'To test or not to test', the arguments for and against thrombophilia testing in obstetrics

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Abstract

Clinicians increasingly investigate women for thrombophilias due to their associations with venous thromboembolism and placenta-mediated pregnancy complication. These associations, however, are modest and based largely on retrospective data from studies with heterogeneous classifications and populations, leading to discordance between evidence and guidelines. Current evidence suggests a contributory rather than causative role for thrombophilia in placenta-mediated pregnancy complication and venous thromboembolism. With little evidence of benefit from antithrombotic therapy in placenta-mediated pregnancy complication, thrombophilia screening remains controversial. Given the low absolute risk of placenta-mediated pregnancy complication and gestational venous thromboembolism with heritable thrombophilia, universal screening is inappropriate. Selective screening for antiphospholipid syndrome is supported by robust evidence of benefit. Conversely, selective screening for heritable thrombophilia has not been shown to effectively manage placenta-mediated pregnancy complication. Therefore, at present heritable thrombophilia screening is not warranted for placenta-mediated pregnancy complication. Until we have better evidence from better stratified patient groups, caution should remain if we wish to practice evidence-based medicine.

Keywords

High-risk pregnancy, haematology, maternal–fetal medicine, complications

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Introduction

Pregnancy is a hypercoagulable state, likely designed to protect the mother from the haemostatic challenges of childbirth. This hypercoagulability, however, increases the risk of venous thromboembolism (VTE), a leading cause of maternal death.¹ Heritable thrombophilia is an established risk factor for VTE.² The haemostatic system also appears important for placental function. Placenta-mediated pregnancy complications (PMPCs), which include pre-eclampsia, fetal growth restriction (FGR), recurrent and late miscarriage and placental abruption, are associated with prothrombotic mechanisms,^{3,4} perhaps best illustrated by antiphospholipid syndrome (APS).^{5–7} This has led to the use of antithrombotic agents, particularly low-molecular-weight-heparin (LMWH), for secondary (or even primary) prevention of such complications. Despite this, outside of APS, benefits of such interventions have not yet been established.

Screening for thrombophilia in obstetric practice remains controversial because of limited evidence of a true causal relationship with PMPC and lack of a proven effective intervention.⁸ Furthermore, the diagnosis of thrombophilia based on coagulation tests rather than genotypes to identify single-nucleotide polymorphisms (SNPs) may lack precision and may be affected by the haemostatic changes in pregnancy and the postpartum period.

In order to evaluate the role of thrombophilia screening, it is important to understand the relative and absolute risks of thrombosis and PMPC complicated by thrombophilia, as well as the financial, physical and emotional burden of screening and the relative risk reduction by available therapies.

The principles of a good screening test

The criteria for a good screening test have previously been defined by Wilson and Jungner.⁹ Their 10 criteria have largely been upheld as a gold standard. The broad principles are the condition should be an important health problem, which has a known natural history and is

identifiable before the disease occurs; the test should be simple, safe and acceptable; the intervention should have better outcomes than 'late' treatment; and the screening programme should be cost effective at reducing morbidity and/or mortality.⁹

Although a modest relative increase in risk of VTE and PMPC has been demonstrated with heritable thrombophilia, it is the absolute risk that is most important clinically. While the prevalence of heritable thrombophilias is relatively high (collectively the known heritable thrombophilias are found in 4–10% of the population^{10,11}), the frequency of thrombophilia-associated complications is still relatively low. This is evidenced by the fact that the majority of carriers of heritable thrombophilias remain clinically unaffected by VTE or PMPC. Further, if a thrombophilia is identified through screening, the evidence for effective interventions is scarce and often conflicting.

This paper aims to explore these principles in relation to both universal and selective thrombophilia screening in order to propose potential evidence-based recommendations.

Epidemiology

The commonest acquired thrombophilia is APS, which is a retrospective diagnosis defined by the presence of at least one clinical and one

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Table 1. Prevalence of different thrombophilias.

Thrombophilia	Prevalence
Antiphospholipid syndrome	Antiphospholipid Ab present in 3–5% of population without thrombosis/obstetric complications ^{13,14} APS clinical syndrome 0.04–0.05% ¹⁵
Factor V Leiden	2–7% in Caucasian population ¹⁶
Prothrombin G20210A	2% ¹⁶
Dysfunction in protein C and protein S systems	0.14–0.5% ¹⁷
Antithrombin deficiency	0.25–0.5% ¹⁶

APS: antiphospholipid syndrome.

