

MATERNAL AND FETAL COMPLICATIONS OCCURRING IN HEREDITARY THROMBOPHILIA

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ABSTRACT

Objective. To identify qualitative and quantitative changes involving coagulation factors engaged in maternal and fetal complications, to determine the level of correlation between them, and to highlight the involvement of hereditary thrombophilia among pregnant women.

Material and method. The article is based on 92 publications from 1995 to 2017, including a total of 49,127 thrombophilic patients, of whom 1272 were controls, with inclusion criteria as preeclampsia, intrauterine growth retardation, or early or late pregnancy loss

Results. 31 studies based on preeclampsia- demonstrate the involvement of G1691A factor V Leiden gene mutation, G20210A Prothrombin gene mutation and/or C677T and A1298C MTHFR gene mutation as the main factors in the development of this complication. 10 studies focuses on the intrauterine growth restriction place G20210A Factor V Leiden gene mutation, G20210A Prothrombin gene mutation, C677T and A1298C MTHFR gene mutation, protein C and protein S deficiency as the main factors involved. Another 32 studies cite the involvement of factor V Leiden mutation, Prothrombin mutation and MTHFR mutation in the development of early or late pregnancy losses.

Conclusion. Based on 92 rigorously selected publications, we were able to demonstrate the relationship between medium/increased risk thrombophilia and pregnancy outcome, especially due to the presence of factor V Leiden gene mutation, Prothrombin gene mutation but also MTHFR gene mutation homozygous status.

Keywords: hypercoagulability, homozygous, coagulation factors, preeclampsia, intrauterine growth restriction, recurrent miscarriage

INTRODUCTION

It is well known that inherited or acquired thrombophilia are pro-thrombotic conditions, which can lead to complications such as venous thromboembolism (VTE), more frequently than in healthy people. The prevalence of this condition is increasing and more than 50% of patients with deep vein thrombosis of unknown causes show mutations in clotting factors (1). Patients may be more or less symptomatic depending on the condition of double heterozygous or homozygous mutation.

Thrombosis and its pathophysiology are based on the Virchow triad: damage to the walls of blood

vessels, blood flow turbulence or stasis and blood hypercoagulability (2).

Further we try to underline the importance of this disease in pregnant women through the complications that may arise.

Hereditary thrombophilia

First of all, inherited thrombophilia can lead to serious complications, especially in combination with risk factors. These are hereditary polymorphisms affecting mainly genes encoding factors involved in coagulation which represents an important risk factor for thrombosis. Homozygous state,

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less frequent than the heterozygous one, makes the risk of thrombosis to grow significantly. Also, the presence of several mutations in coagulation factors in the same individual (double heterozygous status), predisposes to notable consequences (3).

- Based on the frequency can appear:
- G1691A factor V Leiden gene mutation,
- G20210A Prothrombin gene mutation,
- Antithrombin III deficiency,
- C677T and A1298C methylenetetrahydrofolate reductase (MTHFR) gene mutation,
- Hyperhomocysteinemia
- Protein C and S deficiency
- Increased plasminogen activator inhibitor (PAI)

Hereditary thrombophilia with great frequency in the population and high risk are: factor V Leiden (hetero/homozygous), prothrombin mutation (hetero/homozygous), double heterozygous factor V Leiden and prothrombin mutation. Thrombophilia with much lower frequency but with high risk for thrombosis are antithrombin III deficiency, protein C and S deficiency (false positives in pregnancy). It has been demonstrated on several occasions that separately, each of these may not produce significant changes in pregnant women, but by association, they can dramatically increase the occurrence of venous thrombosis (4). Associations with acquired risk factors like cancers, oral contraceptives, pregnancies or postpartum, prolonged immobilization aggravates the state of hypercoagulability.

Thrombophilia and pregnancy

Pregnancy is also a hypercoagulability condition, but physiological, with increased risk of venous thrombosis development. In pregnant women other than VTE this pro-thrombotic state, thrombophilia, may lead to complications like preeclampsia, early or late pregnancy loss, intrauterine growth restriction (IUGR) and even placental abruption. But it is very important to know that not all pregnant women with thrombophilia may develop these complications, and precisely because of this, the screening for this disease is not routinely per-

formed. It must be carried out only if there are risk factors for developing thrombosis (5).

