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**Date:** 27 February 2018

**Sources Searched:** Embase, Medline.

## Plasminogen Activator Inhibitor 1 4G Mutation and Pregnancy Loss

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### **1. Plasminogen Activator Inhibitor-1 Polymorphism Confers a Genetic Contribution to the Risk of Recurrent Spontaneous Abortion: An Updated Meta-Analysis.**

**Author(s):** Huang, Zhan; Tang, Wenqian; Liang, Zhikun; Chen, Qiaopei; Li, Mingyi; Li, Yingfeng; Lao, Shaoxing; Pan, Huimin; Huang, Liying; Huang, Min; Hu, Xuehua; Zhao, Jiangyang

**Source:** Reproductive sciences (Thousand Oaks, Calif.); Nov 2017; vol. 24 (no. 11); p. 1551-1560

**Publication Date:** Nov 2017

**Publication Type(s):** Journal Article

**PubMedID:** 28395596

**Abstract:** Various studies have investigated the risk of recurrent spontaneous abortion (RSA) with plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphism. However, the results have been somewhat contradictory. Therefore, an updated meta-analysis based on 31 studies (5617 cases and 3952 controls) was undertaken to clarify this relationship. The degree of RSA risk was estimated using the odds ratio (OR) and the 95% confidence interval (CI). Overall, the random effects OR was 1.464 (95% CI: 1.269-1.690) for 4G versus 5G, 2.075 (95% CI: 1.563-2.754) for 4G/4G versus 5G/5G, 1.457 (95% CI: 1.211-1.753) for 4G/5G versus 5G/5G, 1.743 (95% CI: 1.358-2.236) for 4G/4G versus 4G/5G + 5G/5G, and 1.600 (95% CI: 1.327-1.930) for 4G/4G + 4G/5G versus 5G/5G, indicating that PAI-1 4G/5G polymorphism could confer an increased risk of RSA. Furthermore, a subgroup analysis showed a significantly elevated susceptibility to RSA in Asians, Caucasians, and Africans. Thus, this study demonstrated that PAI-1 4G/5G polymorphism likely confers a genetic contribution to the development of RSA. The results may aid in developing a theoretical basis for effective strategies to prevent and treat RSA.

**Database:** Medline

## **2. Meta-analysis of the association between plasminogen activator inhibitor-1 4G/5G polymorphism and recurrent pregnancy loss.**

**Author(s):** Li, Xuejiao; Liu, Yukun; Zhang, Rui; Tan, Jianping; Chen, Libin; Liu, Yinglin

**Source:** Medical science monitor : international medical journal of experimental and clinical research; Apr 2015; vol. 21 ; p. 1051-1056

**Publication Date:** Apr 2015

**Publication Type(s):** Meta-analysis Journal Article

**PubMedID:** 25862335

Available at [Medical Science Monitor](#) - from Europe PubMed Central - Open Access

Available at [Medical Science Monitor](#) - from PubMed Central

**Abstract:**BACKGROUNDThe association between plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphism and recurrent pregnancy loss (RPL) risk is still contradictory. We thus performed a meta-analysis.MATERIAL AND METHODSRelevant studies were searched for in PubMed, Web of Science, Embase, and Cochrane Library. An odds ratio (OR) with a 95% confidence interval (CI) was used to assess the association between PAI-1 4G/5G polymorphism and RPL risk.RESULTSA total of 22 studies with 4306 cases and 3076 controls were included in this meta-analysis. We found that PAI-1 4G/5G polymorphism was significantly associated with an increased RPL risk (OR=1.89; 95% CI 1.34-2.67; P=0.0003). In the subgroup analysis by race, PAI-1 4G/5G polymorphism was significantly associated with an increased RPL risk in Caucasians (OR=2.23; 95% CI 1.44-3.46; P=0.0003). However, no significant association was observed in Asians (OR=1.47; 95% CI 0.84-2.59; P=0.18).CONCLUSIONS In conclusion, this meta-analysis suggests that PAI-1 4G/5G polymorphism might be associated with RPL development in Caucasians.

**Database:** Medline

### **3. Association between plasminogen activator inhibitor-1 gene polymorphisms and recurrent pregnancy loss: a systematic review and meta-analysis.**

**Author(s):** Chen, Hui; Nie, Shuping; Lu, Ming

**Source:** American journal of reproductive immunology (New York, N.Y. : 1989); Apr 2015; vol. 73 (no. 4); p. 292-300

**Publication Date:** Apr 2015

**Publication Type(s):** Meta-analysis Journal Article Review

**PubMedID:** 25250948

Available at [American journal of reproductive immunology \(New York, N.Y. : 1989\)](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

**Abstract:** Human plasminogen activator inhibitor-1 (PAI-1) is closely related to embryonic development and pregnancy success. The association between PAI-1 gene polymorphisms (PAI-1-844G/A and PAI-1-675G/A) and the risk of recurrent pregnancy loss (RPL) is controversial. Therefore, we perform this review to clarify the association between PAI-1 gene polymorphisms and RPL risk. We performed a systematic search for studies that described the effect of PAI-1 polymorphisms on RPL risk. The odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were considered under recessive genetic models. Furthermore, we conducted a subgroup analysis based on the studies' geographic regions of origin. Data were analyzed using Stata 11.2 software. Eighteen studies were included, and a high degree of statistical heterogeneity existed among the studies. In this study, we found a significant association between the PAI-1-675G/A polymorphism and the risk of RPL under the recessive model (OR = 1.70, 95% CI = 1.21-2.38). However, no significant association between the PAI-1-844G/A polymorphism and RPL was noted. PAI-1-675G/A (4G/5G) polymorphisms play a potential role in RPL. The screening of PAI-1 (4G/5G) gene mutations should be included during an RPL diagnostic workup, and patients should be treated using anticoagulant therapy during pregnancy if necessary.

