41].

The risk of anticoagulant prophylaxis with heparin is relatively low and estimated for major bleeding lower than 0.5% [54,55]. The Expert Panel considers that anticoagulant prophylaxis is not generally justified and should be adapted based on the type of thrombophilic defect; in particular, the presence of natural anticoagulant deficiencies or combined thrombophilic defects, and the presence of other risk factors. Risk factors for VTE in pregnancy and puerperium are those reported in the guidelines of the Royal College of Obstetricians and Gynaecologists [61]. In the absence of studies that directly examine the risks of VTE and of anticoagulant prophylaxis in pregnancy the following recommended strategies derive from formal consent of the Expert Panel.

There are no studies to prove the potential benefits and risks of antithrombotic prophylaxis in asymptomatic women with a family history of VTE or obstetric complications. In the absence of evidence the following recommendations are a consensus of the Expert Panel according to the indication for prophylaxis of VTE.

The following recommendations apply to all asymptomatic carrier women, with or without a family history of VTE or obstetric complications.

Recommendations

We suggest prophylactic doses of LMWH ante-partum plus post-partum for 6 weeks after delivery in women with no prior VTE and one of the following thrombophilic defects: deficiency of protein C, protein S, double heterozygous carriers of FVL and PTM or homozygous carriers of FVL or PTM (Grade D).

We suggest moderate doses of LMWH ante-partum plus post-partum for 6 weeks after delivery in women with no prior VTE and deficiency of antithrombin (Grade D). At the time of delivery the use of antithrombin concentrates should be evaluated, in order to allow reduction of LMWH to prophylactic doses and decrease the haemorrhagic risk. The dosage warranted is 40 IU/Kg, to achieve a functional circulating level of 0.8 U/ml of antithrombin.

We suggest surveillance or, in presence of additional risk factors [61], ante-partum prophylactic doses of LMWH in women with no prior VTE and heterozygous carriers of FVL or PTM. We also suggest post-partum prophylactic doses of LMWH for 6 weeks after delivery (Grade D).

We suggest ante-partum prophylactic doses of LMWH and/or aspirin in asymptomatic women with APLA. We also suggest post-partum prophylactic doses of LMWH for 6 weeks after delivery (Grade D).

It is advisable to refer women with natural anticoagulant deficiency to specialized centres for a more precise diagnosis and for correct counselling. Monitoring platelet count during prophylaxis with LMWH is advisable. LMWH is preferable to vitamin K antagonists as antithrombotic prophylaxis during puerperium.

Indication for antithrombotic prophylaxis in women with prior VTE

One prospective study assessed the risk of recurrence in pregnant women with a history of VTE showing a risk of 6% in women in which the first event was idiopathic and/or with a thrombophilic abnormality [45]. In two retrospective studies the risk of antepartum recurrent VTE was higher in women with a previous idiopathic VTE, or pregnancy or estrogen-related event [46,47]. Therefore, the cirumstances of any previous thromboembolism and the type of thrombophilia should be considered, while an universal antepartum prophylaxis is not warranted. Women with high risk thrombophilia, such as natural anticoagulant deficiency or combined defects may have a higher risk of recurrence compared to women with lower risk thrombophilia [48]. The available evidence on the efficacy of secondary prophylaxis with heparin in pregnancy derives from 3 small randomized studies [57,62,63] and from cohort studies [46,64–71] showing efficacy of treatment. These studies are heterogeneous for study populations, type of heparin used and dosages; therefore, the level of evidence of efficacy should be considered moderate, but it is balanced by the strong evidence of safety of LMWH in pregnancy [54,55].

Recommendations

We suggest moderate doses of LMWH ante-partum plus post-partum for 6 weeks after delivery in women with prior VTE and one of the following thrombophilic defects: deficiency of protein C, protein S, double heterozygous carriers of FVL and PTM, homozygous carriers of FVL or PTM, APLA. In women with APLA we suggest administering ALSO ante-partum aspirin (Grade C).

We suggest therapeutic doses of LMWH ante-partum plus post-partum for 6 weeks after delivery in women with prior VTE and deficiency of antithrombin (Grade C). At the time of delivery the use of antithrombin concentrates should be evaluated, in order to allow reduction of LMWH to prophylactic doses and decrease the haemorrhagic risk. The dosage warranted is 40 IU/Kg, to achieve a functional circulating level of 0.8 U/ml of antithrombin.

