We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter 4

Pharmacogenetics and the Treatment of Thrombophilia

Ivana Novaković, Nela Maksimović and Dragana Cvetković

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/56566

1. Introduction

Inherited forms of thrombophilia such as factor V Leiden mutation (FVL), prothrombin gene mutation (PT 20210A), and deficiencies of natural anticoagulants protein C, protein S, and antithrombin are well known. DNA tests for factor V Leiden and PT 20210A mutation have been incorporated in clinical practice for several years [1,2,3]. A number of studies have analyzed how this and other molecular genetic testing alter the clinical management and treatment of patients with thromboembolic disease or pregnancy complications. Data regarding the influence of the genotype to the disease phenotype as well as pharmacogenetic data are still controversial and emerging.

Several topics are of particular interest. Usually genetic tests follow standard investigation of coagulation cascade, but some laboratories perform them in initially. Testing of first-degree relatives of a diagnosed carrier of a thrombophilic trait is still not consecutive. Administration of anticoagulant therapy is followed by genetic tests also; DNA variations are associated with variations in drug efficacy and toxicity, particularly in cases of warfarin and clopidogrel. Investigation of inherited thrombophilia and its treatment in women with reproductive challenges, including *in vitro* fertilization (IVF), is another important question. Finally, recommendation for genetic testing and treatment of thrombophilia in children, as vulnerable group, should be clarified.

2. Thromophilia screening and treatment in asymptomatic adult carriers

Thrombophilia testing is one of the most common genetic tests ordered by clinicians [4]. Current guidelines recommend screening for inherited thrombophilia only in selected group of patients with venous thromboembolism, dependently of the age of onset, the circumstances of thrombosis, and the severity of the clinical manifestations [5,6].

INTECH
open science | open minds

© 2013 Novaković et al.; licensee InTech. This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

When the results of the index patients are positive asymptomatic relatives often come with requests for thrombophilia testing. To date, there is variety of published guidelines. However, the utility of family testing remains matter of debate and it should be done with caution. It is a general knowledge that genetic testing is justified only if the results are likely to change medical management. American College of Medical Genetics (ACMG) and Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group published consensus statements on FVL and FII. According to ACMG it is not recommended to perform random screening of general population or prenatal and routine newborn screening [7]. Based on the current knowledge, identification of thrombophilic disorders in asymptomatic individuals would not lead to long-term treatment with anticoagulants since the risk of bleeding is higher than the risk of venous thromboembolism (VTE) [7]. The overall annual incidence of the first VTE in individuals with antithrombin, protein C or protein S deficiency is ~1.5 %, whereas for the factor V Leiden or prothrombin 20210A mutation heterozygote this risk is ~0.5% [8]. Annual major bleeding risk associated with continuous anticoagulant treatment is around 2% and it overweighs the risk of VTE [9]. The results of Middeldorp et al. on asymptomatic carriers of FVL, are in agreement with the above and since there is no clear evidence of the benefit of thrombophylaxis they do not recommend routine screening of families of symptomatic patients [10]. Also, Coppens et al. do not recommend testing first degree relatives of probands with the prothrombin 20210A mutation based on the results of a large prospective cohort study in which the annual incidence of a first VTE in PT carriers was 0.37% [11]. For asymptomatic family members who are homozygous for FVL mutation the risk increases to closely 2%. According to EGAPP the risk is sufficient to consider anticoagulation therapy but there are still no data about the outcomes [12].

The practice of family testing has been most useful for women from thrombophilic families who intend to be pregnant. Affected female relatives with antithrombin, protein C and protein S deficiency as well as FVL and 20210A mutation carriers have VTE incidence as high as 4% per pregnancy while women homozygous for FVL have the risk of 16% per pregnancy in the absence of prophylaxis [13]. In these cases anticoagulant therapy, usually low molecular heparin injections, is frequently applied.

Genetic testing is also very useful for women from thrombophilic families who wish to use oral contraceptives. Use of oral contraceptives increases the risk of VTE for women with antithrombin, protein C or protein S protein deficiency or FVL and 20210A mutation. However, it is important to know that women from thrombophilic families are at the increased risk (compared with the general population) even if they do not have these specific deficiencies or mutations, due to the other cosegregating thrombophilic defects [8]. Thus, a negative thrombophilia test may give them false reassurance.

Family testing may also help reduce VTE risk for women who tested positive through avoidance of postmenopausal hormone therapy. Advantages of testing are even higher for women considering postmenopausal hormone therapy than oral contraceptives, due to the much higher absolute risk of VTE in middle-aged than in younger women [13].

3. Antithrombotic therapy and the promise of pharmacogenetics

The expansion of pharmacogenetics, the study of genetic variants relevant to variations in drug efficacy and toxicity, and pharmacogenomics, referred to as a whole-genome application of pharmacogenetics, allowed rapid progress towards the goal of personalized therapy, tailored for individual patients [14-17].