**Database:** Medline

#### **4. Polymorphism of the PAI-1 gene (4G/5G) may be linked with Polycystic Ovary Syndrome and associated pregnancy disorders in South Indian Women.**

**Author(s):** Mary, Maniraja Jesintha; Saravanan, Lakshmanan; Deecaraman, Munuswamy; Vijayalakshmi, Melantharu; Umashankar, Vetrivel; Sailaja, Jaigopal

**Source:** Bioinformation; 2017; vol. 13 (no. 5); p. 149-153

**Publication Date:** 2017

**Publication Type(s):** Journal Article

**PubMedID:** 28690381

Available at [Bioinformation](#) - from Europe PubMed Central - Open Access

Available at [Bioinformation](#) - from PubMed Central

**Abstract:** Polycystic Ovary syndrome (PCOS) is the most common endocrine disorder affecting 5 - 10% of all women of reproductive age group. The present research was carried out to study the impact of Plasminogen Activator Inhibitor (PAI-1) 4G/5G polymorphism (rs1799889) in PCOS, and the risk of developing PCOS in South Indian Population. The study was carried out in 60 subjects of South Indian population (30 PCOS and 30 Non PCOS) recruited from ARC Research and Fertility Centre, Chennai, India. Genotype and Allelic frequencies were compared by Fisher exact test, Hardy Weinberg equilibrium.  $p < 0.05$  was considered statistically significant. The Genotype frequency difference between PCOS and non-PCOS was observed as statistically non-significant ( $p = 0.4647$ ,  $OR = 1.3077$ , 95% CI 0.63-2.68). The allelic frequency distribution in Spontaneous Abortion (SAB) cases in total subjects is not found to be statistically significant ( $p = 0.29$ ), however the PCOS women carrying mutant homozygous and heterozygous genotype are more prone to recurrent pregnancy loss. Out of 17 Implantation failure cases, 23.52% were found to carry mutant homozygous (4G/4G), and 66.66% carried mutant heterozygous (4G/5G), and 5.88% carried wild type homozygous (5G/5G), the allelic difference was highly significant with 4G (62.5%), and 5G (37.5%). P value is highly significant and recorded at  $p = 0.0164$ . The positive correlation between PAI-1 4G/5G polymorphism and PCOS risk was not observed in this study, however, the correlation between Recurrent Pregnancy Loss (RPL) and Implantation failures were observed in PCOS cases.

**Database:** Medline

## **5. Thrombophilic gene polymorphisms and recurrent pregnancy loss in Greek women.**

**Author(s):** Chatzidimitriou, M; Chatzidimitriou, D; Mavridou, M; Anetakis, C; Chatzopoulou, F; Lialiaris, T; Mitka, S

**Source:** International journal of laboratory hematology; Dec 2017; vol. 39 (no. 6); p. 590-595

**Publication Date:** Dec 2017

**Publication Type(s):** Journal Article

**PubMedID:** 28603947

Available at [International Journal of Laboratory Hematology](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

**Abstract:**INTRODUCTIONRecurrent pregnancy loss (RPL) is a multifactorial disorder. The aim of this study was the detection of various genetic polymorphisms and their correlation to RPL, in Greek women.METHODSThe impact of 12 thrombophilic polymorphisms was evaluated, among 48 Greek women with a history of RPL, vs 27 healthy parous women. Multiplex PCR and in situ hybridization on nitrocellulose films were performed, to investigate 12 genetic polymorphisms previously reported as risk factors for RPL.RESULTSHeterozygous FV Leiden, homozygous PAI-1 4G/4G, heterozygous MTHFR C677T, homozygous MTHFR A1298C, as much as the combined thrombophilic genotypes MTHFR 677T + ACE I/D, MTHFR 677T/1298C + ACE D/D, ACE I/D + b-fibrinogen -455 G/A, FV HR2 + b-fibrinogen -455 G/A showed a correlation as risk factors for RPL, whereas the rest of the investigated polymorphisms and their combinations did not render statistically significant differences between the two groups in study.CONCLUSIONThe results of this study, as well as those of similar studies, concerning the detection of genetic, environmental, and physiological factors underlying RPL, will prove of critical significance in the investigation and treatment of thrombophilic predisposition, in cases of RPL.

**Database:** Medline

## 6. Correlation between factor VII and PAI-1 genetic variants and recurrent miscarriage.

**Author(s):** Barlik, Magdalena; Seremak-Mrozikiewicz, Agnieszka; Drews, Krzysztof; Klejewski, Andrzej; Kurzawińska, Grażyna; Łowicki, Zdzisław; Wolski, Hubert

**Source:** Ginekologia polska; 2016; vol. 87 (no. 7); p. 504-509

**Publication Date:** 2016

**Publication Type(s):** Journal Article

**PubMedID:** 27504943

Available at [Ginekologia polska](#) - from Free Medical Journals . com

**Abstract:**BACKGROUND Polymorphisms which are presented below may be the cause of inherited thrombophilia and may result in pregnancy loss. The hypothesis is based on a number of cardiology studies which have confirmed the involvement of these polymorphisms in thrombotic incidents. OBJECTIVE To evaluate the role of polymorphisms of factor VII gene (Arg353Gln, -122T > C) and PAI-1 gene (-675 4G/5G) in the etiology of recurrent miscarriage. MATERIAL AND METHOD The study group included 152 women with a positive history of  $\geq 2$  consecutive pregnancy losses (114 and 38 women with 2 and  $\geq 3$  miscarriages, respectively), while 180 healthy women were recruited as controls. Genetic analysis was performed with the use of PCR/RFLP. RESULTS Lower frequency of Arg353/Gln353 was observed in women with 2 and  $\geq 3$  miscarriages as compared to controls (21.1% vs. 23.9% and 13.2% vs. 23.9%, respectively). The frequency of Gln353 was lower in women with  $\geq 3$  miscarriages as compared to controls (6.6% vs. 11.9%,  $p = \text{ns}$ ). The frequency of -122TT was higher in women with  $\geq 3$  miscarriages as compared to controls (86.84% vs. 76.67%,  $p = \text{ns}$ ), whereas -122TC was more frequent in controls (13.16% vs. 22.78% in controls,  $p = \text{ns}$ ). The frequency of -122T was higher in patients with  $\geq 3$  abortions as compared to controls (93.42% vs. 88.06%,  $p = \text{ns}$ ), and -122C was observed more frequently in controls (6.58% vs. 11.94% in controls,  $p = \text{ns}$ ). There were no significant differences as far as the -675 4G/5G polymorphism was concerned. CONCLUSIONS The obtained results suggest a possible protective role of Gln353 and -122C alleles in recurrent miscarriage.