Source: Biggoggero and Meroni¹³, Myers,¹⁴ Mehrania,¹⁵ Eid and Rihani¹⁶ and Salvagno et al.¹⁰

laboratory criteria. The laboratory criteria are strict due to misdiagnosis problems reflecting the transient nature of the antibodies secondary to infection or drugs. Laboratory criteria include the presence of either lupus anticoagulant, anticardiolipin or anti- β 2 glycoprotein-1 on more than one occasion more than 12 weeks apart.¹² The clinical criteria for APS include a previous thrombosis or pregnancy morbidity (unexplained fetal death beyond 10 weeks' gestation, severe pre-eclampsia or eclampsia requiring delivery before 34 weeks' gestation or recurrent miscarriage).¹²

The most common inherited thrombophilias are factor V Leiden (FVL) and prothrombin (FII) gene mutation, G20210A. Other significant inherited thrombophilias include deficiencies in protein S, protein C and antithrombin.

The prevalence of individual thrombophilias is low as demonstrated in Table 1.^{10,13–16}

Thrombophilia testing

Venepuncture and subsequent laboratory testing is required to identify a thrombophilia. Although relatively simple to perform, interpretation is costly and difficult. Components of a full thrombophilia screen in contemporary practice include the endogenous anticoagulant systems measuring antithrombin, protein C and protein S levels; identification of SNPs that can enhance the coagulation responses, namely FVL and prothrombin G20210A; and functional coagulation and immunoserological testing for lupus anticoagulant, anticardiolipin and anti- β 2-glycoprotein 1 antibodies.¹⁷

Thrombophilia testing, other than for SNPs, should ideally be performed outside of pregnancy due to the gestational haemostatic changes, such as reduced protein S. These physiologic changes begin at conception and extend up to 12 weeks postnatally.¹⁸ Given that low protein S levels are found in 25% of women in the first trimester, 60% in the second and up to 100% in the third trimester, antenatal testing has high false-positive rate.¹⁹ Other physiologic changes that affect test reliability include a reduction in antithrombin levels by 20%²⁰; and pregnancy-associated aPC resistance, which negatively impacts on functional testing for FVL.¹⁹

The cost-effectiveness of universal and selective thrombophilia screening programmes in pregnancy has previously been modelled in a hypothetical population of 10,000 screened at the onset of pregnancy (week 6 of gestation) for FVL, prothrombin G20210A, deficiencies of antithrombin, protein C and protein S, lupus anticoagulants and anticardiolipin antibodies.²¹ Those tested positive were considered at increased risk and prescribed thromboprophylaxis. In the selective screening model, previous personal and/or family history of VTE were used to identify those for thrombophilia testing. In both scenarios the incremental cost-effectiveness ratio was in excess of £81,000.²¹ This

study concluded that universal screening was not supported by current evidence and comparatively selective screening was more cost effective but prevented fewer adverse outcomes.²¹

Thrombophilia and pregnancy

The association between thrombophilia and pregnancy complications is contributory rather than causative.²² The current evidence base for inherited thrombophilias and pregnancy complications is largely retrospective, with heterogeneity in classifications and populations, leading to conflicting results.²³ At present, universal thrombophilia screening is not recommended and recommendations for which clinical subgroups should undergo screening vary nationally and internationally.²⁴ This discordance between guidelines reflects the paucity of evidence of cost-effectiveness including therapeutic efficacy.²⁵

VTE

VTE remains a leading cause of direct maternal mortality in the developed world.¹ Identifiable risk factors are increasingly recognised to be present in these cases.¹ Pregnancy per se is a well-known risk factor for VTE. This is considered due to its contribution to all three components of Virchow's triad: hypercoagulability due to the procoagulant changes of pregnancy, venous stasis due to alterations in venous tone and later the pressure of the gravid uterus on the inferior vena cava and iliac veins, and lastly endothelial damage secondary to trauma at delivery or obstetric complications such as pre-eclampsia. Although the relative risk of VTE is higher in women with thrombophilia, this is modest and varies between different thrombophilic defects.