Obstetrics and gynecology guides include pregnancy with thrombophilia in several categories depending on the thromboembolic risk factor and frequency.

Presence of heterozygous state Antithrombin III deficiency, cause an increased risk of thrombosis but with low frequency (Table 1). The presence of factor V Leiden/ resistance to activated protein C and G20210A prothrombin mutation, homozygous state are the only ones with high risk of thrombosis and with high frequency. Also in this category with high risk are included the association between factor V Leiden and G20210A prothrombin mutation (double heterozygous). The following depending on the risk (moderate risk) are the presence of factor V Leiden/ resistance to activated protein C and G20210A prothrombin mutation, this time heterozygous state. And with low frequency and moderate risk are the protein C and protein S deficiency (6).

OBJECTIVES

To analyze the role of clotting mutations in all the occurrence of maternal and fetal complications and to review the latest updates on their implications, to identify qualitative and quantitative changes involving coagulation factors engaged in maternal and fetal complications and to determine the level of correlation between them and, to highlight a better vision of the prognosis of these patients.

MATERIAL AND METHOD

Extensive review of the articles was conducted by two independent evaluators. A total of 92 publications have been included in the journal. To narrow the research area, relevant keywords were used – thrombophilia, venous thromboembolism, pregnancy, preeclampsia, intrauterine growth restriction (IUGR), pregnancy loss, coagulation factors and their correlation with maternal and fetal com-

TABLE 1. Thromboembolic risk and frequency of coagulations factors

	High risk	Moderate risk	Low risk	Frequency
Factor V Leiden	Homozygous status	Heterozygous status		High
Antithrombin III	Hetero/homozygous status			Low
Prothrombin mutation	Homozygous status	Heterozygous status		High
Protein C/S		Hetero/homozygous status		Low
MTHFR			Hetero/homozygous status	High
PAI			Hetero/homozygous status	High

plications. Were used randomized trials, review, prospective and retrospective studies.

The inclusion criteria was based on the female population diagnosed with thrombophilia in the presence or absence of a personal or familial risk factor for venous thromboembolism (VTE), but also the presence of maternal and fetal complications such as IUGR, preeclampsia, late or early pregnancy loss.

Statistical analysis: data extraction was done systematically by selecting the suggestive studies published using electronic database publications such as Pub-med (Medline) between 1995 and 2017, Cochrane publications, google.scholar, Embase and the OVID interface, also specialized journals publications, conferences, study sessions. We selected all publications that met the inclusion criteria.

Data quality was evaluated using Newcastle-Ottawa Scale (NOS) and two independent evaluators analyzed the data quality using standardized forms for data usage.

All collected data were saved in a computer archive for being reviewed more than ones and by more than one assessor. The statistical analysis was performed mainly using computer software and calculation formulas for odds ratio (OR) and confidence intervals (CI), Fisher's test, student t-tests, Chi-square (χ^2) test.

RESULTS

Hereditary thrombophilia and preeclampsia

There were selected twenty-seven articles demonstrating the association between hereditary thrombophilia and preeclampsia to emphasize the involved of mutations of clotting factors in the development of this complication. From selected publications, an increased risk of preeclampsia and severe preeclampsia has been reported in pregnant women with heterozygous V Leiden gene mutation, heterozygous prothrombin gene mutation and homozygous MTHFR gene mutation (7). A total of 2264 pregnant women were included in all 27 studies, without risk factors.

A meta-analysis by Lin J et. Al. based on 31 studies highlight that an important part of preeclampsia patients has changes in coagulation factors, namely factor V Leiden gene mutation with odds ratio 5.3 (95% CI; 1.8-15.6), MTHFR homozygous OR 3.9 (95% CI; 0.7-20.6), or prothrombin gene mutation OR 4.7 (95% CI; 1.5-15.0) (8).

Even if there were minor differences in the odds ratio (OR) in the selected publication for our re-

view, the conclusions remain the same, that in the face of a pregnant woman with preeclampsia or severe preeclampsia and inherited thrombophilia, the main risk factors for these complication remain the presence of heterozygous factor V Leiden gene mutation, heterozygous G20210A prothrombin gene mutation and homozygous MTHFR gene mutation. A smaller proportion of studies, especially due to the low frequency, have also demonstrated the implication of antithrombin III deficiency and protein C and protein S deficiency in this feared complication with an OR 9.7 (95% CI 1.2-7.8) with p 0.01 (9-10).