The research in this field provides large amounts of individual-specific information concerning risk for adverse reactions or lack of drug efficacy, thus it could have significant influence on clinical practice. The question of how to use the pharmacogenetic information to improve health outcomes gains continuously increasing attention [18-20]. Specifically, it has been shown that pharmacogenetic information has the potential to improve the efficacy and safety of major antithrombotic drugs (e.g. [21]).

3.1. Warfarin: A case in point

One of the most compelling examples of potential benefits from pharmacogenomic testing is warfarin [22]. Warfarin is a widely prescribed oral anticoagulant; for decades it has been used as standard drug to prevent and treat thrombotic events in patients with deep vein thrombosis, various hypercoagulable states, atrial fibrillation, surgical cardiac valve replacement, etc.

One of the major problems with its use in clinical practice is large interindividual variation – patients differ in sensitivity to warfarin, hence the dose requirements vary widely (up to 20-fold) [19,23]. The consequences of over- or under-anticoagulation can be serious. In patients less sensitive than typical, the standard doses may be too low to achieve anticoagulation and therapeutic failure may occur, while in highly sensitive individuals the same doses may lead to serious adverse effects, such as hemorrhage.

Numerous factors are known to impact dose variation, including age, dietary vitamin K intake, presence of other comorbidities and interactions with other drugs, as well as genetic variants. The identification of these variants, and the potential use of pharmacogenetic testing to predict the appropriate drug dosing have attracted much research interest [23-28].

Prior work pointed to significant genetic component underlying variations in warfarin sensitivity. Pharmacogenetic studies identified polymorphisms in genes *CYP2C9* and *VKORC1* as principal genetic determinants of warfarin dose [23,24,29].

CYP2C9 gene encodes one of the major cytochrome P450 drug-metabolizing enzymes; it is involved in metabolic clearance of S-warfarin, the more potent isomer of warfarin, which is largely responsible for its therapeutic effects. Two common alleles are described, *CYP2C9**2* and *CYP2C9*3*, based on non-synonymous SNPs that result in Arg144Cys (*2) and Ile358Leu (*3) substitutions; both variants are associated with reduced metabolic clearance of S-warfarin, thus lowering dose requirements [24]. Carriers of these variants show high sensitivity to drug and increased risk for hemorrhagic complications compared to individuals homozygous for allele *1. It is estimated that SNPs in *CYP2C9* gene account for approximately 12% of the total variance in required warfarin dose [23] (range 6–18%, [18]).

Larger proportion of the dose variance, up to 30%, is explained by SNPs in the gene *VKORC1* [25,29]. *VKORC1* encodes vitamin K epoxide reductase complex, the target enzyme inhibited by warfarin; this enzyme is necessary for the recycling of vitamin K and consequently for activation of several clotting factors. Currently, several *VKORC1* SNPs are described (the major one being *VKORC1* -1639G>A, a common polymorphism of the promoter sequence) that define two common haplotypes, A and B. Haplotype A is associated with higher warfarin sensitivity, and hence lower mean drug doses required, contrary to B haplotype [29].

With respect to frequencies of these variants, genetic differences between populations are also a matter of great interest. The common *CYP2C9* alleles *2 and *3, associated with high warfarin sensitivity, are present in approximately 30% of people of European descent (range 13-35%), but are less frequent in those of Asian (1-12%) and African descent (0-12%) [21,25,30]. *VKORC1* B haplotype, associated with low warfarin sensitivity, is more common in European and African populations, while 'high sensitivity' A haplotype predominates in Asian populations. The frequency of A is reported as 75–92% in Asians, compared to approximately 40% in Europeans or 9–12% in people of African descent [21].

To predict response to treatment, considering polymorphisms in both genes simultaneously is of great importance. Carriers of variants associated with 'high sensitivity' at both loci are at much higher risk of over-anticoagulation [31]. On the other hand, individuals who are *CYP2C9**1*1-*VKORC1*BB show less warfarin sensitivity and require higher drug dose for therapeutic anticoagulation [25]. The associated variants in both genes are thought to account for approximately 45% of response variance in European and 30% in African populations [21].

The frequency of *VKORC1* and *CYP2C9* alleles was also investigated in Serbian population, among patients under oral anticoagulant therapy [32,33]. In a group of patients with extremely unstable anticoagulant response, 89.7% were carriers of 'sensitivity' alleles, and 25% carried these variants at both *CYP2C9* and *VKORC1* loci [33].

A recent genome wide association study (GWAS) by Takeuchi et al. confirmed polymorphisms in genes *VKORC1* and *CYP2C9* as principal genetic determinants of warfarin dose and also found weaker, but still significant effect of polymorphism in another CYP gene, *CYP4F2* [23]. The effect of *CYP4F2* rs2108622 was confirmed by other authors (e.g. [26,34]).