We suggest prophylactic doses of LMWH ante-partum plus post-partum for 6 weeks after delivery in women with prior idiopathic or estrogen or pregnancy related VTE and heterozygous carriers of FVL or PTM (Grade C).

We suggest surveillance or, in the presence of additional risk factors [61], ante-partum prophylactic doses of LMWH in women with prior VTE associated with a transient risk factor that is no longer present and heterozygous carriers of FVL or PTM. We also suggest post-partum prophylactic doses of LMWH for 6 weeks after delivery (Grade C).

We suggest prophylactic doses of LMWH ante-partum plus post-partum for 6 weeks after delivery in women without thrombophilia and with prior idiopathic or estrogen or pregnancy related VTE (Grade C).

We suggest surveillance or, in the presence of additional risk factors [61], ante-partum prophylactic doses of LMWH in women without thrombophilia with prior VTE associated with a transient risk factor that is no longer present. We also suggest post-partum prophylactic doses of LMWH for 6 weeks after delivery (Grade C).

Monitoring platelet count during prophylaxis with LMWH is advisable. LMWH is preferable to vitamin K antagonists as antithrombotic prophylaxis during puerperium. Elastic stockings are recommended in all women with previous VTE both in pregnancy and puerperium.

Indication for antithrombotic prophylaxis in women with prior obstetric complications and thrombophilia

There are no studies that directly evaluated the potential benefits of antithrombotic prophylaxis against the potential risks in women with obstetric complications and one of the following thrombophilic defects: deficiency of antithrombin, protein C, protein S, double heterozygous carriers of FVL and PTM or homozygous carriers of FVL or PTM. In the absence of studies the recommended strategies in these conditions derive from formal consent of the Expert Panel according to the indication for prophylaxis of VTE.

One study compared the use of prophylactic doses of LMWH and aspirin in women with a single pregnancy loss and the presence of heterozygous FVL or PTM, or deficiency of protein S showing benefit from LMWH [50]. Another randomized controlled study of women with recurrent pregnancy loss and thrombophilia (above all FVL or PTM or the presence of APLA) compared two different doses of enoxaparin resulting in a similar number in live birth rate in the two arms of the study (84% in the group of enoxaparin 40 mg daily and 78% in the group of enoxaparin 40 mg twice daily) [51]. There are no data from randomized controlled trials that evaluated benefits and risks of prophylactic administration of heparin versus placebo in women with previous pregnancy losses. Due to the absence of clinical trials the same therapeutic uncertainty exists for women with other obstetric complications and thrombophilia.

A recent Cochrane review in women with RPL and APLA evaluated the efficacy and risks of antithrombotic prophylaxis (heparin, aspirin or both) showing benefit from treatment based on the combination of aspirin and heparin [52].

Recommendations

In the absence of specific studies, according to the indication for prophylaxis of VTE, we suggest prophylactic doses of LMWH ante-partum plus post-partum for 6 weeks after delivery in women with prior obstetric complications and one of the following thrombophilic defects: deficiency of protein C, protein S, double heterozygous carriers of FVL and PTM or homozygous carriers of FVL or PTM (Grade D).

In the absence of specific studies, according to the indication for prophylaxis of VTE, we suggest moderate doses of LMWH ante-partum plus post-partum for 6 weeks after delivery in asymptomatic women with prior obstetric complications and deficiency of antithrombin (Grade D). At the time of delivery the use of antithrombin concentrates should be evaluated, in order to allow reduction of LMWH to prophylactic doses and decrease the haemorrhagic risk. The dosage warranted is 40 IU/Kg, to achieve a functional circulating level of 0.8 U/ml of antithrombin.

We suggest ante-partum prophylactic doses of LMWH in women who are heterozygous carriers of FVL or PTM and had prior recurrent pregnancy loss. According to the indication for prophylaxis of VTE we also suggest post-partum prophylactic doses of LMWH for 6 weeks after delivery (Grade C).

We suggest ante-partum prophylactic doses of LMWH in women who are heterozygous carriers of FVL or PTM and and previously had one of the following obstetric complications: unexplained IUFD, preeclampsia, HELLP syndrome, abruptio placentae, FGR. According to the indication for prophylaxis of VTE we also suggest post-partum prophylactic doses of LMWH for 6 weeks after delivery (Grade D). In the absence of evidence on the risk/benefit ratio of antithrombotic prophylaxis in women with obstetric complications other than RPL or IUFD, the aforementioned recommendation has been obtained using RAND method [1]. We remark that one member of the Panel considers the administration of antithrombotic prophylaxis incorrect and 3 members consider it uncertain.