Hereditary thrombophilia and pregnancy loss

This is the most feared complication that may occur in pregnant women with this pro-thrombotic condition, which is why this disease is being studied more and more intensely to show a strict correlation between hereditary or acquired thrombophilia and complications that may occur (11).

Of all articles included in our study, we selected thirty-two most significant based on late or early pregnancy losses (12). In over 80% of publications, the involvement of factor V Leiden (FVL) gene mutation and G20210A prothrombin gene mutation in late pregnancy loss (second and third trimesters) was particularly strong (10-21). On the other hand, homozygous MTHFR gene mutation, protein C and S deficiency have been implicated to a lesser extent in the occurrence of this complication, being a small number of articles that could demonstrate a link between the presence of these mutations and the early pregnancy loss (13).

It was difficult for us to evaluate the implication of antithrombin III and pregnancy loss because of the low frequency of this anomaly. Even though in most articles this mutation was found in less than 10% of the cases, all these have specified the association between antithrombin III deficiency and early pregnancy loss (14).

From a total of 4,520 patients with early or late pregnancy loss, we could notice a close correlation between factor V Leiden gene mutation and the prothrombin gene mutation with late pregnancy loss with a significant OR 3.2 (95% CI 1.0-10.9) for FVL, and OR 3.3 (95% CI 1.0-10.9) for prothrombin P 0.001 but also the association to a lesser extent of the MTHFR mutation, antithrombin III deficiency, protein C and S deficiency, and early pregnancy loss with significant higher risk OR 5.2 (95% CI; 1.5-18.1)/ OR 2.3 (95% CI; 0.6-8.3) respectively OR 3.3 (95% CI;1.0-11.3). It was possi-

ble to demonstrate the close relationship between pregnancy loss and pregnancy with thrombophilia to witnesses. OR 3.6 compared to OR 1.20 in the control group (12-15).

Turki et al. try to correlate the recurrent pregnancy loss with thrombophilic polymorphisms. The study demonstrate a significant association between FVL, G20210A prothrombin gene mutation, C677T MTHFR gene mutation and high risk of recurrent pregnancy loss (in particular late pregnancy loss) from 171 cases with recurrent pregnancy loss (RPL). The OR estimated for patients with pregnancy loss and FVL was OR 2.3, for prothrombin OR 3.9 and OR 1.9 for MTHFR. The higher OR for pregnancy losses was with combined defects OR 14.3 compared to the risk arising in the absence of association (14).

Isaoglu U et al. in their study found a relation between recurrent pregnancy loss (RPL) and inherited thrombophilia. Their results show that from 60 cases with RPL, 13 were carriers of factor V Leiden gene mutation and 6 of them G20210A prothrombin gene mutation (13).

Also Parand A. et. al. tried to demonstrate the same thing, the implication of protein S deficiency in RPL from 90 patients with recurrent miscarriage with significant results, with $p=0.03$. (14)

Our study further demonstrates on the basis of the large number of results that thrombophilia is associated with feared complications in pregnant women (12-17). In terms of pregnancy loss, it has been demonstrated in many ways that factor V Leiden and prothrombin gene mutation are particularly involved in late pregnancy losses OR 2.4 (95% CI; 0.78-7.61) $P < 0.001$ (16-18). Even if we encountered difficulties in highlighting a correlation between antithrombin III deficiency and recurrent pregnancy loss, based on 10% of all reviewed articles, we could state that this anomaly, and protein C and S deficiency were and are involved in early pregnancy losses OR 2.9 (95% CI; 1.8-4.8) $P < 0.02$. With the specification that they were made out of pregnancy, because it is well known that these proteins decrease physiologically in pregnancy (17).

Inherited thrombophilia and IUGR

It has been demonstrated in many publications that the female population suffering from thrombophilia is susceptible to intrauterine growth restriction and not only.

Excessively investigated, we can say that thrombophilia has become more and more common

among pregnant women. But it is extremely important to know the risk factors that pose problems in the evolution of pregnancy (6). There are a large number of women with mutations in clotting factors, but without individual risk factors, with no history of pregnancy loss in second or third trimester, without significant family history, this women will have a normal pregnancy progression without complications. When homozygous Factor V Leiden gene mutation or G20210A prothrombin gene mutation is present, we can frame the thrombophilia at high risk of developing complications (3-5).