The results concerning possible contribution of other candidate genes are still inconsistent. The investigation of other SNPs and CNVs (copy number variations) did not reveal new significant warfarin associations [23], however, limited positive data was obtained for polymorphisms in additional candidate genes such as *POR* (encoding cytochrome P450 oxidoreductase) or *CALU* (encoding calumenin) (review in [27]).

The additional polymorphisms in these or other genes relevant to blood coagulation may be worth further investigation, especially in non-European populations that were less studied pharmacogenetically [27,28].

http://dx.doi.org/10.5772/56566

4. Clinical application of pharmacogenetic testing — Promises and problems

What are the promises and problems of the genotype-guided antithrombotic therapy? Pharmacogenetic testing has the potential to improve the efficacy and safety of warfarin and other antithrombotic drugs [21].

Recognizing the significance of the genetic information, US FDA added it to warfarin label in 2007 and suggested that clinicians considered genetic testing before initiating therapy. Genetic tests for *CYP2C9* and *VKORC1* 'sensitivity' variants are available for clinical use, and so are dosing algorithms that combine genetic and clinical data [35,36]. Including *CYP4F2* rs2108622 in testing procedures and algorithms is also suggested [27].

However, the question of routine adoption of pharmacogenetic testing for warfarin sensitivity into clinical practice has led to vigorous debates. Numerous problems and challenges arise, from cost-effectiveness analyses, possibility of development of alternative drugs [27], complexity, quality and time demands, the need for additional education and training, to ethical and regulatory issues [19,21,36].

The major issue for clinical application of pharmacogenetic testing is that this approach must provide significant benefit to patients compared to nongenetic approach only. Cost-effectiveness emerges as another important question in modern health care; currently, discussions are focused on the cost of genetic testing *vs.* potential savings by reducing severe health complications [18,19,31,37]. Also, the aim is to identify specific groups of patients who will benefit most from the pharmacogenetic testing [20], and to obtain diversity of warfarin dosing algorithms that should reflect genetic diversity of populations [28].

A multicenter study, published in 2009 by the International Warfarin Pharmacogenetics Consortium, demonstrated that algorithms for warfarin dosing that incorporate pharmacogenomic information were better than those using clinical data alone [35]. The greatest benefits were observed in patients with extreme (very low or very high) dose requirements. A recent Medco-Mayo Warfarin Effectiveness study demonstrated that application of warfarin genotyping significantly reduced the incidence of hospitalizations due to bleeding and thromboembolism [37]. Eckman and colleagues analyzed cost-effectiveness of using pharmacogenetic approach for patients with atrial fibrillation and concluded that genotype-guided warfarin therapy might be cost effective in a high-risk group [31].

However, general consensus regarding these questions is lacking. The results of the ongoing studies and trials, conducted on large scales and diverse populations, are expected to clarify these issues [21].

With the current pace of pharmacogenetic discoveries, integrating the growing amount of individual-specific data into clinical practice to improve health outcome will remain the challenging task.

5. Genetics and treatment of reproductive adversity in thrombophilia

Clinical manifestations and morbidity associated with thrombophilia in pregnancy include pregnancy loss, as well as other adverse outcomes eg. preeclampsia, placental abruption, and intrauterine growth restriction. Pregnancy-related thromboembolism is also part of thrombophilia spectrum making the influence of thrombophilia in pregnancy is an important and interesting research topic.

The effect of preventive anticoagulant therapy during the pregnancy in women with inherited thrombophila is still controversial. Early investigations were characterized by small participant numbers, poor study design and heterogeneity. The debate on the efficacy of aspirin and heparin has advanced with recently published randomised-controlled trials. One large Italian study encompassed 1011 pregnancies of 416 women who were carriers of factor V Leiden (FVL) mutation and/or prothrombin gene variant G20210A (PTG) [38]. The outcome was evaluated according to the type of treatment (low molecular weight heparin and/or aspirin) and the period of pregnancy when the treatment started. The results showed that low molecular weight heparin (LMWH) had a protective effect on miscarriages (odds ratio, OR 0.52) and venous thromboembolism (OR 0.05) while aspirin administration showed no advantage on the prevention of obstetric complications and venous thromboembolism (OR 2.2 and 0.48, respectively). These results suggest that LMWH prophylaxis reduces the risk of obstetric complications in carriers of FVL and/or PTG, particularly in those with previous obstetric events. Mitic et al. also reported significant improvement of pregnancy outcome after implementation of thromboprophylaxis in Serbian patients with inherited thrombophilia and previous pregnancy losses [39].