In asymptomatic thrombophilia, the risk of pregnancy-associated VTE increases with combined defects, homozygous states and those defects associated with a positive family history of VTE.² This significantly higher relative risk was demonstrated in all thrombophilias, with the highest absolute risk in homozygous FVL of 3.4%² (OR 34.40, 95% CI 9.86–210.05).²¹ This is compared with an underlying incidence of VTE in pregnancy of 0.10%.²⁶ Although this demonstrates a significant increase in relative risk and therefore potential benefit of universal screening, the absolute risk remains low. Conversely Bezemer et al.'s²⁷ case-control study demonstrated a two- to fourfold increase in VTE risk in those with a family history of VTE (requiring no invasive testing) irrespective of thrombophilia status. The fact that thrombophilia-negative patients with a family history of heritable thrombophilia are at increased risk of VTE negates the value of a negative screen. In contrast, Gerhardt et al.²⁸ reported that high-risk thrombophilias, including antithrombin deficiency and compound heterozygotes for FVL and prothrombin G20210A have significant absolute risks of gestational VTE (6.1–9.0 and 5.5–8.2%, respectively) independent of family history.

Both outside and within pregnancy, the strongest risk factor for predicting VTE recurrence is whether the first episode was provoked or unprovoked,²⁹ with information derived from the clinical history alone. Although heritable thrombophilia is found in 20–40% of women with a previous gestational VTE,³⁰ the value of selective screening in those with a history of VTE should not be determined by detection rate but instead by its effect on management. Although some guidelines recommend varying thromboprophylactic doses depending on the type of thrombophilia, the evidence base for these recommendations is limited.

RCOG guidelines place emphasis on higher dose thromboprophylaxis (50–100% treatment dose) in pregnant women whose previous VTE event was associated with antithrombin deficiency or APS.³¹ They recommend selective screening only for those with a personal or family history of VTE. In the non-pregnant population, NICE recommends screening only when there is a plan to stop anticoagulation: this includes APS screening in those with unprovoked VTE and heritable thrombophilia screening in those with a family history of VTE.³²

Based on these guidelines, knowledge of any familial known thrombophilia may influence management. Conversely, women with a previous VTE, which was unprovoked, pregnancy- or oestrogen-related, can be managed with thromboprophylaxis in a subsequent pregnancy based on clinical risk alone. The American College of Chest Physicians (ACCP)³³ offers further conflicting guidance. Despite Brill-Edwards et al.'s³⁴ report of increased prevalence of gestational VTE recurrence in those with thrombophilia (5.9%; 95% CI 1.2–16.0%) compared with those without (0%; 95% CI 0.0–8.0%), ACCP recommends postnatal thromboprophylaxis regardless of thrombophilia status and does not feature thrombophilia status as a trigger for antenatal thromboprophylaxis in women with prior VTE.³³ Thus, even in the situation of VTE the value of thrombophilia screening remains controversial, as reflected by differing current (evidence based) clinical guidelines.²⁵

Early and late pregnancy loss

In APS with recurrent miscarriage, benefit has been demonstrated from combination treatment with low-dose aspirin (LDA) and LMWH, which significantly increases live birth rate over LDA alone.³⁵ It is also possible to stratify these women by serology in terms of their risks. Antibodies directed against domain I of a β 2-GPI are associated with second trimester pregnancy loss, while aCL antibodies are associated with both early and late recurrent pregnancy loss.⁷ Thus, screening for acquired thrombophilia impacts on both treatment and the outcome prognosis. This contrasts with heritable thrombophilia screening in this situation. Screening for antiphospholipid antibodies in women with recurrent miscarriage is recommended by UK guidelines,³⁶ which is appropriate given the impact on management.