From all the reviewed publications we selected 10 most suitable, involving 470 pregnant women with thrombophilia, of which 343 with intrauterine growth restriction (18).

Coriu et al, in a study of 151 patients with intrauterine growth restriction found thrombophilic gene, particularly the G20210A prothrombin mutation, and in a smaller percentage could be found G1691A FVL gene mutation and C677T MTHFR gene mutation The risk of IUGR in patients with factor V Leiden is 2.66 times higher than the control group (OR 2.66 95% CI 0.96-7.37 $P=0.059$) (18).

Livrinova et al. try highlighting the association between preeclampsia, IUGR, placental abruption and the presence of factor V Leiden mutation, G20210A prothrombin mutation and MTHFR gene mutation in 109 cases. The study included 40 patients with preeclampsia, 17 with placental abruption, 22 with growth restriction and 30 control patients. Significant results were observed – relative risk (RR) in patients with FVL and IUGR was 2.58, and in patients with IUGR and homozygous MTHFR was 2.03, $p < 0.05$ (19).

Another study, a meta-analysis based on 42 studies involving Factor V Leiden mutation in IUGR development. This association between LVL and IUGR was significant with an OR of 1.32 (95% CL 0.15-11.30), $p < 0.05$ (21)

Kupferminc et al. in their study highlighting that homozygous factor V mutation, homozygous G20210A prothrombin gene mutation, protein S deficiency had a significant prevalence of IUGR (10)

Our selective review for intrauterine growth restriction (IUGR) has provided significant evidence of the implications of coagulation factors in this complication. Thus, in more than 70% of the reviewed publications, the authors encountered over 75% of pregnant women with intrauterine growth restriction as carriers of the factorV Leiden mutation (either homozygous or heterozygous) or

G20210A prothrombin gene mutation (either homozygous or heterozygous), the only one presenting a significant risk to develop IUGR (OR 4.2; 95% CI; 1.6-10.9, $p < 0.001$) (17-23). In the rest of the cases, the authors failed to demonstrate a correlation between IUGR and the mutations of coagulation factors compared to controls. There are also a number of publications that have attempted to highlight the association of intrauterine growth restriction with A1298C or/and C677T MTHFR mutation but without a significant risk of developing IUGR ($p > 0.05$) (15-20).

We can affirm based on the most important publications selected for our study that factor V Leiden gene mutation, G20210A prothrombin gene mutation, homozygous A1298C or C677T MTHFR gene mutation have the greatest risk of developing maternal and fetal complications based on the odds ratio calculated for each study (Table 2).

Inherited thrombophilia and placental abruption

Another terrible complication could be associated with hereditary thrombophilia, this has been supported by a multitude of studies over the past 10 years. This time, 24 publications based on the association between hereditary thrombophilia and placental abruption (PA), including about 21,000 women, were selected to establish a close correlation between this complication and thrombophilia. We have had positive results so far, so in most studies, we have seen a close correlation between placental abruption and heterozygous Factor V Leiden

gene mutation with an OR of approximately 9 (20-22).

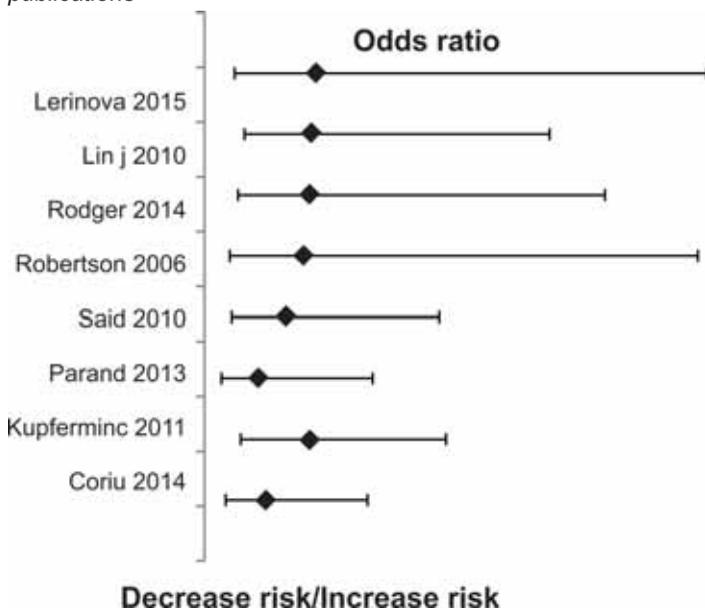
A study by Said and colleagues comprised 117 cases with complications during pregnancy: pre-eclampsia (45), IUGR (44), placental abruption (14), stillbirth (10), and 115 controls, trying to get a correlation between the most common complications during pregnancy and hereditary thrombophilia. Their results were interpreted with caution because there were only 16 cases that developed placental abruption in the presence of heterozygous FVL gene mutation OR 3.68 (95% CI 1.20-10.61) (20).