One Bulgarian group reported their first experience with management of inherited thrombophilia during pregnancy [40]. After the testing for factor V Leiden, prothrombin G20210A, plasminogen activator inhibitor-1 (PAI-1) 4G/4G and PAI-1 4G/5G they established a diagnosis of inherited thrombophilia in 72% (24 out of 38) patients with history of an abnormal pregnancy (miscarriage, still birth, placental abruption, preeclampsia and intrauterine fetal growth restriction). All diagnosed patients were treated with aspirin (75mg) prior to conception and low molecular heparin after detection of fetal heart sounds. Anticoagulant treatment of these patients was deemed successful with 87.5% (21 out of 24) giving birth to a term newborn.

However, several investigators have reported confounding experiences [41-43]. In a recently published review, de Jong et al suggest that the association between inherited thrombophilia and recurrent miscarriage is not very strong, and the evidence does not indicate that the use of anticoagulants improves the chance of live birth in these women [41]. The authors conclude that by the current state of evidence, testing for inherited thrombophilia should not lead to altered clinical management and so, should not be performed routinely in women with recurrent miscarriage. In light of the available data, a well-designed, multi-center collaboration is required to ascertain the effect of inherited thrombophilia on early pregnancy loss and to establish evidence-based treatment recommendations [44].

It may be possible that in women with recurrent pregnancy loss multiple thrombophilic gene mutations rather than specific single gene changes play a role. In one study, 10 gene mutations

were analyzed: factor V Leiden, factor V H1299R (R2), factor V Y1702C, prothrombin gene G20210A, factor XIII V34L, beta-fibrinogen -455G>A, PAI-1 4G/5G, human platelet alloantigen a/b (L33P), methylenetetrahydrofolate reductase C677T and A1298C [45]. There were no differences in the frequency of specific mutations in women with recurrent miscarriage compared to healthy control. However, the prevalence of homozygous mutations and total gene mutations was significantly higher in patients compared to controls. Homozygous mutations were found in 59% of women with a history of recurrent pregnancy loss vs. 10% of control women. More than three gene mutations were observed in 68% of women with recurrent miscarriage compared to 21% of controls. It would be of especial interest to explore how number of detected mutations influences effects of prophylactic therapy and further reproductive outcome.

The possible connection between inherited thrombophilia and outcomes of *in vitro* fertilization (IVF) is another challenging topic. A number of investigations suggest no association of thrombophilic mutations and IVF pregnancy failure [46,47]. Rudick et al. found a very low prevalence of FVL mutation in women in their IVF program (1.6%), and suggested a positive association between this genetic marker and pregnancy [47]. The authors suggested that routine testing in a general IVF population for FVL mutation as a cause of IVF failure and infertility is not indicated. Ricci et al. compared the prevalence of FVL and PTG mutation in women undergoing IVF to women with spontaneous pregnancy, as well as IVF outcomes and the risk of complications in FVL and PTG carriers to non-carriers [48]. In this prospective cohort study they found the same prevalence of thrombophilic mutations in women requiring IVF and in women with spontaneous pregnancy. The results of this study also suggested the presence of FVL and PTG in asymptomatic women and in the absence of other risk factors did not influence IVF outcome, represent a risk for ovarian hyperstimulation syndrome, or favor thrombosis after IVF. According to these authors, screening for FVL and PTG does not appear to be justified to identify the patients at the risk for IVF failure or associated complications.

However, some studies have shown positive effects of LMWH treatment for women with thrombophilia and recurrent IVF- embrio transfer failures [49,50]. In one prospective randomized placebo-controlled trial Qublan et al. observed that implantation rate, pregnancy and live birth rates are significantly increased with LMWH compared to placebo [49]. At this moment, diagnostic tools to identify patients at risk of implantation failure are still limited and therapeutic options to improve implantation rates are far from being established. In addition to genetic markers of thrombophilia and thromboprophylaxis, different immunological mechanisms and consecutive immunomodulatory treatments are the subjects of intensive investigations [51].

6. Thrombophilia screening in asymptomatic children

Parents with known specific thrombophilic defect frequently ask whether or not their child(ren) should also be screened for thrombophilia. Many of them are concerned about their

children's health, mostly the risk of having VTE or reproductive issues, especially if the mother was diagnosed during pregnancy or after several pregnancy losses. Genetic testing is particularly controversial in children since their decision-making capability is non-existent or is limited [52].

The recommendation of The American Academy of Pediatrics (AAP) and the ACMG is that predictive genetic testing for late-onset disorders should not be performed unless there is a specific intervention during childhood that will reduce morbidity or mortality [53,54]. Also, the AAP does not support the broad use of carrier testing or screening in children or adolescents. As for any genetic testing, a medical benefit should be the primary justification for testing in children and adolescents. It is very important for parents to understand the limitations of testing before they sign informed consent for their children. The results of thrombophilia testing rarely influence medical management decisions and at the moment there is no evidence that thrombophilia testing could benefit a young healthy child. The incidence of venous thrombosis in healthy children is extremely low (0.07/100000), and the long-term use of anticoagulants in an asymptomatic healthy child would be unjustified [55].