**Database:** Medline

## **7. Coexistence of ACE (I/D) and PAI-1 (4G/5G) gene variants in recurrent miscarriage in Polish population.**

**Author(s):** Kurzawińska, Grażyna; Barlik, Magdalena; Drews, Krzysztof; Różycka, Agata; Seremak-Mrozikiewicz, Agnieszka; Ożarowski, Marcin; Klejewski, Andrzej; Czerny, Bogusław; Wolski, Hubert

**Source:** Ginekologia polska; 2016; vol. 87 (no. 4); p. 271-276

**Publication Date:** 2016

**Publication Type(s):** Journal Article

**PubMedID:** 27321098

Available at [Ginekologia polska](#) - from Free Medical Journals . com

**Abstract:**OBJECTIVESRecurrent miscarriage (RM) is one of the most common obstetric complications. Numerous studies have suggested that genetic variants leading to an impaired balance between coagulation and fibrinolysis may contribute to elevated risk of pregnancy loss. The aim of the study was to investigate a possible association between angiotensin-converting enzyme (ACE, rs1799752) I/D and plasminogen activator inhibitor type 1 (PAI-1, rs1799768) 4G/5G polymorphisms with RM among Polish women.MATERIAL AND METHODSDNA was extracted from peripheral blood samples of 152 women with a history of  $\geq 2$  consecutive pregnancy losses before 22 weeks of gestation, and 180 healthy controls with at least 1 live birth at term and no history of pregnancy loss. Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) were used to identify the polymorphisms.RESULTSNo statistically significant differences were found in genotype and allele frequencies of the studied polymorphisms. The most relevant difference between the study group and controls was found for the ID genotype distribution of the ACE gene (52.6 vs. 46.7%, OR = 1.27,  $p = 0.28$ ). The analysis of genotype coexistence revealed a higher incidence of the combination of the ACE II and the PAI-1 4G/4G genotypes in the control group (10.0 vs. 5.9% in control group;  $p = 0.17$ ).CONCLUSIONSThe obtained results suggest no apparent association between the ACE I/D, PAI-1 4G/5G polymorphisms and increased RM susceptibility in the analyzed Polish population.

**Database:** Medline

## **8. Hereditary thrombophilia-prenatal manifestation and care on different stages of pregnancy**

**Author(s):** Veropotvelyan N.; Pogulyay J.

**Source:** Journal of Maternal-Fetal and Neonatal Medicine; 2016; vol. 29 ; p. 218

**Publication Date:** 2016

**Publication Type(s):** Conference Abstract

**Abstract:**Introduction: One of the probable reproductive losses causes is considered to be hereditary thrombophilia. As the observation and analysis of clinical cases show, the manifestation of this disease can occur on different stages of pregnancy and have different manifestations - from early reproductive losses to stillbirths. Our objective was to examine the frequency of main factors of hereditary thrombophilia polymorphic variants in a group of early reproductive losses and chorionic\placental abruption, antenatal fetal deaths and stillbirths. Materials and methods: A study to determine the SNP's in genes associated with susceptibility to blood clots and abnormal folate metabolism (FGB G455A, FII G20210A, FV 1691A, PAI-1 5G/4G, MTHFR C677T, MTR A2756G) in groups of women with early pregnancy losses episodes (n = 781) and women who had a history of one or more episodes of placental/chorionic abruption, stillbirth or antenatal fetal death (n = 59) were conducted. Clinical cases and summary results: Analysis of the survey results showed that the genotype frequency FII G/A group of early miscarriage is 4 times higher than population prevalence of mutations G20210A FII (5.8% vs. 1.4%;  $p < 0.05$ ); frequency of genotype G/A FV group of miscarriage is 2.2 times lower than this mutation prevalence; combination heterozygous genotype C/T 677 MTHFR + A/G 2756 MTR significantly to 2.98 times more common in the group of women with multiple episodes of early abortion (20.56% vs. 6.9%;  $p < 0.01$ ); genotype FGB A/A 455 at 4.66 times significantly more common in placental/chorionic abruption (77.78% versus 21.7%;  $p < 0.01$ ); associative links with the pregnancy losses and the polymorphic variant gene PAI-1 could not be found. Conclusion: Thus, today there are two approaches to the management of the patients with hereditary thrombophilia factors: prevention of early reproductive losses and placental abruption in women with history of this pathology; and maintenance of the current pregnancy with the presence of retrochorial hematoma choosing an optimal treatment strategy and balanced use of hemostatic agents and lowmolecular -weight -heparins.

**Database:** EMBASE



### **9. Thrombomodulin and plasminogen activator inhibitor-1 expression in recurrent miscarriages**

**Author(s):** Papamitsou T.; Toskas A.; Papadopoulou K.; Economou Z.; Sioga A.

**Source:** Analytical and Quantitative Cytopathology and Histopathology; 2016; vol. 38 (no. 6); p. 350-356

**Publication Date:** 2016

**Publication Type(s):** Article

**Abstract:**OBJECTIVE: To study the possible relationship between plasminogen activator inhibitor-1 (PAI-1) and thrombomodulin expression on deciduas and recurrent firsttrimester miscarriages of unknown etiology. STUDY DESIGN: The miscarriage group consisted of 16 women who miscarried during the first trimester of gestation, and controls consisted of 16 healthy women who had electively terminated their pregnancies during the first trimester of gestation. The abortion material was processed, and specimens taken were studied using immunohistochemical methods. Specimens were taken from decidua basalis and decidua parietalis. Monoclonal antibodies were used against PAI-1 and thrombomodulin. The results were statistically analyzed with Mann- Whitney test. RESULTS: PAI-1 and thrombomodulin expression was detected in decidua basalis and parietalis from both the miscarriage group and controls. No statistically significant difference was detected in the expression of PAI-1 and thrombomodulin between the miscarriage group and controls ( $p < 0.05$ ). CONCLUSION: Our study was a first attempt to investigate the possible involvement of decidual thrombomodulin in recurrent pregnancy loss of unknown etiology. Due to lack of published data, further investigation is needed. Copyright © Science Printers and Publishers, Inc.