In the meta-analysis based on 10 publications, conducted by Rodger et al., was attempted to demonstrate an association between pregnancy outcomes and the presence of V Leiden gene mutation or G 20210A prothrombin gene mutation. That could not be sustained in their meta-analysis (21).

Of a total of 20175 women with placental abruption, 14.1% were carriers of heterozygous FVL gene mutation – a work done by Prochazka et al. in order to establish a correlation between placental abruption and women with hereditary thrombophilia. So it could be sustained by them, the close correlation between placental abruption and heterozygous factor V Leiden gene mutation with OR (1.24-2.92) (20-23).

In another study by Robertson et al. a meta-analysis, was a significant association between heterozygous FVL gene mutation and placental abruption with an OR 4.70 and also between heterozygous

TABLE 2. Odds ratio encountered in the most significant publications



prothrombin gene mutation OR 4.9 (1.1-22.30) (22).

DISCUSSIONS

The study is a review demonstrating the relationship between major thrombophilia, high risk of thrombosis, or low risk thrombophilia and complications in pregnancy development (preeclampsia, IUGR, recurrent pregnancy loss, placental abruption). This is evidenced by all the information obtained from the review of 92 articles based exclusively on the relationship between pregnancy outcome and thrombophilia using odds ratio, confidence interval (CI) and the value of $p < 0.05$.

From the point of view of changes in clotting factors, we could see that the heterozygous / homozygous factor V Leiden gene mutation was involved in a large proportion in most complications developed during pregnancy, particularly preeclampsia, IUGR, recurrent pregnancy loss, placental abruption, this mutation being the most frequent and at high risk of developing VTE. Also homozygous MTHFR gene mutation was found in patients with IUGR, preeclampsia and early pregnancy loss.

A similar thing was observed in the case of G20210A prothrombin mutation both hetero and homozygous status, being present in most patients who developed complications during pregnancy evolution, so all review publications describe prothrombin mutation as involved in preeclampsia, IUGR, but also in the other major complications that occurred in these patients.

We found substantial statistical data regarding the correlation between factor V Leiden gene mutation, prothrombin gene mutation and pregnancy loss especially late ones, and we fail to demonstrate a close correlation between protein S, protein C and antithrombin III deficiency, primarily because of their low frequency. The latter two shows the situation more delicate due to false-positive results during pregnancy, knowing very well that they decrease physiologically with pregnancy, which is why they should be performed outside of it. Due to the absence of data to certify that thrombophilia tests were performed in the absence of pregnancy, it is difficult to say that protein C or protein S deficiency is implicated in the pregnancy outcome. Even though antithrombin III deficiency is considered as having the highest risk of developing thrombosis, due to low incidence, it was difficult to appreciate its implications among pregnant women in the 92 publications included in our study.

Of all the publications involved in the study, a proportion of 76% could demonstrate the association of coagulation factors mutations with the complications that occurred, but we considered it important that about 20% of articles could not be proved in comparison with controls. So it could be demonstrated on several occasions that major thrombophilias, the hetero/ homozygous factor V Leiden gene mutation, prothrombin gene mutation and their association may produce notable complications among pregnant women. Also that besides these coagulation factors, without other personal or family risk factors, the evolution of pregnancy is similar to that of controls.

Focusing on the main objective of the study, we tried to establish major thrombophils at high risk of thrombosis or notable complications during pregnancy, based on 92 articles that included > 23,000 pregnant women with thrombophilia, primarily to stop the abuse of thrombophilia testing and to prevent anticoagulation when not applicable. This is possible mostly because of patients who abuse thrombophilia tests without having personal or family risk factors indicating these tests.