Tormene et al. performed a prospective cohort study of children aged 1-14 years from families with a single identified inherited thrombophilia. The children were tested for FVL, prothrombin G20210A mutations and antithrombin, protein C and protein S deficiency and followed for the evidence of thrombosis 1-8 years (mean 5 years). No children with or without thrombophilia developed VTE during the study period [56]. Thrombophilia testing could show more benefit for children with the acute or chronic medical conditions. The overwhelming majority of pediatric TEs are associated with central venous lines (CVLs) [52].

Other acquired risk factors depend on the age of the child. Within the entire childhood population neonates are at the greatest risk of thromboembolism (5.1/100 000 live births per year in white children) [57]. Neonatal risk factors include birth asphyxia, respiratory distress syndrome, maternal diabetes, infections, necrotizing enterocolitis, dehydration, congenital nephrotic syndrome and polycythemia [57]. Children of any age may have antiphospholipid or anticardiolipin antibodies which are associated with thrombophilia [52]. Meta-analysis of Young et al. on impact of inherited thrombophilia on venous thromboembolism in children showed significant association with recurrent VTE for all inherited thrombophilia traits except the factor V variant and elevated lipoprotein (a) [58]. A second peak of incidence of thrombosis is during adolescence [59]. Adolescents may have the same risk factors as the adults including smoking, pregnancy, obesity, and oral contraceptives which increase the risk of thrombosis [52]. Adolescents identified with an inherited thrombophilia may benefit from avoiding high-risk situations (prolonged immobility, dehydration), pursuing healthy lifestyles (regular exercise and weight control), and recognizing early signs and symptoms of VTE [60].

There are some situations in which the presence of an inherited defect may influence medical decision making. The first is in an adolescent female who is interested in using oral contraceptive pills (OCPs). Knowledge of a congenital thrombophilia provide the opportunity to consider lower-risk alternatives for contraception, such as progesterone-only preparations. In

limited cases, the presence of inherited thrombophilia might lead to targeted thrombophylaxis in high risk situations, e.g., after a femur fracture in an obese teenager, though there are few data to document the efficacy of this approach [60].

7. Genetic counseling

It is of major importance to provide genetic counseling to patients as well as to their asymptomatic family members who are interested in thrombophilia testing, including pharmacogenetic tests. Based on detailed information about a family history, personal history and the reasons for testing genetic counselor should provide education and support for the family members. During the pre-test genetic counseling patient or family member should understand that the testing is optional and that it will be performed only after signed informed consent. It must be clarified that this is a testing for susceptibility gene and not for the disease state and that an individual's thrombotic risk is determined by a complex interplay of genetic, acquired and circumstantial risk factors [1]. It must be clear to the family member that if thrombophilia mutation is inherited the risk of VTE is higher than it is in the general population but although the inheritance pattern is dominant the penetrance of the mutation is not 100%. In order to achieve a better understanding of potential risk when counseling a family member regarding the risk of thrombosis it is most useful to provide the absolute risk (e.g., incidence) of thrombosis among persons with particular thrombophilia [61]. Pre-test genetic counseling should include discussion not only about the risks but also about the benefits and limitations of testing for the patient and for the entire family. Asymptomatic family member should understand that testing for thrombophilia may have lower benefit to risk ratio as compared to symptomatic relative [62]. Post-test counseling is equally as important for family members who tested positive and negative. In case when the result is negative family members should understand that currently available tests might not identify all inherited risk factors for thrombosis [52]. In the other case discussion should include signs and symptoms of thrombosis, risk factors to avoid and the risks and benefits of prophylactic therapy [63]. Clinical geneticist should also be aware of psychological response of the tested individual. Results of the study of Louzada et al. do not support the concern that asymptomatic relatives are at risk of psychological distress as a consequence of thrombophilia screening [64]. However it is general conclusion that characteristics of the genetic predisposition, including the likelihood of developing the disease, perceived severity and availability of treatments for the condition are likely contributors to the psychological response [64]. It means that adequate genetic counseling is of key importance for education of family members, in order to increase their awareness of risk factors and effective interventions to prevent VTE.

As a conclusion, genetic tests are part of modern management and treatment of thrombophilia, but several medical and ethical dilemmas are still open. Healthcare professionals should apply evidence-based guidelines regarding indications for genetic and pharmacogenetic testing, as well as principles of genetic counseling in thrombophilia. In the upcoming era of personalized genomic medicine, genetic tests day after day become more available, but their real power and relevance is fully expressed in the context of clinical data.

Acknowledgements

This work was supported by Ministry of Education and Science, Republic of Serbia (Grant No. 175091).