We suggest ante-partum aspirin and prophylactic doses of LMWH in women with recurrent pregnancy loss and APLA (Grade B).

We suggest ante-partum aspirin and prophylactic doses of LMWH in women with APLA and one of the following obstetric complications: unexplained IUFD, preeclampsia, HELLP syndrome, FGR and abruptio placentae (Grade D).

In the absence of specific studies, according to the indication for prophylaxis of VTE, we also suggest post-partum prophylactic doses of LMWH for 6 weeks after delivery in women with prior obstetric complications and APLA (Grade D).

Indication for antithrombotic prophylaxis in women with mild hyperhomocysteinemia

In women who have mild hyperhomocysteinemia the use of folic acid beyond the tenth week of gestation should be considered, although this strategy is not supported by specific studies and the recommendation derives from formal consent of the Expert Panel.

Recommendations

We suggest the use of folic acid for the whole pregnancy in women with mild hyperhomocysteinemia (Grade D).

Discussion

Review of the literature has highlighted the lack of good quality studies both on the usefulness of thrombophilia tests and the efficacy and safety of prophylaxis with anticoagulant drugs. The low prevalence of some thrombophilic abnormalities makes it difficult to carry out prospective clinical studies to estimate the risks of thrombotic and obstetric complications for each single thrombophilic defect. Moreover, the ethical problems connected with it have, up to now, limited randomized clinical studies aimed at addressing the safety and the efficacy of drug prophylaxis versus placebo. At present there are some ongoing methodologically valid studies from which important indications are expected.

The expert panel believes that clinical research in this field should promote prospective studies to establish more accurately the predictive value of thrombophilia tests for thromboembolic events and obstetric complications. Moreover, randomized clinical trials of treatment are needed to evaluate in women, with or without thrombophilia, the efficacy of antithrombotic prophylaxis.

Finally, future studies should use homogenous definitions for the different obstetric complications to obtain comparable and conclusive results.

Conflict of interest statement

The authors do not have any commercial association, which might pose a conflict of interest.