Our study demonstrated significant discoveries, that the prothrombin gene mutation, factor V-Leiden gene mutation and, to a lesser extent, MTHFR gene mutation or their combinations are particularly strong in the occurrence of preeclampsia, IUGR, late pregnancy loss and placental abruption, being the only mutations at high risk of developing complications, except for the antithrombin III deficiency, where we have encountered difficulties in demonstrating the relationship with pregnancy due to low incidence.

CONCLUSIONS

Recent debates have focused on correlating coagulation factor mutations with the development of complications during pregnancy.

In conclusion, mutations in clotting factors interfere with complications during pregnancy. Thus, based on the calculated probability risk, factor V Leiden is the main mutation involved in preeclampsia, intrauterine growth retardation and especially late trimester pregnancy loss with an OR of 4.7 (95% CI; 1.5-15.0), OR 5.5 (95% CI ; 1.37-22.4) respectively OR 3.48 (95% CI; 1.58-7.69). MTHFR gene mutation was particularly involved in preeclampsia with OR 3.9 (95% CL; 0.7-20.6).

Based on 10% of all reviewed articles, we could state that antithrombin III deficiency, protein C and S deficiency were and are involved in early preg-

nancy losses OR 2.9 (95% CI; 1.8-4.8), p 0.02. The higher OR for pregnancy losses was with combined defects OR 14.3 compared with no association.

In view of the incontestable evidence, a better approach to this disease is needed, first of all informing the masses as there is still inappropriate use of thrombophilic tests among pregnant women, secondly well-established screening programs.

We underline once again that hetero/homozygous V-Leiden gene mutation, the hetero/homozygous prothrombin mutation or their association are those that can evolve with complications during

pregnancy, but also the presence of other changes in coagulation factors in the absence of a risk factor, history of late pregnancy loss, stillbirth, the personal or family history of thrombophilia, the personal or family history of deep vein thrombosis under the age of 40 years, the evolution of pregnancy is similar to that without thrombophilia.

There is a need for a better understanding of the phenomenon, this being insufficiently researched because there are still many loopholes in the system.