**Database:** EMBASE

### **10. Inherited and acquired thrombophilia in Indian women experiencing unexplained recurrent pregnancy loss.**

**Author(s):** Patil, Rucha; Ghosh, Kanjaksha; Vora, Sonal; Shetty, Shrimati

**Source:** Blood cells, molecules & diseases; Oct 2015; vol. 55 (no. 3); p. 200-205

**Publication Date:** Oct 2015

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 26227844

**Abstract:**The most frequently hypothesized cause of unexplained recurrent pregnancy loss (RPL) refers to a defective maternal haemostatic response leading to uteroplacental thrombosis. Approximately 20% women suffering from pregnancy loss (PL) are associated with autoimmune disorders and more than 50% remain idiopathic after common traditional investigations. The present study aims to investigate the prevalence of different genetic and acquired thrombophilia markers in a large series of Indian women with RPL. Such studies will help analyze the markers which pose maximum risk and help in the appropriate treatment in subsequent pregnancies. The study comprised of 587 women with no apparent etiological causes of RPL and 115 healthy women controls. p values were calculated with two tailed Fisher's exact test; statistical significance was assumed at  $p < 0.05$ , 95% confidence interval. Relative risks were also calculated. Among genetic thrombophilia, the risk of PL was highest with protein S deficiency (16%,  $p = 0.006$ ) followed by plasminogen activator inhibitor-1 4G/4G (23%,  $p = 0.007$ ) polymorphism. Among acquired markers, the risk of PL was the highest in women with anti-cardiolipin antibodies (24%,  $p = 0.0001$ ), followed by anti-annexin V antibodies (23%,  $p = 0.0009$ ) and lupus anticoagulants (8%,  $p = 0.02$ ). Thrombophilia, inherited and acquired, is an important contributing factor in unexplained RPL and should be screened in the order of its prevalence.

**Database:** Medline

# 11. 4G/5G polymorphism of PAI-1 as risk factor for recurrent miscarriage in greek population

**Author(s):** Drakakis P.; Vlismas A.; Siahami D.; Mavrogianni D.; Loutradis D.

**Source:** Human Reproduction; Jun 2015; vol. 30

**Publication Date:** Jun 2015

**Publication Type(s):** Conference Abstract

Available at [Human Reproduction](#) - from Oxford Journals - Medicine

Available at [Human Reproduction](#) - from HighWire - Free Full Text

**Abstract:** Study question: The aim of this study was to investigate whether the 4G/5G polymorphism of plasminogen activator inhibitor-1 (PAI-1) is associated with increased risk for recurrent miscarriage in Greek population. Summary answer: The 4G/4G genotype has been found to be associated with higher rate of recurrent miscarriage. What is known already: PAI-1 is principal inhibitor of tissue plasminogen activator (t-PA) and major regulator of fibrinolysis. PAI-1 seems to play important role in the initial steps of embryo implantation. 4G variant has been shown to be associated with increased risk of venous thrombosis. Several other reports have linked the 4G allele with complications in pregnancy, although these associations remain controversial. Recent meta-analysis found significant association between 4G/5G polymorphism of PAI-1 and the risk of recurrent miscarriage. Study design, size, duration: Prospective case - control study of the prevalence of 4G/5G polymorphism of PAI-1 was performed from April 2007 till January 2014. We evaluated 197 patients with recurrent miscarriage and 92 healthy parous women with at least two live births and no history of miscarriages or terminations as control. Participants/materials, setting, methods: Peripheral blood was collected from 197 patients with recurrent miscarriage defined as above two consecutive pregnancy losses and 92 parous women who attended for the regular smear test the gynaecology outpatient department. Following DNA extraction, real-time PCR was performed for the detection of the polymorphism 4G/5G of PAI-1. Main results and the role of chance: Both groups had the same demographic characteristics apart from the age, number of miscarriages and parity. The 4G/4G genotype is statistically more frequent in women with recurrent miscarriage compared to control (41.6 vs 20.7%, OR: 2.06, 95% CI: 1.32-3.21, p-value <0.001). Statistical significance was also found for the presence of 4G allele in women with recurrent miscarriages (60.1 vs 39.1%, p-value <0.001). However, the frequency distribution of 4G/5G genotype is similar in both groups (37.1 vs 37%). When we only include patients with history of more than three consecutive recurrent miscarriages the statistical significance for the 4G/4G genotype is maintained (37.6 vs 20.7%, OR: 1.55, 95% CI: 1.06-2.29, p-value = 0.013). Limitations, reason for caution: In the group of recurrent miscarriages we included women with history of two or more miscarriages, although, in the subgroup analysis where patients with three or more consecutive miscarriages were included, the statistical significance was maintained. We also did not measure the PAI-1 levels in view of performing genotype-phenotype correlations. Wider implications of the findings: The available data on the association of 4G/5G polymorphism of PAI-1 with increased risk of recurrent miscarriages are still controversial with conflicting findings in the different ethnic populations. This is the first study to associate the 4G/5G polymorphism of PAI-1 with recurrent miscarriages in the Greek population. Our results demonstrate a strong correlation between recurrent miscarriages and 4G/4G genotype. We propose the 4G/5G polymorphism of PAI-1 as important marker of recurrent pregnancy loss.

**Database:** EMBASE

## 12. Hereditary and acquired thrombophilias and women

**Author(s):** Elezovic I.; Antic D.A.; Mitrovic M.

**Source:** Journal of Thrombosis and Haemostasis; Jun 2015; vol. 13 ; p. 705

**Publication Date:** Jun 2015

**Publication Type(s):** Conference Abstract

Available at [Journal of thrombosis and haemostasis : JTH](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

Available at [Journal of thrombosis and haemostasis : JTH](#) - from IngentaConnect - Open Access