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References

[1] Iorio A, Ageno W, Cosmi B, Imberti D, Lussana F, Siragusa S, et al. Objectives and methodology: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET). Thromb Res 2009;124:e1–5.
[2] Scottish Intercollegiate Guidelines Network, SIGN 50: A guideline developers' handbook, SIGN Publication No. 50. February 2001, last updated May 2004. Available from: http://www.sign.ac.uk.
[3] National Institute for Clinical Excellence, Guideline Development Methods: Information for National Collaborating Centres and Guideline Developers, London: National Institute for Clinical Excellence, February 2004, updated 2005. Available from: www.nice.org.
[4] Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJ. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. J Thromb Haemost 2008;6:632–7.
[5] Greer IA. Thrombosis in pregnancy: maternal and fetal issues. Lancet 1999;353: 1258–65.
[6] Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton III LJ. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: A 30-year population-based study. Ann Intern Med 2005;143:697–706.
[7] McColl MD, Ramsay JE, Tait RC, Walker ID, McCall F, Conkie JA, et al. Risk factors for pregnancy associated venous thromboembolism. Thromb Haemost 1997;78: 1183–8.
[8] Gerhardt A, Scharf RE, Beckmann MW, Struve S, Bender HG, Pillny M, et al. Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium. New Engl J Med 2000;342:374–80.
[9] Middeldorp S, Libourel EJ, Hamulyak K, Van der Meer J, Buller HR. The risk of pregnancy-related venous thromboembolism in women who are homozygous for factor V Leiden. Br J Haematol 2001;113:553–5.
[10] Martinelli I, Legnani C, Bucciarelli P, Grandone E, De Stefano V, Mannucci PM. Risk of pregnancy-related venous thrombosis in carriers of severe inherited thrombophilia. Thromb Haemost 2001;86:800–3.
[11] Martinelli I, De Stefano V, Taioli E, Paciaroni K, Rossi E, Mannucci PM. Inherited thrombophilia and first venous thromboembolism during pregnancy and puerperium. Thromb Haemost 2002;87:791–5.
[12] Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. Lancet 2003;9361:901–8.
[13] Wu O, Robertson L, Twaddle S, Lowe GD, Clark P, Greaves M, et al. Screening for thrombophilia in high-risk situations: Systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Health Technol Assess (Winchester, England) 2006;10: 1–110.
[14] Robertson L, Wu O, Langhorne P, Twaddle S, Clark P, Lowe GD, et al. Thrombophilia in pregnancy: a systematic review. Br J Haematol 2006;132:171–96.
[15] Kovalevsky G, Gracia CR, Berlin JA, Sammel MD, Barnhart KT. Evaluation of the Association between Hereditary Thrombophilias and Recurrent Pregnancy Loss: A Meta-analysis. Arch Intern Med 2004;164:558–63.
[16] Kosmas IP, Tatsioni A, Ioannidis JP. Association of C677T polymorphism in the methylenetetrahydrofolate reductase gene with hypertension in pregnancy and pre-eclampsia: a meta-analysis. J Hypertens 2004;22:1655–62.
[17] Alfirevic Z, Roberts D, Martlew V, Alfirevic Z, Roberts D, Martlew V. How strong is the association between maternal thrombophilia and adverse pregnancy outcome? A systematic review. Eur J Obstet Gynecol Reprod Biol 2002;101:6–14.
[18] Biron-Andreani C, Schved JF, Daures JP. Factor V Leiden mutation and pregnancy-related venous thromboembolism: What is the exact risk? results from a meta-analysis. Thromb Haemost 2006;96:638–46.
[19] Dudding TE, Attia J, Dudding TE, Attia J. The association between adverse pregnancy outcomes and maternal factor V Leiden genotype: a meta-analysis. Thromb Haemost 2004;91:700–11.
[20] Howley HE, Walker M, Rodger MA, Howley HEA, Walker M, Rodger MA. A systematic review of the association between factor V Leiden or prothrombin gene variant and intrauterine growth restriction. Am J Obstet Gynecol 2005;192: 694–708.
[21] Kujovich JL, Kujovich JL. Thrombophilia and pregnancy complications. Am J Obstet Gynecol 2004;191:412–24.