Thromboprophylaxis has not been shown to prevent early or late pregnancy loss in women with inherited thrombophilias.^{35,37} This evidence is based on summarising mostly small cohort or case-control studies where higher risk thrombophilic defects may be under-represented in study samples (i.e. most women will be heterozygous carriers of FVL or prothrombin gene mutations). Nonetheless in some studies such as the single-centre NOHA cohorts, benefit has been reported.³⁸

Large-scale randomised controlled trials (RCTs) such as ALIFE2 (registration number NTR3361), currently underway, provide a more homogeneous patient group to examine whether LMWH can positively affect pregnancies complicated by miscarriage, late pregnancy loss/stillbirth.³⁹ ALIFE2 is a multicentre RCT targeting women with heritable thrombophilia and a history of recurrent miscarriage³⁹ to determine the effect of enoxaparin versus placebo on live birth rate, when commenced prior to seven weeks' gestation.³⁹ In the meantime, given the lack of clear benefit from treatment or any impact on prognosis, screening for heritable thrombophilia in the situation of pregnancy loss is not warranted.

Recurrent implantation failure (RIF)

A recent meta-analysis demonstrated a significant improvement in live birth rate when LMWH was given for RIF (three or more) following *in vitro* fertilisation (IVF).⁴⁰ However, this was irrespective of thrombophilia status. Qublan et al.'s⁴¹ RCT specifically targeted women with RIF and thrombophilia and demonstrated a significant improvement in live birth rate with the administration of LMWH compared with placebo (23.8 and 2.8%, respectively; $p \leq 0.05$). Despite Lodigiani et al.'s⁴² striking results, the value of selective thrombophilia screening in this group is questionable as thromboprophylaxis appears beneficial regardless of thrombophilia status. Plasminogen activator inhibitor-1 (PAI-1) inhibits fibrinolysis and is recruited during implantation to promote haemostasis.⁴³ Although not routinely included in thrombophilia screening, PAI-1 is increasingly being included in the context of IVF, due to its association with recurrent miscarriage^{44–46} and RIF.⁴⁷ Despite biological plausibility, the increasing use of LMWH in cases

with raised PAI-1 is not yet supported by evidence. Further research is required to assess its efficacy.

Other PMPCs

The assessment of the association between inherited thrombophilia and PMPC is similarly impaired by heterogeneity of the groups studied. For example, the classification of FGR is based on either birthweight percentile or absolute birthweight, and different severities of pre-eclampsia are classified as single outcome groups. Additionally, most of the data that support the modest association between FVL, prothrombin 20210A and MTHFR C677T homozygosity and pre-eclampsia derive from retrospective studies.² A meta-analysis of prospective cohort studies did not support this association, although it did find a modest association with pregnancy loss (OR for pregnancy loss in women with FVL 1.52 (95% CI 1.06–2.19)).²² Despite the lack of conclusive evidence in prospective studies, a large Danish National Birth Cohort study, looking at 2032 cases and 1851 random controls, demonstrated a significant but modest association between FVL and placental abruption (OR 1.7, 95% CI 1.2–2.4).⁴⁸ While these data suggest an association, it is likely that these pregnancy complications do not reflect a single disease process. Therefore, in many PMPC, thrombotic mechanisms may not be the principal process. This is important when considering thrombophilia as a biomarker to guide treatment. Thrombophilia is relatively common and may coexist with a PMPC, without a major causative role. Without a more selective approach to identify women at risk through a thrombotic-mediated process, it will remain difficult to demonstrate benefit from antithrombotic intervention. Annexin 5 (ANXA5) M2 haplotype is increasingly recognised as a procoagulant biomarker which might serve to identify such women. Despite the worse prognosis associated with ANXA5 M2 carriers,^{49,50} Fishel et al.⁵¹ demonstrated a similar live birth rate (37.8%) when LMWH was administered to controls (33.0%). This highlights the value of a more homogenous group, when investigating the efficacy of different interventions. This precision medicine approach is widely in use outside of obstetrics, including receptor typing in oncology⁵² and endotyping in asthma care,⁵³ where intervention is targeted at pathological-specific cohorts rather than diagnosis-specific cohorts.

The FRUIT trial randomised 139 women with inherited thrombophilia and previous early onset gestational hypertensive disease (before 34 weeks' gestation) to either LMWH and LDA or LDA alone before 12 weeks' gestation.⁵⁴ It demonstrated a reduction in early onset pre-eclampsia and premature delivery for pre-eclampsia/FGR in the LMWH group, with a risk reduction of 8.7% (CI 1.9–15.5%; $P = 0.012$).⁵⁴ The clinical relevance of this is uncertain, since the overall pre-eclampsia rate and maternal and fetal outcomes were unaffected.