**Abstract:**Background: Women with hereditary thrombophilia (HT) and/or acquired thrombophilia due to antiphospholipid antibodies (APA) are at an increased risk of venous thromboembolism (VTE), miscarriages and obstetric complications. Aims: Acquired and HT were tested at 987 women, aged 9-76 years (Med = 32), with thrombosis, miscarriages, obstetric complications, or with positive family history. Methods: Deficiency of antithrombin, protein C, protein S, factor XII, and lupus anticoagulant measured with coagulation tests, ACA and anti b2GPI antibodies with ELISA and FV Leiden, prothrombin 20,210, MTHFR and PAI-1 4G variant with PCR methods. Results: Results showed HT at 873 women and 226 with APA. One HT detected in 426/761 women (56%), and two or more in 335/761 (44%). In 112/873 women (13%) with HT simultaneously were detected APA. At 112/226 women with APA HT were detected (50%). Thrombosis has had 176/761 (23%) of women with HT, 44/112 (39%) with HT and APA, and 49/114 (43%) with APA alone. Two or more thrombosis had 66/176 (37%) of women with HT and 26/49 (53%) with APA. This difference is significant. Two or more miscarriages have had 509/761 (67%) women with HT, 48/114 (42%) with APA and 65/112 (58%) with both. During pregnancy 217 women with previous 313 miscarriages, after diagnosed of thrombophilias were treated prophylactically with LMWH +/- folic acid (for MTHFR). They delivered 244 babies, and 24 of them during pregnancy were diagnosed and treated for thrombosis. In addition, 28 women have had 32 successful delivery after 79 unsuccessful in vitro fertilisations. Conclusion: Intensively examines the efficacy of LMWH in the prevention of recurrent miscarriage in women with HT and/or APA, is confirmed by our results, as well as efficiency of prevention and treatment of VTE in pregnancy.

**Database:** EMBASE

**13. The PAI-1 4G/5G and ACE I/D polymorphisms and risk of recurrent pregnancy loss: a case-control study.**

**Author(s):** Kim, Jin Ju; Choi, Young Min; Lee, Sung Ki; Yang, Kwang Moon; Paik, Eun Chan; Jeong, Hyeon Jeong; Jun, Jong Kwan; Han, Ae Ra; Hong, Min A

**Source:** American journal of reproductive immunology (New York, N.Y. : 1989); Dec 2014; vol. 72 (no. 6); p. 571-576

**Publication Date:** Dec 2014

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 25078885

Available at [American journal of reproductive immunology \(New York, N.Y. : 1989\)](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

**Abstract:**PROBLEMThrombophilia has been postulated to be a contributor to the pathophysiology of recurrent pregnancy loss (RPL). We investigated the role of the plasminogen activator inhibitor type 1 (PAI-1) 4G/5G and angiotensin converting enzyme (ACE) I/D polymorphisms in Korean patients with RPL.METHOD OF STUDYGenotyping was performed using the TaqMan assay in 227 RPL patients and 304 controls.RESULTSThe genotype distributions of both polymorphisms in the RPL group did not differ from those of controls. Because the frequency of being homozygous for ACE D/D and the PAI-I 4G/4G combination has been reported to be significantly higher in RPL patients, this was also analyzed. However, no significant difference was noted; 3.1% of RPL patients had both ACE D/D and PAI-I 4G/4G, as did 4.9% of controls (P = 0.791).CONCLUSIONThe current study suggests that both polymorphisms, either alone or in combination, are not major determinants of the development of RPL in Korean women.

**Database:** Medline

**14. Prevalence of coagulation factor XIII and plasminogen activator inhibitor-1 gene polymorphisms among Egyptian women suffering from unexplained primary recurrent miscarriage.**

**Author(s):** Elmahgoub, Iman Rifaat; Afify, Reham Abdelaleem; Abdel Aal, Asmaa Ahmed; El-Sherbiny, Walid Sayed

**Source:** Journal of reproductive immunology; Jun 2014; vol. 103 ; p. 18-22

**Publication Date:** Jun 2014

**Publication Type(s):** Journal Article Observational Study

**PubMedID:** 24702949

**Abstract:**Recurrent miscarriage (RM) is an obstetric challenge. Polymorphisms of factor XIII (FXIII) and plasminogen activator inhibitor-1 (PAI-1) may cause an imbalance between coagulation and fibrinolysis that can end in RM. The aim of the work was to determine the prevalence of FXIII Val34Leu and PAI-1 4G/5G gene polymorphisms in Egyptian women presenting with unexplained primary first trimester RM. Genotyping of 120 unexplained primary first trimester RM patients and 130 healthy controls by polymerase chain reaction (PCR) amplification of target genes followed by the allele-specific restriction enzyme digestion (RFLP technique). Among the cases, 67.5% of individuals had wild-type FXIII; 21.7% were heterozygous and 10.8% were homozygous for the FXIII Val34Leu polymorphism. Among controls, the proportions were 89.2%, 8.5% and 2.3% respectively. In addition, comparison between the two groups regarding Leu and 4G allele frequencies showed statistically significant differences (P values=0.0001 and 0.027 respectively). RM is more frequent in women with combined polymorphisms than in women with a single gene polymorphism (RR=3.91; OR=4.51; 95% CI=1.79-11.38; P=0.002). FXIII Val34Leu and PAI-1 4G/5G polymorphisms are prevalent in Egyptian women, with unexplained primary first trimester RM and combined polymorphisms statistically increasing the risk.

**Database:** Medline

**15. The obstetric, gynaecological and fertility implications of homozygous PAI-1 deficiency: Single-centre experience**

**Author(s):** Heiman M.; Gupta S.; Shapiro A.D.

**Source:** Haemophilia; May 2014; vol. 20 (no. 3); p. 407-412

**Publication Date:** May 2014

**Publication Type(s):** Article

**PubMedID:** 24261743

Available at [Haemophilia : the official journal of the World Federation of Hemophilia](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

**Abstract:**Complete plasminogen activator inhibitor type 1 (PAI-1) deficiency is an exceedingly rare autosomal recessive bleeding disorder previously identified and reported in a large Old Order Amish (OOA) kindred in Indiana [Fay et al. Blood 1997; 90: 204]. Mouse models suggest that proteolysis via the plasminogen activator/plasmin system plays a crucial role in reproduction including degradation of the follicular wall during ovulation, fertilization, embryo implantation and embryogenesis [Leonardsson et al., Proc Natl Acad Sci USA 1995; 92: 12446]. We report the obstetric, gynaecological and fertility histories of OOA individuals with homozygous PAI-1 deficiency. In this family, there are 10 affected members identified to date ranging in age between 10 and 32 years, including seven female patients and three male patients. To date, two women have achieved pregnancies without difficulty; however, they experienced antenatal bleeding and preterm labour. The early initiation and continuation of antifibrinolytic agents, Epsilon-aminocaproic acid or tranexamic acid, during the

pregnancy and in the postpartum period, was believed to be successful in preventing major bleeding complications in our patients with complete PAI-1 deficiency. © 2013 John Wiley & Sons Ltd.