[22] Opatrny L, David M, Kahn SR, Shrier I, Rey E. Association between antiphospholipid antibodies and recurrent fetal loss in women without autoimmune disease: a meta-analysis. J Rheumatol 2006;33:2214–21.
[23] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.
[24] Lindqvist PG, Svensson PJ, Marsal K, Grennert L, Luterkor M, Dahlback B. Activated protein C resistance (FV:Q506) and pregnancy. Thromb Haemost 1999;81:532–7.
[25] Lindqvist PG, Svensson P, Dahlback B. Activated protein C resistance - In the absence of factor V Leiden - And pregnancy. J Thromb Haemost 2006;4:361–6.
[26] McColl MD, Ramsay JE, Tait RC, Walker ID, McCall F, Conkie JA, et al. Superficial vein thrombosis: Incidence in association with pregnancy and prevalence of thrombophilic defects. Thromb Haemost 1998;79:741–2.
[27] Bank I, Libourel EJ, Middeldorp S, Van Pampus EC, Koopman MM, Hamulyák K, et al. Prothrombin 20210A mutation: A mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study. Arch Intern Med 2004;164:1932–7.
[28] Friederich PW, Sanson BJ, Simioni P, Zanardi S, Huisman MV, Kindt I, et al. Frequency of pregnancy-related venous thromboembolism in anticoagulant factor-deficient women: implications for prophylaxis. Ann Intern Med 1996;125: 955–60.
[29] Dizon-Townson D, Miller C, Sibai B, Spong CY, Thom E, Wendel Jr G, et al. The relationship of the factor V Leiden mutation and pregnancy outcomes for mother and fetus. Obstet Gynecol 2005;106:517–24.
[30] Volzke H, Grimm R, Robinson DM, Robinson C, Kohlmann T, Schuster G, et al. Factor V Leiden and the risk of stillbirth in a German population. Thromb Haemost 2003;90:429–33.
[31] Murphy RP, Donoghue C, Nallen RJ, D'Mello M, Regan C, Whitehead AS, et al. Prospective evaluation of the risk conferred by factor V Leiden and thermolabile methylenetetrahydrofolate reductase polymorphisms in pregnancy. Arterioscler Thromb Vasc Biol 2000;20:266–70.
[32] Dizon-Townson DS, Nelson LM, Jang H, Varner MW, Ward K. The incidence of the factor V Leiden mutation in an obstetric population and its relationship to deep vein thrombosis. Am J Obstet Gynecol 1997;176:883–6.
[33] Middeldorp S, Henkens CM, Koopman MM, van Pampus EC, Hamulyàk K, van der Meer J, et al. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. Ann Intern Med 1998;128:15–20.
[34] Clark P, Twaddle S, Walker ID, Scott L, Greer IA. Cost-effectiveness of screening for the factor V Leiden mutation in pregnant women. Lancet 2002;359:1919–20.
[35] Grandone E, Colaizzo D, Brancaccio V, Ciampa A, Di Minno G, Margaglione M. Impact of prothrombotic mutations and family history on the occurrence of intrauterine fetal deaths. Haematologica 2002;87:1118–9.
[36] Couturaud F, Kearon C, Leroyer C, Mercier B, Abgrall JF, Le Gal G, et al. Incidence of venous thromboembolism in first-degree relatives of patients with venous thromboembolism who have factor V Leiden. Thromb Haemost 2006;96:744–9.
[37] Pabinger I, Schneider B, Pabinger I, Schneider B. Thrombotic risk in hereditary antithrombin III, protein C, or protein S deficiency. A cooperative, retrospective study. Gesellschaft fur Thrombose- und Hamostaseforschung (GTH) Study Group on Natural Inhibitors. Arterioscler Thromb Vasc Biol 1996;16:742–8.
[38] Simioni P, Sanson B-J, Prandoni P, Tormene D, Friederich PW, Girolami B, et al. Incidence of venous thromboembolism in families with inherited thrombophilia. Thromb Haemost 1999;81:198–202.
[39] Tormene D, Simioni P, Prandoni P, Luni S, Zerbinati P, Sartor D, et al. Factor V Leiden mutation and the risk of venous thromboembolism in pregnant women. Haematologica 2001;86:1305–9.
[40] Tormene D, De Stefano V, Grandone E, Za T, Perlati M, Rossi E, et al. The G20210A prothrombin variant and the risk of venous thromboembolism or fetal loss in pregnant women: a family study. J Thromb Haemost 2007;5:2193–6.
[41] Martinelli I, Battaglioli T, De Stefano V, Tormene D, Valdrè L, Grandone E, et al. The risk of first venous thromboembolism during pregnancy and puerperium in double heterozygotes for factor V Leiden and prothrombin G20210A. J Thromb Haemost 2008;6:494–8.