Author details

Ivana Novaković[1], Nela Maksimović[1] and Dragana Cvetković[2]

1 Faculty of Medicine, University of Belgrade, Belgrade, Serbia

2 Faculty of Biology, University of Belgrade, Belgrade, Serbia

References

[1] Varga EA, Kujovich JL. Management of inherited thrombophilia: guide for genetics professionals. Clin Genet. 2012;81(1):7-17.

[2] Novaković I, Maksimovic N, Cvetkovic S, Cvetkovic D: Gene polymorphisms as markers of disease susceptibility. J Med Biochem., 2010;29(3):1-5.

[3] Novaković I, Cvetković D, Maksimović N: Inherited Thrombophilia and the risk of vascular events. in: Luigi Tranquilli A. (ed.): Thrombophilia. ISBN 978-953-307-872-4, InTech, Croatia, 2011, 59-74.

[4] Hellmann EA, Leslie ND, Moll S. Knowledge and educational needs of individuals with the factor V Leiden mutation. J Thromb Haemost. 2003;1(11):2335–9.

[5] Walker P, Gregg AR. Screening, testing, or personalized medicine: where do inherited thrombophilias fit best? Obstet Gynecol Clin North Am. 2010;37(1):87-107.

[6] Favaloro EJ, McDonald D, Lippi G. Laboratory investigation of thrombophilia: the good, the bad, and the ugly. Semin Thromb Hemost. 2009 Oct;35(7):695-710.

[7] American College of Medical Genetics. Principles of screening: report of the subcommittee of the American College ofMedical Genetics Clinical Practice Committee. http://www.acmg.net/resources/policies/pol-026.asp1997.

[8] Middeldorp S. Is thrombophilia testing useful? Hematology. American Society of Hematology Education Program Book. 2011;2011(1):150-5.

[9] Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. Ann Intern Med. 2003;139(11):893-900.

[10] Middeldorp S, Meinardi JR, Koopman MM, van Pampus EC, Hamulyak K, van Der Meer J, et al. A prospective study of asymptomatic carriers of the factor V Leiden mutation to determine the incidence of venous thromboembolism. Ann Intern Med. 2001;135(5):322–7.

[11] Coppens M, van de Poel MH, Bank I, Hamulyak K, van der Meer J, Veeger NJ et al. A prospective cohort study on the absolute incidence of venous thromboembolism and arterial cardiovascular disease in asymptomatic carriers of the prothrombin 20210A mutation. Blood 2006; 108(8):2604-7.

[12] Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group. Recommendations from the EGAPP Working Group: Routine testing for Factor V Leiden (R506Q) and prothrombin (20210G>A) mutations in adults with a history of idiopathic venous thromboembolism and their adult family members. Genetics in Medicine. 2011;13(1):67-76.

[13] Cushman M. Inherited Risk Factors for Venous Thrombosis. Hematology. American Society of Hematology Education Program Book. 2005;2005(1):452-7.

[14] Jekic B, Lukovic L, Bunjevacki V, Milic V, Novakovic I, Damnjanovic T, Milasin J, Popovic B, Maksimovic N, Damjanov N, Radunovic G, Kovacevic L, Krajinovic M. Association of the TYMS 3G/3G genotype with poor response and GGH 354GG genotype with the bone marrow toxicity of the methotrexate in RA patients. Eur J Clin Pharmacol. 2012 Jul 5. [Epub ahead of print], DOI 10.1007/s00228-012-1341-3

[15] Milic V, Jekic B, Lukovic L, Bunjevacki V, Milasin J, Novakovic I, Damnjanovic T, Popovic B, Maksimovic N, Damjanov N, Radunovic G, Pejnovic N, Krajinovic M. Association of dihydrofolate reductase (DHFR) -317AA genotype with poor response to methotrexate in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2012;30(2): 178-83.

[16] Todorovic Z, Džoljić E, Novaković I, Mirković D, Stojanović R, Nešić Z, Krajinović M, Prostran M, Kostić V. Homocysteine serum levels and MTHFR C677T genotype in patients with Parkinson's disease, with and without levodopa therapy. J Neurol Sci. 2006; 248(1-2),56-61.

[17] Krcunović Z, Novakovic I, Maksimovic N, Bukvic D, Simic-Ogrizovic S, Jankovic S, Djukanovic L, Cvetkovic D. Genetic clues to the etiology of Balkan endemic nephropathy: Investigating the role of ACE and AT1R polymorphisms. Arch Biol Sci 2010;62(4),957-65.

[18] Pereira NL and Weinshilboum RM. Cardiovascular pharmacogenomics and individualized drug therapy. Nat Rev Cardiol. 2009; 6(10): 632–8.

[19] Damani SB, Topol EJ. Emerging clinical applications in cardiovascular pharmacogenomics. Wiley Interdiscip Rev Syst Biol Med. 2011; 3(2):206-15.