In the TIPPS trial, Rodger et al.²³ randomised 289 pregnant women with thrombophilia and previous PMPCs or VTE to either LMWH or no LMWH.²³ A non-significant 1.8% risk reduction of pregnancy complications was demonstrated in the LMWH arm (95% CI of difference –10.6 to 7.1%).²³ Although this is the largest multicentre RCT to date, with reduced heterogeneity compared with single-centre trials, this study has its own limitations. A number of heritable and acquired thrombophilias were included in a 'basket' of different PMPC conditions making the group heterogeneous for type of thrombophilia and previous event. Recruitment challenges prolonged the trial duration to 12 years, potentially increasing heterogeneity in participant characteristics and co-intervention. There was also a higher proportion of the LMWH arm receiving LDA; and 8.8% of the LMWH arm were enrolled after 12 weeks' gestation, potentially masking positive effects of LMWH peri-implantation. Additionally, these data may only be reliably extrapolated to management of FVL heterozygosity as this contributed to 60% of the cohort.

Interestingly in the single-centre studies by Gris et al.,^{55,56} there was significant reduction in pre-eclampsia and abruption from LMWH treatment. Further in an uncontrolled trial, obstetric outcomes were improved when the dose of LMWH was adjusted according to prior

obstetric history, personal and family VTE history, and presence of thrombophilia.⁵⁷ This raises the possibility that a more homogeneous group with an underlying thrombotic process might benefit from LMWH.

Despite evidence of only a modest association and no clear benefit from antithrombotic treatment,²³ some obstetricians have offered prophylactic LMWH to women with a previous history of PMPC. This is based on biological plausibility, with clinical observation of micro and macro-vascular thrombotic lesions, and extrapolation from APS. This approach can be pragmatic based solely on a previous event, informed by laboratory evidence of a heritable thrombophilia, or by findings of thrombotic changes from placental pathology specimens in the affected pregnancy suggesting a thrombotic mechanism.

Apart from homozygous FVL mutation, the Stillbirth Collaborative Research Network demonstrated no significant association between stillbirth and heritable thrombophilias.⁵⁸ Despite this, RCOG guidelines⁵⁹ recommend a thrombophilia screen to investigate late intrauterine fetal death. This is therefore a controversial approach and likely reflects in part the limited treatment options for subsequent pregnancies, and a clinical view that thrombosis of the placenta may have been a factor. Clearly this is not evidence based. However, just as with PMPC, late intrauterine fetal death is a heterogeneous group of conditions where better stratification may identify a more homogeneous group where thrombotic mechanisms may respond to antithrombotic treatment. Therefore, before excluding such treatment it is important to consider a stratified approach.

There is a stronger evidence base for the association between acquired thrombophilia (APS) and late pregnancy complications compared to inherited thrombophilia. Despite this, the evidence for an association between aCL antibodies and late pregnancy loss is weak and relies on large retrospective meta-analysis of small cohort and case-control studies. There is an association between LA and pre-eclampsia and late fetal loss, but again the absolute risk remains small.⁶⁰ Most of the evidence suggests a beneficial effect of LDA to prevent early pregnancy loss in these women. Therefore, treatment should be based on both the clinical phenotype of APS and the laboratory investigations, rather than laboratory investigations alone.

Conclusion

Despite observed associations between heritable thrombophilia and adverse pregnancy outcome from PMPC, the absolute risk is low. Universal thrombophilia screening is therefore not appropriate. Selective screening leading to LMWH prophylaxis based on general thrombophilia status and previous PMPC has not been effective in RCTs. Thus, at present neither universal nor selective thrombophilia screening (other than APS) is warranted for PMPC, as it adds significant costs without clear benefit. Before discarding screening and treatment however, we should consider developing better stratification with biomarkers, such as the ANXA5 M2 haplotype,⁵¹ for a thrombotic process underlying PMPC. A better understanding of the molecular mechanisms of PMPC is required and data from previous trials could be retrospectively assessed for possible biomarkers. With that approach, sufficiently powered RCTs could address the issues in better stratified and more homogenous patient groups. The value of thrombophilia screening is also limited in VTE, particularly because a negative thrombophilia screen does not exclude thrombotic tendency. For this reason, thrombophilia screening should only be employed where it will influence management.