**Database:** EMBASE

**16. Plasminogen activator inhibitor type 1 activity: Impaired fibrinolysis and early pregnancy wastage**

**Author(s):** Ivanov P.; Komsa-Penkova R.; Konova E.; Ivanov V.; Gecheva S.; Kovacheva K.; Simeonova M.

**Source:** Thrombosis Research; May 2014; vol. 133

**Publication Date:** May 2014

**Publication Type(s):** Conference Abstract

**Abstract:**Background: The aim of the study was to assess the independent role of polymorphism 4G/5G (PL 4G/5G)-genotype 4G/4G in plasminogen activator inhibitor type 1 (PAI-1) in the development of very early recurrent pregnancy loss (RPL)-before 10 weeks of gestation of pregnancy. Methods: The polymorphism 4G/5G as well as Factor V Leiden (FVL), prothrombin (FII) gene mutation 20210G>A and polymorphism 677 C>T in methylenetetrahydrofolate reductase (MTHFR) gene was investigated in 110 women with recurrent pregnancy loss before 10 weeks of gestation and in 97 healthy women with at least one uncomplicated full-term pregnancy. Results: A significant prevalence of PL 4G/5G in women with RPL was found in comparison to prevalence of the polymorphism in controls (41.8% versus 26.8% respectively in patients and controls, OR: 1.96, 95% CI: 1.05-3.69, p = 0.034). The difference in prevalence of the polymorphism remains still significant after exclusion of patients and control carriers of FVL, FII 20210G>A and 677 C>T in MTHFR (the prevalence of PL 4G/5G alone was 44.1% and 24% respectively in patients and controls, OR: 2.5, 95% CI: 1.15-5.45, p = 0.018). Conclusions: The found association of PL 4G/5G in PAI-1 with early recurrent pregnancy loss encourage an extension of the list of inherited thrombophilic factors with this one. This result also could have had an implication for adjustment of further prophylactic low-molecular weight heparin implication in further pregnancy to prevent a poor foetal outcome.

**Database:** EMBASE

**17. Plasminogen activator inhibitor-1, factor V, factor II and methylenetetrahydrofolate reductase polymorphisms in women with recurrent miscarriage.**

**Author(s):** Pietropolli, A; Giuliani, E; Bruno, V; Patrizi, L; Piccione, E; Ticconi, C

**Source:** Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology; Apr 2014; vol. 34 (no. 3); p. 229-234

**Publication Date:** Apr 2014

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 24484533

**Abstract:**The present study investigated the association between genetic polymorphisms of selected thrombophilic factors with recurrent miscarriage (RM). The genetic polymorphisms for plasminogen activator inhibitor-1 4G/5G (PAI-1), Factor V Leiden (FVL), Factor II G20210A (FII) and methylenetetrahydrofolate reductase MTHFR C677T were determined in 186 RM women and 129 healthy women. In RM women, the frequency of heterozygosity for PAI-1 5G/4G (31%) was significantly higher than in controls (5G/4G: 22%) whereas no difference was found in the case of homozygosity 4G/4G and 5G/5G. The frequencies of genotype G/A for FVL and FII were significantly higher in RM women (FVL, 10%; FII, 8%) than in controls (FVL, 3%; FII, 2%). No difference was found in the case of MTHFR C677T. The polymorphisms of FVL and FII should be screened in RM women, whereas PAI-1 seems to be weakly associated with RM. The role of MTHFR C677T polymorphisms without hyperhomocysteinemia appears negligible.

**Database:** Medline

**18. Association between plasminogen activator inhibitor 1 gene mutation and different subgroups of recurrent miscarriage and implantation failure.**

**Author(s):** Khosravi, Farhad; Zarei, Saeed; Ahmadvand, Negah; Akbarzadeh-Pasha, Zahra; Savadi, Elham; Zarnani, Amir-Hassan; Sadeghi, Mohammad-Reza; Jeddi-Tehrani, Mahmood

**Source:** Journal of assisted reproduction and genetics; Jan 2014; vol. 31 (no. 1); p. 121-124

**Publication Date:** Jan 2014

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 24189965

Available at [Journal of Assisted Reproduction and Genetics](#) - from SpringerLink

Available at [Journal of Assisted Reproduction and Genetics](#) - from Europe PubMed Central - Open Access

Available at [Journal of Assisted Reproduction and Genetics](#) - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:****PURPOSE**To compare plasminogen activator inhibitor type1 (PAI-1) mutation rates in different groups of patients with the record of recurrent miscarriage (RM) or implantation failure (IF) with special emphasis on the number of missed pregnancies and/or implantation failures ( $RM \geq 2$ ,  $IF \geq 2$ ,  $RM + IF \geq 2$ ,  $RM \geq 3$ ,  $IF \geq 3$  and  $RM + IF \geq 3$ ).**METHOD**Case-control study from PCR products and RFLP data of DNA from blood of patients who referred to the infertility clinic including 595 patients (421  $RM \geq 2$ , 119  $IF \geq 2$  and 55  $RM + IF \geq 2$ ) as the case groups and 100 healthy women as the control group.**RESULTS**All six different subgroups of patients showed increased frequencies of the mutant allele (4G) in comparison to the control group ( $p < 0.001$ ) suggesting a role for PAI-1 mutation in RM and IF.**CONCLUSIONS**The different patient subgroups suffer similar rates of risk in developing RM and IF when compared to controls.