[20] Voora D, Ginsburg GS. Clinical application of cardiovascular pharmacogenetics. J Am Coll Cardiol. 2012; 60(1):9-20.

[21] Seip RL, Duconge J, Ruaño G. Implementing genotype-guided antithrombotic therapy. Future Cardiol. 2010; 6(3):409-24.

[22] Dumas TE, Hawke RL, Lee CR. Warfarin dosing and the promise of pharmacogenomics. Curr Clin Pharmacol. 2007; 2(1): 11-21.

[23] Takeuchi F, McGinnis R, Bourgeois S, Barnes C, Eriksson N, et al. A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. PLoS Genet. 2009; 5(3):e1000433.

[24] Higashi MK, Veenstra DL, Kondo LM, Wittkowsky AK, Srinouanprachanh SL et al. Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. JAMA 2002; 287(13):1690-8.

[25] Moyer TP, O'Kane DJ, Baudhuin LM, Wiley CL, Fortini A et al. Warfarin sensitivity genotyping: a review of the literature and summary of patient experience. Mayo Clin Proc. 2009; 84(12):1079-94.

[26] Singh O, Sandanaraj E, Subramanian K, Lee LH, Chowbay B. Influence of CYP4F2 rs2108622 (V433M) on warfarin dose requirement in Asian patients. Drug Metab Pharmacokinet. 2011; 26(2): 130-6.

[27] Daly AK. Optimal dosing of warfarin and other coumarin anticoagulants: the role of genetic polymorphisms. Arch Toxicol. 2013; 87:407–20.

[28] Suarez-Kurtz G, Botton MR. Pharmacogenomics of warfarin in populations of African descent. Br J Clin Pharmacol. 2013; 75(2): 334–46.

[29] Rieder MJ, Reiner AP, Gage BF, Nickerson DA, Eby CS et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med. 2005; 352(22): 2285-93.

[30] Ross KA, Bigham AW, Edwards M, Gozdzik A et al. Worldwide allele frequency distribution of four polymorphisms associated with warfarin dose requirements. J Hum Genet. 2010; 55(9):582-9.

[31] Eckman MH, Rosand J, Greenberg SM, Gage BF. Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. Ann Intern Med. 2009; 150(2):73-83.

[32] Kovač M, Maslać A, Rakićević Lj, Radojković D. The c.-1639G>A polymorphism of the VKORC1 gene in Serbian population: retrospective study of the variability in response to oral anticoagulant therapy. Blood Coagulation & Fibrinolysis 2010; 21(6): 558–63.

[33] Kovač M, Rakićević Lj, Kusić-Tišma J, Radojković D. Pharmacogenetic tests could be helpful in predicting of VKA maintenance dose in elderly patients at treatment initiation. Journal of Thrombosis and Thrombolysis, 2012; DOI: 10.1007/s11239-012-0769-8.

[34] Zhang X, Li L, Ding X, Kaminsky LS. Identification of cytochrome P450 oxidoreductase gene variants that are significantly associated with the interindividual variations in warfarin maintenance dose. Drug Metab Dispos. 2011; 39(8): 1433-9.

[35] International Warfarin Pharmacogenetics Consortium, Klein TE, Altman RB, Eriksson N et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med 2009; 360(8):753-64.

[36] Sorich M, McKinnon R. Personalized Medicine: Potential, Barriers and Contemporary Issues. Current Drug Metabolism 2012; 13(7): 1000-6.

[37] Epstein RS, Moyer TP, Aubert RE, O'Kane DJ, Xia F et al. Warfarin Genotyping Reduces Hospitalization Rates. Results From the MM-WES (Medco-Mayo Warfarin Effectiveness Study). Journal of the American College of Cardiology 2010; 55 (25): 2804-12.

[38] Tormene D, Grandone E, De Stefano V, Tosetto A, Palareti G, Margaglione M, Castaman G, Rossi E, Ciminello A, Valdrè L, Legnani C, Tiscia GL, Bafunno V,Carraro S, Rodeghiero F, Simioni P. Obstetric complications and pregnancy-related venous thromboembolism: the effect of low-molecular-weight heparin on their prevention in carriers of factor V Leiden or prothrombin G20210A mutation. Thromb Haemost. 2012;107(3):477-84.

[39] Mitić G, Novakov Mikić A, Povazan L, Mitreski A, Kopitović V, Vejnović T. Thromboprophylaxis implementation during pregnancy in women with recurrent foetal losses and thrombophilia. Med Pregl. 2011;64(9-10):471-5.

[40] Marinov B, Pramatarova T, Andreeva A, Iarukova N, Slavov A. Our experience with management of inherited thrombophilia during pregnancy. Preliminary report. Akush Ginekol (Sofiia). 2011;50(6):15-7.