[42] Tormene D, Simioni P, Prandoni P, Luni S, Innella B, Sabbion P, et al. The risk of fetal loss in family members of probands with factor V Leiden mutation. Thromb Haemost 1999;82:1237–9.
[43] Meinardi JR, Middeldorp S, de Kam PJ, Koopman MM, van Pampus EC, Hamulyàk K, et al. Increased risk for fetal loss in carriers of the factor V Leiden mutation. Ann Intern Med 1999;130:736–9.
[44] Brouwer JL, Veeger NJ, Kluin-Nelemans HC, Van Der MJ. The pathogenesis of venous thromboembolism: evidence for multiple interrelated causes. Ann Intern Med 2006;145:807–15.
[45] Brill-Edwards P, Ginsberg JS, Gent M, Hirsh J, Burrows R, Kearon C, et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. Recurrence of Clot in This Pregnancy Study Group. New Engl J Med 2000;343:1439–44.
[46] Pabinger I, Grafenhofer H, Kaider A, Kyrle PA, Quehenberger P, Mannhalter C, et al. Risk of pregnancy-associated recurrent venous thromboembolism in women with a history of venous thrombosis. J Thromb Haemost 2005;3:949–54.
[47] De Stefano V, Martinelli I, Rossi E, Battaglioli T, Za T, Mannucci PM, et al. The risk of recurrent venous thromboembolism in pregnancy and puerperium without antithrombotic prophylaxis. Br J Haematol 2006;135:386–91.
[48] Simioni P, Tormene D, Prandoni P, Girolami A. Pregnancy-related recurrent events in thrombophilic women with previous venous thromboembolism. Thromb Haemost 2001;86:929.
[49] Lissalde-Lavigne G, Fabbro-Peray P, Cochery-Nouvellon E, Mercier E, Ripart-Neveu S, Bladucchi JP, et al. Factor V Leiden and prothrombin G20210A polymorphisms as risk factors for miscarriage during a first intended pregnancy: The matched case-control 'NOHA first' study. J Thromb Haemost 2005;3:2178–84.
[50] Gris JC, Mercier E, Quere I, Lavigne-Lissalde G, Cochery-Nouvellon E, Hoffet M, et al. Low-molecular-weight heparin versus low-dose aspirin in women with one fetal loss and a constitutional thrombophilic disorder. Blood 2004;103:3695–9.
[51] Brenner B, Hoffman R, Carp H, Dulitsky M, Younis J. Efficacy and safety of two doses of enoxaparin in women with thrombophilia and recurrent pregnancy loss: the LIVE-ENOX study. J Thromb Haemost 2005;3:227–9.
[52] Empson M, Lassere M, Craig J, Scott J. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. Cochrane Database Syst Rev 2005(2):CD002859.
[53] Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(3 Suppl):627S–44S.
[54] Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood 2005;106:401–7.
[55] Sanson BJ, Lensing AW, Prins MH, Ginsberg JS, Barkagan ZS, Lavenne-Pardonge E, et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review. Thromb Haemost 1999;81:668–72.
[56] Gates S, Brocklehurst P, Davis LJ, Gates S, Brocklehurst P, Davis LJ. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. Cochrane Database Syst Rev 2002(2):CD001689.
[57] Pettila V, Kaaja R, Leinonen P, Ekblad U, Kataja M, Ikkala E. Thromboprophylaxis with low molecular weight heparin (dalteparin) in pregnancy. Thromb Res 1999;96:275–82.
[58] Dahlman TC. Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. Am J Obstet Gynecol 1993;168:1265–70.
[59] Lindqvist P, Dahlback B, Marsal K. Thrombotic risk during pregnancy: A population study. Obstet Gynecol 1999;94:595–9.
[60] De Stefano V, Leone G, Mastrangelo S, Tripodi A, Rodeghiero F, Castaman G, et al. Thrombosis during pregnancy and surgery in patients with congenital deficiency of antithrombin III, protein C, protein S. Thromb Haemost 1994;71:799–800.
[61] Royal COG. Thromboprophylaxis during pregnancy, labour and after vaginal delivery 6013. Guideline N37; 2004. www.rcog.org.uk.
[62] Howell R, Fidler J, Letsky E, de Swiet M. The risks of antenatal subcutaneous heparin prophylaxis: a controlled trial. Br J Obstet Gynaecol 1983;90:1124–8.
[63] Gates S, Brocklehurst P, Ayers S, Bowler U, Thromboprophylaxis in Pregnancy Advisory Group. Thromboprophylaxis and pregnancy: two randomized controlled pilot trials that used low-molecular-weight heparin. Am J Obstet Gynecol 2004;191:1296–303.
[64] Tengborn L, Bergqvist D, Matzsch T, Bergqvist A, Hedner U. Recurrent thromboembolism in pregnancy and puerperium. Is there a need for thromboprophylaxis? Am J Obstet Gynecol 1989;160:90–4.
[65] Nelson-Piercy C, Letsky EA, de SM, Nelson-Piercy C, Letsky EA, de Swiet M. Low-molecular-weight heparin for obstetric thromboprophylaxis: experience of sixty-nine pregnancies in sixty-one women at high risk. Am J Obstet Gynecol 1997;176:1062–8.
[66] Ellison J, Walker ID, Greer IA, Ellison J, Walker ID, Greer IA. Antenatal use of enoxaparin for prevention and treatment of thromboembolism in pregnancy. BJOG 2000;107:1116–21.
[67] Hunt BJ, Doughty HA, Majumdar G, Copplestone A, Kerslake S, Buchanan N, et al. Thromboprophylaxis with low molecular weight heparin (Fragmin) in high risk pregnancies. Thromb Haemost 1997;77:39–43.
[68] Lepercq J, Conard J, Borel-Derlon A, Darmon JY, Boudignat O, Francoual C, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. BJOG 2001;108:1134–40.
[69] Deruelle P, Denervaud M, Hachulla E, Ducloy-Bouthors AS, Valat AS, Puech F, et al. Use of low-molecular-weight heparin from the first trimester of pregnancy: A retrospective study of 111 consecutive pregnancies. Eur J Obstet Gynecol Reprod Biol 2006;127:73–8.
[70] Rowan JA, McLintock C, Taylor RS, North RA. Prophylactic and therapeutic enoxaparin during pregnancy: indications, outcomes and monitoring. Aust N Z J Obstet Gynaecol 2003;43:123–8.
[71] Blomback M, Bremme K, Hellgren M, Siegbahn A, Lindberg H. Thromboprophylaxis with low molecular mass heparin, 'Fragmin' (dalteparin), during pregnancy - A longitudinal safety study. Blood Coagul Fibrinolysis 1998;9:1–9.