On a practical level thrombophilia screening requires counselling and careful interpretation of both positive and negative results. It is often performed in early pregnancy where results may be misleading. It is also frequently performed in women with poor obstetric outcomes, IVF failures and recurrent miscarriage, which are emotionally charged situations. It is important to consider the psychological impact of a new thrombophilia diagnosis on the individual embarking on pregnancy and their relatives. Counselling about the increased relative

risks of vascular complications can provoke fear and anxiety disproportionate to the absolute risk, with limited evidence in support of effective treatments.

Careful thought is required before embarking on thrombophilia screening. Situations where this will have proven clinical benefit are few at present. Until we have better evidence from stratified patient groups caution should remain if we wish to practice evidence-based medicine.

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References

1. Knight M, Kenyon S, Brocklehurst P, et al. *Saving lives, improving mothers' care: lessons learned to inform future maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2009–12*. Oxford: National Perinatal Epidemiology Unit, University of Oxford, 2014.
2. Robertson L, Wu O, Langhorne P, et al. Thrombophilia in pregnancy: a systematic review. *Br J Haematol* 2006; 132: 171–196.
3. Aharon A, Katzenell S, Tamari T, et al. Microparticles bearing tissue factor and tissue factor pathway inhibitor in gestational vascular complications. *J Thromb Haemost* 2009; 7: 1047–1050.
4. Arias F, Romero R, Joist H, et al. Thrombophilia: a mechanism of disease in women with adverse pregnancy outcome and thrombotic lesions in the placenta. *J Matern Fetal Med* 1998; 7: 277–286.
5. Branch DW, Dudley DJ, Mitchell MD, et al. Immunoglobulin G fractions from patients with antiphospholipid antibodies cause fetal death in BALB/c mice: a model for autoimmune fetal loss. *Am J Obstet Gynecol* 1990; 163: 210–216.
6. Yetman DL and Kutteh WH. Antiphospholipid antibody panels and recurrent pregnancy loss: prevalence of anticardiolipin antibodies compared with other antiphospholipid antibodies. *Fertil Steril* 1996; 66: 540–546.
7. Opatrny LDM, Kahn SR, Shrier I, et al. Association between antiphospholipid antibodies and recurrent fetal loss in women without autoimmune disease: a metaanalysis. *J Rheumatol* 2006; 33: 2214–2221.
8. Rodger MA, Walker MC, Smith GN, et al. Is thrombophilia associated with placenta-mediated pregnancy complications? A prospective cohort study. *J Thromb Haemost* 2014; 12: 469–478.
9. Wilson JM and Jungner YG. [Principles and practice of mass screening for disease]. *Bol Oficina Sanit Panam* 1968; 65: 281–393.
10. Salvagno GL, Lippi G, Franchini M, et al. The cost-benefit ratio of screening pregnant women for thrombophilia. *Blood Transfus* 2007; 5: 189–203.
11. Eid SS and Rihani G. Prevalence of factor V Leiden, prothrombin G20210A, and MTHFR C677T mutations in 200 healthy Jordanians. *Clin Lab Sci* 2004; 17: 200–202.
12. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite

- antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; 4: 295–306.
13. Biggoggero M and Meroni PL. The geoepidemiology of the antiphospholipid antibody syndrome. *Autoimmun Rev* 2010; 9: A299–304.
 14. Myers BPS. Diagnosis and management of antiphospholipid syndrome in pregnancy. *Obstet Gynaecol* 2011; 13: 15–21.
 15. Mehrania TPM. *Epidemiology of the antiphospholipid*. Amsterdam: Elsevier, 2009.
 16. Eid SS and Rihani G. Prevalence of factor V Leiden, prothrombin G20210A, and MTHFR C677T mutations in 200 healthy Jordanians. *Clin Lab Sci* 2004; 17: 200–202.
 17. Haemostasis, Thrombosis Task Force BCfSiH. Investigation and management of heritable thrombophilia. *Br J Haematol* 2001; 114: 512–528.
 18. Kamel H, Navi BB, Sriram N, et al. Risk of a thrombotic event after the 6-week postpartum period. *N Engl J Med* 2014; 370: 1307–1315.
 19. Clark P, Brennand J, Conkie JA, et al. Activated protein C sensitivity, protein C, protein S and coagulation in normal pregnancy. *Thromb Haemost* 1998; 79: 1166–1170.
 20. James AH, Rhee E, Thams B, et al. Characterization of antithrombin levels in pregnancy. *Thromb Res* 2014; 134: 648–651.
 21. Wu O, Robertson L, Twaddle S, 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* 2006; 10: 1–110.
 22. Rodger MA, Betancourt MT, Clark P, et al. The association of factor V Leiden and prothrombin gene mutation and placenta-mediated pregnancy complications: a systematic review and meta-analysis of prospective cohort studies. *PLoS Med* 2010; 7: e1000292.
 23. Rodger MA, Hague WM, Kingdom J, et al. Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial. *Lancet* 2014; 384: 1673–1683.
 24. Okoroh EM, Azonobi IC, Grosse SD, et al. Prevention of venous thromboembolism in pregnancy: a review of guidelines, 2000–2011. *J Womens Health (Larchmt)* 2012; 21: 611–615.
 25. Bates SMM, Rodger S, James M, et al. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. *J Thromb Thrombolysis* 2016; 41: 92–128.
 26. Greer IA and Thomson AJ. Management of venous thromboembolism in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2001; 15: 583–603.
 27. Bezemer ID, van der Meer FJ, Eikenboom JC, et al. The value of family history as a risk indicator for venous thrombosis. *Arch Intern Med* 2009; 169: 610–615.
 28. Gerhardt AS, Greer RE, Zotz IA, et al. Hereditary risk factors of thrombophilia and probability of venous thromboembolism during pregnancy and the puerperium. *Blood* 2016; 128(19): 2343–49.
 29. Cohen HOBP. *Disorders of thrombosis and hemostasis in pregnancy, a guide to management*. London: Springer-Verlag, 2012.
 30. Lim W, Eikelboom JW and Ginsberg JS. Inherited thrombophilia and pregnancy associated venous thromboembolism. *BMJ* 2007; 334: 1318–1321.
 31. Nelson-Piercy C, MacCallum P and MacKillop L. *Green-top guideline no. 37a – reducing the risk of venous thromboembolism during pregnancy and the puerperium*. London: Royal College of Obstetricians and Gynaecologists, 2015.
 32. Howard LS and Hughes RJ. NICE guideline: management of venous thromboembolic diseases and role of thrombophilia testing. *Thorax* 2012; 68: 391–393.
 33. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141: e691S–736S.
 34. Brill-Edwards P, Ginsberg JS, Gent M, et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. Recurrence of clot in this pregnancy study group. *N Engl J Med* 2000; 343: 1439–1444.
 35. Empson M, Lassere M, Craig J, et al. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. *Cochrane Database Syst Rev* 2005; 2: CD002859.
 36. (RCOG) RCoOaG. *The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage*. London: Royal College of Obstetricians and Gynaecologists (RCOG), 2011, 18 p. (Green-top guideline; no. 17).
 37. Skeith L, Carrier M, Kaaja R, et al. A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. *Blood* 2016; 127: 1650–1655.
 38. Lissalde-Lavigne G, Fabbro-Peray P, Cochery-Nouvellon E, 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: 2178–2184.
 39. de Jong PG, Quenby S, Bloemenkamp KW, et al. ALIFE2 study: low-molecular-weight heparin for women with recurrent miscarriage and inherited thrombophilia—study protocol for a randomized controlled trial. *Trials* 2015; 16: 208.
 40. Potdar N, Gelbaya TA, Konje JC, et al. Adjunct low-molecular-weight heparin to improve live birth rate after recurrent implantation failure: a systematic review and meta-analysis. *Hum Reprod Update* 2013; 19: 674–684.
 41. Qublan H, Amarin Z, Dabbas M, et al. Low-molecular-weight heparin in the treatment of recurrent IVF-ET failure and thrombophilia: a prospective randomized placebo-controlled trial. *Hum Fertil (Camb)* 2008; 11: 246–253.
 42. Lodigiani C, Di Micco P, Ferrazzi P, et al. Low-molecular-weight heparin in women with repeated implantation failure. *Womens Health (Lond)* 2011; 7: 425–431.
 43. Feng Q, Liu K, Liu YX, et al. Plasminogen activators and inhibitors are transcribed during early macaque implantation. *Placenta* 2001; 22: 186–199.
 44. Ivanov P K-PR, Ivanov I, Konova E, et al. Plasminogen activator inhibitor type 1 activity in women with unexplained very early recurrent pregnancy loss. *Akush Ginekol (Sofia)* 2010; 49: 3–8.
 45. Li XLY, Zhang R, Tan J, et al. Meta-analysis of the association between plasminogen activator inhibitor-1 4G/5G Polymorphism and recurrent pregnancy loss. *Med Sci Monit* 2015; 21: 1051–1056.
 46. Buchholz TLP, Rogenhofer N, Kosian E, et al. Polymorphisms in the ACE and PAI-1 genes are associated with recurrent spontaneous miscarriages. *Hum Reprod* 2003; 18: 2473–2477.
 47. Ivanov PIP, Gacheva S, Konova E, et al. Implication of PAI-1 4G/5G polymorphism in recurrent implantation failure after IVF. *Akush Ginekol (Sofia)* 2014; 53: 25–29.
 48. Lykke JA, Bare LA, Olsen J, et al. Thrombophilias and adverse pregnancy outcomes: results from the Danish National Birth Cohort. *J Thromb Haemost* 2012; 10: 1320–1325.
 49. Tiscia G, Colaizzo D, Chinni E, et al. Haplotype M2 in the annexin A5 (ANXA5) gene and the occurrence of obstetric complications. *Thromb Haemost* 2009; 102: 309–313.
 50. Bogdanova N, Horst J, Chlystun M, et al. A common haplotype of the annexin A5 (ANXA5) gene promoter is associated with recurrent pregnancy loss. *Hum Mol Genet* 2007; 16: 573–578.
 51. Fishel S, Baker D, Elson J, et al. Precision medicine in assisted conception: a multicenter observational treatment cohort study of the annexin A5 M2 haplotype as a biomarker for antithrombotic treatment to improve pregnancy outcome. *EBioMedicine* 2016; 10: 298–304.
 52. Carels N, Spinasse LB, Tilli TM, et al. Toward precision medicine of breast cancer. *Theor Biol Med Model* 2016; 13: 7.