[41] de Jong PG, Goddijn M, Middeldorp S. Testing for inherited thrombophilia in recurrent miscarriage. Semin Reprod Med. 2011;29(6):540-7.

[42] Lund M, Nielsen HS, Hviid TV, Steffensen R, Nyboe Andersen A, Christiansen OB. Hereditary thrombophilia and recurrent pregnancy loss: a retrospective cohort study of pregnancy outcome and obstetric complications. Hum Reprod. 2010;25(12): 2978-84.

[43] Tang AW, Quenby S. Recent thoughts on management and prevention of recurrent early pregnancy loss. Curr Opin Obstet Gynecol. 2010;22(6):446-51.

[44] McNamee K, Dawood F, Farquharson RG. Thrombophilia and early pregnancy loss. Best Pract Res Clin Obstet Gynaecol. 2012;26(1):91-102.

[45] Coulam CB, Jeyendran RS, Fishel LA, Roussev R. Multiple thrombophilic gene mutations rather than specific gene mutations are risk factors for recurrent miscarriage. Am J Reprod Immunol. 2006;55(5):360-8.

[46] Simon A, Laufer N. Repeated implantation failure: clinical approach. Fertil Steril. 2012;97(5):1039-43.

[47] Ricci G, Bogatti P, Fischer-Tamaro L, Giolo E, Luppi S, Montico M, Ronfani L, Morgutti M. Factor V Leiden and prothrombin gene G20210A mutation and in vitro fertilization: prospective cohort study. Hum Reprod. 2011;26(11):3068-77.

[48] Rudick B, Su HI, Sammel MD, Kovalevsky G, Shaunik A, Barnhart K.Is factor V Leiden mutation a cause of in vitro fertilization failure? Fertil Steril. 2009;92(4):1256-9.

[49] Qublan H, Amarin Z, Dabbas M, Farraj AE, Beni-Merei Z, Al-Akash H, Bdoor AN,Nawasreh M, Malkawi S, Diab F, Al-Ahmad N, Balawneh M, Abu-Salim A. 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(4):246-53.

[50] Coulam CB, Jeyendran RS, Fishel LA, Roussev R. Multiple thrombophilic gene mutations are risk factors for implantation failure. Reprod Biomed Online. 2006;12(3): 322-7.

[51] Toth B, Würfel W, Germeyer A, Hirv K, Makrigiannakis A, Strowitzki T. Disorders of implantation--are there diagnostic and therapeutic options? J Reprod Immunol. 2011;90(1):117-23.

[52] Thornburg CD, Dixon N, Paulyson-Nunez K, Ortel T. Thrombophilia screening in asymptomatic children. Thrombosis Research.2008; 121:597-604.

[53] Nelson RM, Botkjin JR, Kodish ED, Levetown M, Truman JT, Wilfond BS, et al. Ethical issues with genetic testing in pediatrics. Pediatrics. 2001;107(6):1451–5.

[54] Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. American Society of Human Genetics Board of Directors, American College of Medical Genetics Board of Directors. Am J Hum Genet. 1995;57(5):1233–41.

[55] Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. Blood. 1994;83:1251-7.

[56] Tormene D, Simioni P, Prandoni P, Franz F, Zerbinati P, Tognin G, et al. The incidence of venous thromboembolism in thrombophilic children: a prospective cohort study. Blood. 2002;100(7):2403–5.

[57] Nowak-Gottl U, Duering C, Kempf-Bielack B, Strater R. Thromboembolic diseases in neonates and children. Pathophysiol Haemost Thromb. 2003;33(5–6):269–74.

[58] Young G, Albisetti M, Bonduel M et al. Impact of Inherited Thrombophilia on Venous Thromboembolism in Children : A Systematic Review and Meta-Analysis of Observational Studies. Circulation. 2008;118:1373-82.

[59] Andrew M, Marzinotto V, Pencharz P, et al. A cross-sectional study of catheter-related thrombosis in children receiving total parenteral nutrition at home. J Pediatr. 1995;126:358-63.

[60] Raffini L. Thrombophilia in Children: Who to Test, How, When, and Why? Hematology. American Society of Hematology Education Program Book. 2008; 2008(1):228-35.

[61] Heit JA. Thrombophilia: Common Questions on Laboratory Assessment and Management. Hematology. American Society of Hematology. 2007; 127-35

[62] Reich LM, Bower M, Key NS. Role of the geneticist in testing and counseling for inherited thrombophilia. Genet Med 2003;5(3):133–43.

[63] College of American Pathologists Consensus Conference XXXVI: diagnostic issues in thrombophilia. Arch Pathol Lab Med 2002;126(11):1277–433.

[64] Louzada ML, Taljaard M, Langlois NJ. Psychological impact of thrombophilia testing in asymptomatic family members. Thrombosis Research. 2011;128:530-5.

IntechOpen

IntechOpen

IntechOpen