REFERENCES

- Varga E.A., Kujovich J.L. Management of inherited thrombophilia: guide for genetics professionals. *Clin Genet.* 2012;81(1):7-17.
- David R. Kumar, Erin Hanlin, Ingrid Glurich, Joseph J. Mazza, Steven H. Yale. Virchow's Contribution to the Understanding of Thrombosis and Cellular Biology. *Clin Med Res.* 2010 Dec; 8(3-4): 168–172. doi: 10.3121/cm.2009.866. PMID: PMC3006583
- 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
- Novaković I., Maksimovic N., Cvetkovic S., Cvetkovic D. Gene polymorphisms as markers of disease susceptibility. *J Med Biochem.* 2010; 29(3):1-5.
- Walker P., Gregg A.R. Screening, testing, or personalized medicine: where do inherited thrombophilias fit best? *Obstet Gynecol Clin North Am.* 2010;37(1):87-107.
- Royal College of Obstetricians and Gynaecologists – Guidelines 2016, <https://www.rcog.org.uk/en/guidelines-research-services/guidelines/>
- Bellussi F., Contro E., Legnani C., Galletti S., Cosentino A., Rizzo N., Ghi T. Obstetric implications of fetal inherited thrombophilia in thrombophilic women. *Pregnancy Hypertens.* 2014 Jan;4(1):54-8. doi: 10.1016/j.preghy.2013.11.001. Epub 2013 Nov 19. PMID: 26104255
- Okoye H.C., Eweputanna L.I., Okpani A.O., Ejele O.A. Associations between pre-eclampsia and protein C and protein S levels among pregnant Nigerian women. *Int J Gynaecol Obstet.* 2017 Apr;137(1):26-30. doi: 10.1002/ijgo.12085. Epub 2017 Jan 16.
- Karimi S., Yavarian M., Azinfar A., Rajaei M., Kootenaee M.A. Evaluation the frequency of factor V Leiden mutation in pregnant women with preeclampsia syndrome in an Iranian population. *Iran J Reprod Med.* 2012;10:59–66. [PMC free article] [PubMed]
- Kupfermink M.J., Rimon E., Many A., Sharon M., Lessing J.B., Gamzu R. Low molecular weight heparin treatment during subsequent pregnancies of women with inherited thrombophilia and previous severe pregnancy complications." *J Matern Fetal Neonatal Med,* Aug 2011; 1042-5.
- Rodger M.A., Walker M.C., Smith G.N., Wells P.S., Ramsay T., Langlois N.J., Carson N., Carrier M., Rennicks White R., Shachkina S. et al. Is thrombophilia associated with placenta-mediated pregnancy complications? A prospective cohort study. *J. Thromb. Haemost.* 2014, 12, 469 478. [CrossRef] [PubMed]
- Lockwood C., Wendel G. Committee on Practice Bulletins - Obstetrics. "Practice Bulletin No. 124: Inherited thrombophilias in pregnancy. American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Obstetrics. *Obstet Gynecol,* Sept 2011: 730-40.
- Isaoglu U., Ulug P., Delibas I.B., Yilmaz M., Kumtepe Y., Dogan H., Tasdemir S. The association between inherited thrombophilia and recurrent pregnancy loss in Turkish women. *Clin Exp Obstet Gynecol.* 2014; 41(2):177-81. PMID: 24779247
- Alireza Parand, Jale Zolghadri, Mozghan Nezam, Abdolreza Afrasiabi, Sezaneh Haghpanah, Mehran Karimi Inherited Thrombophilia and Recurrent Pregnancy Loss. *Iran Red Crescent Med J.* 2013 Dec; 15(12): e13708. Published online 2013 Dec 5. doi: 10.5812/ircmj.13708. PMID: PMC3955508
- Ogawa M., Matsuda Y., Kobayashi A., Mitani M., Makino Y., Matsui H. Plasma antithrombin levels correlate with albumin and total protein in gestational hypertension and preeclampsia. *Pregnancy Hypertens.* 2014;4:174–177. [PubMed]
- Hoffmann E., Hedlund E., Perin T., Lyndrup J. Is thrombophilia a risk factor for placenta-mediated pregnancy complications? *Arch Gynecol Obstet.* 2012 Sep; 286(3):585-9. doi: 10.1007/s00404-012-2342-2. Epub 2012 Apr 28. PMID: 22543699
- Hemsworth E.M., O'Reilly A.M., Allen V.M., Kuhle S., Brock J.K. Association Between Factor V Leiden Mutation, Small for Gestational Age, and Preterm Birth: A Systematic Review and Meta-Analysis; Knowledge Synthesis Group on Determinants of Preterm/LBW Births. *J Obstet Gynaecol Can.* 2016 Oct;38(10):897-908. doi: 10.1016/j.jogc.2016.08.001.
- Letitia Coriu, Elena Copaciu, Dan Tulbure, Rodica Talmaci, Diana Secara, Daniel Coriu, Monica Cirstoiu. Inherited Thrombophilia in Pregnant Women with Intrauterine Growth Restriction. *Maedica (Buchar).* 2014 Dec; 9(4): 351–355. PMID: PMC4316879
- Livrinova V., Hadzi Lega M., Hristova Dimcheva A., Samardziski I., Isjanovska R. Factor V Leiden, Prothrombin and MTHFR Mutation in Patients with Preeclampsia, Intrauterine Growth Restriction and Placental Abruption. *OA Maced J Med Sci.* 2015 Dec 15; 3(4):590-594. <http://dx.doi.org/10.3889/oamjms.2015.099>
- Said J.M., Higgins J.R., Moses E.K., Walker S.P., Borg A.J., Monagle P.T., Brennecke S.P. Inherited thrombophilia polymorphisms and pregnancy outcomes in nulliparous women. *Obstet Gynecol.* 2010 Jan;115(1):5-13. doi: 10.1097/AOG.0b013e3181c68907. PMID: 20027027
- Rodger M.A., Walker M.C., Smith G.N., Wells P.S., Ramsay T., Langlois N.J., Carson N., Carrier M., Rennicks White R., Shachkina S. et al. Is thrombophilia associated with placenta-mediated pregnancy complications? A prospective cohort study. *J. Thromb. Haemost.* 2014, 12, 469 478. [CrossRef] [PubMed]
- Robertson L., Wu O., Langhorne P., Twaddle S., Clark P., Lowe G.D., Walker I.D., Greaves M., Brenkel I., Regan L. et al. Thrombophilia in pregnancy: A systematic review. *Br. J. Haematol.* 2006, 132, 171–196. [CrossRef] [PubMed]