**Database:** Medline

## **19. Association of plasminogen activator inhibitor-type 1 (-675 4G/5G) polymorphism with pre-eclampsia: systematic review.**

**Author(s):** Morgan, Jessie A; Bombell, Sarah; McGuire, William

**Source:** PloS one; 2013; vol. 8 (no. 2); p. e56907

**Publication Date:** 2013

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article Review

**PubMedID:** 23457639

Available at [PLoS ONE](#) - from Public Library of Science (PLOS)

Available at [PLoS ONE](#) - from Europe PubMed Central - Open Access

**Abstract:**BACKGROUND AND AIMSExcessive generation of plasminogen activator inhibitor-type 1 (PAI-1) is implicated in the pathogenesis of pre-eclampsia and related conditions. The PAI-1 (-675 4G/5G) promoter polymorphism (rs1799889) affects transcriptional activity and is a putative genetic risk factor for pre-eclampsia. The aim of this study was identify, appraise and synthesise the available evidence for the association of the PAI-1 (-675 4G/5G) polymorphism with pre-eclampsia.METHODSSystematic review and random effects meta-analysis of genetic association studies.RESULTSWe found 12 eligible genetic association studies in which a total of 1511 women with pre-eclampsia, eclampsia or HELLP syndrome and 3492 controls participated. The studies were generally small (median number of cases 102, range 24 to 403) and underpowered to detect plausible association sizes. Meta-analysis of all of the studies detected statistically significant gene-disease associations in the recessive [pooled odds ratio 1.28 (95% confidence interval 1.09, 1.50); population attributable risk 7.7%] and dominant [pooled odds ratio 1.21 (95% confidence interval 1.01, 1.44); population attributable risk 13.7%] models. We did not find evidence of statistical heterogeneity, funnel plot asymmetry or small study bias.CONCLUSIONSThese data suggest that the fibrinolytic pathway regulated by the PAI-1 gene may contribute to the pathogenesis of pre-eclampsia and related conditions. This association, if confirmed in larger genetic association studies, may inform research efforts to develop novel interventions or help to prioritise therapeutic targets that merit evaluation in randomised clinical trials.

**Database:** Medline

## **20. The Relationship between PAI-1 polymorphism with recurrent implantation failure (RIF)**

**Author(s):** Allafan S.; Khayatzaheh J.; Shahrokh Abadi Kh.; Hasanzadeh Nazarabadi M.; Mojarad M.; Musavifar N.; Jalali M.

**Source:** International Journal of Fertility and Sterility; 2013; vol. 7 ; p. 123-124

**Publication Date:** 2013

**Publication Type(s):** Conference Abstract

**Abstract:**Background: RIF is the most common cause of unsuccessful pregnancy after IVF. Among the various causes of RIF, the role of maternal genetic factors is of great significance. PAI-1 polymorphism is one of the notable polymorphisms in this field. In this study, the relationship between this polymorphism and the recurrent spontaneous abortions and infertility in different populations has been investigated. In other words, the relationship between this polymorphism and the occurrence of RIF has been investigated because there have been no studies on the patients suffering from New definitions of RIF in Iran. Materials and Methods: This descriptive-analytical study was conducted in Montaserieh Research and Clinical Center for Infertility of Mashhad University of Medical Sciences. It was carried out on 80 infertile couples after IVF from 2006 to 2011. Based on the new definitions of RIF, participants were divided into three groups: 1. Control group: Forty participants whose transferred embryos were successfully implanted. The selection criterion



was the observation of gestational sac in ul-trasonography twenty days after IVF 2. Patient group RIF 1: Those participants who received IVF two times and six embryos. In this group, no sign of pregnancy or forming gestational sac was found. 3. Patient group RIF 2: Those participants who received IVF at least three times and ten embryos. Again no sign of pregnancy and gestational sac was found. After receiving 5cc blood containing EDTA from participants, the process of DNA extraction was performed. Genotype of PAI-1 gene was determined by using PCR-ARMS technique. Gained frequencies in different groups were compared with each other using chisquare statistical analysis. Results: The frequency of 4G/5G genotype in control group, total participants, RIF1 group and RIF2 was 75,87, 80 and 95%, respectively. The frequency of 5G/5G genotype in control group, total participants patient group RIF 1, and patient group RIF 2 was orderly 25, 5, 5 and 5%. 4G/4G genotype was observed in none of the control groups and patient group RIF 1, But the observed 15% of patient RIF 2. Conclusion: According to our results, 4G/4G Polymorphism of PAI-1, is seen just in the second group of the patient (RIF 2), with the new definition of recurrent implantation failure. Hypofibrinolysis as a result of the 4G allele of the PAI-1 gene appears to be a risk factor for implantation failure by limiting trophoblastic invasion. So, with increasing number of IVF failure role of genetic factors become more significant.

**Database:** EMBASE

## **21. Risk for early pregnancy loss by factor XIII Val34Leu: the impact of fibrinogen concentration.**

**Author(s):** Dossenbach-Glaninger, Astrid; van Trotsenburg, Mick; Oberkanins, Christian; Atamaniuk, Johanna

**Source:** Journal of clinical laboratory analysis; Nov 2013; vol. 27 (no. 6); p. 444-449

**Publication Date:** Nov 2013

**Publication Type(s):** Journal Article

**PubMedID:** 24218126

Available at [Journal of clinical laboratory analysis](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

**Abstract:**BACKGROUNDWe have already described a significantly elevated overall risk for recurrent pregnancy loss (RPL) in women carrying the coagulation factor XIII (FXIII) Val34Leu and/or the plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphism assuming that these polymorphisms contribute synergistically to RPL because of impaired hypofibrinolysis. Recent studies on FXIII indicate that the impact of the FXIII 34Leu genotype on fibrin structure and fibrinolysis is affected by fibrinogen concentration. Therefore, we reinvestigated the association between fibrinogen concentrations and FXIII Val34Leu with early RPL.MATERIALS AND METHODSIn this case-control study, we enrolled 49 women with a history of two consecutive or three to six nonconsecutive pregnancy losses between the 8th and 12th week of gestation and 48 healthy controls. The risk for RPL in carriers of FXIII 34Leu at fibrinogen levels above or below the median and first tertile of controls was evaluated.RESULTSIn carriers of the 34Leu allele, fibrinogen levels below the median (i.e.,  $\leq 300$  mg/dl) and the first tertile (i.e.,  $\leq 284$  mg/dl) of controls were associated with an increased risk for RPL [(2.9 (1.1-7.7), 3.9(1.0-15.0)].CONCLUSIONSThe FXIII Val34Leu polymorphism may be associated with the development of early RPL in association with fibrinogen concentrations. At fibrinogen levels in the low normal range, FXIII 34Leu may modify fibrin structure toward an increased resistance to fibrinolysis.