53. Lotvall J, Akdis CA, Bacharier LB, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011; 127: 355–360.
54. de Vries JI, van Pampus MG, Hague WM, et al. Low-molecular-weight heparin added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: the FRUIT-RCT. *J Thromb Haemost* 2012; 10: 64–72.
55. Gris JC, Chauleur C, Faillie JL, et al. Enoxaparin for the secondary prevention of placental vascular complications in women with abruptio placentae. The pilot randomised controlled NOH-AP trial. *Thromb Haemost* 2010; 104: 771–779.
56. Gris JC, Chauleur C, Molinari N, et al. Addition of enoxaparin to aspirin for the secondary prevention of placental vascular complications in women with severe pre-eclampsia. The pilot randomised controlled NOH-PE trial. *Thromb Haemost* 2011; 106: 1053–1061.
57. Figueiro-Filho EA, de Oliveira VM, Breda I, et al. [Usefulness of a scoring system on perinatal outcomes in pregnant women with thrombophilia in the effectiveness of an enoxaparin-based intervention]. *Rev Bras Ginecol Obstet* 2012; 34: 459–465.
58. Silver RM, Saade GR, Thorsten V, et al. Factor V Leiden, prothrombin G20210A, and methylene tetrahydrofolate reductase mutations and stillbirth: the Stillbirth Collaborative Research Network. *Am J Obstet Gynecol* 2016; 215: 468.e1–468.e17.
59. Siassakos DFR, Draycott T and Winter C. *Green-top guideline no. 55; late intrauterine fetal death and stillbirth*. London: Royal College of Obstetricians and Gynaecologists, 2010.
60. Abou-Nassar K, Carrier M, Ramsay T, et al. The association between antiphospholipid antibodies and placenta mediated complications: a systematic review and meta-analysis. *Thromb Res* 2011; 128: 77–85.