**Database:** Medline

## **22. Polymorphisms in MTHFR, MTHFD, and PAI-1 and recurrent miscarriage among North Indian women.**

**Author(s):** Parveen, Farah; Tuteja, Moni; Agrawal, Suraksha

**Source:** Archives of gynecology and obstetrics; Nov 2013; vol. 288 (no. 5); p. 1171-1177

**Publication Date:** Nov 2013

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 23685927

Available at [Archives of Gynecology and Obstetrics](#) - from SpringerLink

**Abstract:**PURPOSEThe aim of this study was to investigate the association between MTHFR C677T, A1298C, MTHFD G1958A and plasminogen activator inhibitor type 1 (PAI-1) 4G/5G polymorphism among first trimester recurrent miscarriages.MATERIALS AND METHODSDNA was extracted from peripheral blood samples from 200 patients and 300 controls. Polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP) and sequencing were used to identify the polymorphisms. We have analyzed the frequencies, odds ratio, Hardy-Weinberg equilibrium.RESULTSMTHFR C677T, A1298C, and MTHFD G1958A variant alleles were found to be significantly more prevalent in patients than control. However, variant genotype of MTHFR C677T (OR = 2.54; 95 % CI = 1.23-5.24; p value = 0.014), 1298C (OR = 2.23; 95 % CI = 1.09-4.52; p value = 0.028), and MTHFD-1958 showed significant association with pregnancy loss (OR = 2.36; 95 % CI = 1.39-4.02; p value = 0.002). Both MTHFR 677 and MTHFD 1958 showed susceptible effect under recessive model of inheritance. PAI-1 mutations showed no significance.CONCLUSIONWe observed significant susceptible effects of MTHFR C677T, A1298C, and MTHFD G1958A among RM cases. Our data points toward the multifactorial nature of the recurrent miscarriage as relative contribution of variant genotype of MTHFR C677T is only twofold and further decreased to only onefold, and MTHFD-1958 lost its significance upon meta-analysis.

**Database:** Medline

## **23. Genetic association of five plasminogen activator inhibitor-1 (PAI-1) polymorphisms and idiopathic recurrent pregnancy loss in Korean women.**

**Author(s):** Jeon, Young Joo; Kim, Young Ran; Lee, Bo Eun; Choi, Yi Seul; Kim, Ji Hyang; Shin, Ji Eun; Rah, HyungChul; Cha, Sun Hee; Lee, Woo Sik; Kim, Nam Keun

**Source:** Thrombosis and haemostasis; Oct 2013; vol. 110 (no. 4); p. 742-750

**Publication Date:** Oct 2013

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 23903286

**Abstract:**Plasminogen activator inhibitor-1 (PAI-1) is important for maintaining pregnancy. Aberrantly increased PAI-1 levels may contribute to thrombosis and inflammation, leading to pregnancy loss. This study investigated the association of PAI-1 polymorphisms (PAI-1 rs2227631 [-844G>A], rs1799889 [-675 4G/5G], rs6092 [43G>A], rs2227694 [9785G>A], and rs7242 [11053T>G]) with idiopathic recurrent pregnancy loss (RPL) in Korean women. We screened 308 RPL patients and 227 control participants for five PAI-1 polymorphisms. Genotyping of PAI-1 was performed by polymerase chain reaction-restriction fragment length polymorphism assay. PAI-1 4G4G and -844AA/4G4G/11053GG genotypes were associated with RPL. PAI-1 -844A/4G/43G/9785G/11053G haplotype was connected to hypofibrinolytic status (i.e. increased levels of plasma PAI-1, increased numbers of platelets, reduced prothrombin time, and reduced activated partial thromboplastin time). Moreover, PAI-1 11053TG+GG frequency was positively related to plasma homocysteine and urate levels, whereas -844AA frequency was associated with plasma folate concentrations according

to ordinal logistic regression analysis. Based on these results, we propose that PAI-1 -844G>A, 4G/5G, and 11053T>G polymorphisms are markers of RPL.

**Database:** Medline

#### **24. The association between thrombophilic gene mutations and recurrent pregnancy loss.**

**Author(s):** Poursadegh Zonouzi, Ahmad; Chaparzadeh, Nader; Ghorbian, Saeid; Sadaghiani, Mahzad Mehrzad; Farzadi, Laya; Ghasemzadeh, Alieh; Kafshdooz, Taiebeh; Sakhinia, Masoud; Sakhinia, Ebrahim

**Source:** Journal of assisted reproduction and genetics; Oct 2013; vol. 30 (no. 10); p. 1353-1359

**Publication Date:** Oct 2013

**Publication Type(s):** Journal Article

**PubMedID:** 23989998

Available at [Journal of Assisted Reproduction and Genetics](#) - from SpringerLink

Available at [Journal of Assisted Reproduction and Genetics](#) - from Europe PubMed Central - Open Access

Available at [Journal of Assisted Reproduction and Genetics](#) - from PubMed Central

**Abstract:** PURPOSE To determine whether the Factor V (1691G/A), Factor V HR2 (4070A/G), Prothrombin (20210G/A), PAI-1 (-675 I/D, 5G/4G), ACE (intron 16 I/D), Factor VII (Gln353Arg), Factor XIII (Val34Leu),  $\beta$ -fibrinogen (-455G/A), Glycoprotein Ia (807C/T), tPA (intron 8 D/I) gene mutations could be risk factors for recurrent pregnancy loss (RPL). METHODS Genotyping of thrombophilic gene mutations were carried out by amplification Refractory Mutation System-PCR (ARMS-PCR) method after DNA extraction. RESULTS We found that the mutant allele frequencies of Factor V (1691G/A), Factor V HR2 (4070A/G), Prothrombin (20210G/A), PAI-1 (-675 I/D, 5G/4G), Factor XIII (Val34Leu) and  $\beta$ -fibrinogen (-455G/A) were more seen in the case group compared with the healthy control; However, the difference between the two group is not statistically significant ( $p > 0.05$ ). Whilst the mutant allele frequencies of other studied genes were lower in the case in comparison to the fertile control women ( $p > 0.05$ ). CONCLUSION Taken together, our data has shown that the prevalence of thrombophilic gene mutations was similar in women with RPL and healthy controls. Therefore, it appears that further studies on large-scale population and other genetic variants will be needed to conclusively find candidate genes for RPL unknown etiology in the future.

**Database:** Medline

## **25. Plasminogen activator inhibitor 1 4G/5G and -844G/A variants in idiopathic recurrent pregnancy loss.**

**Author(s):** Magdoud, Kalthoum; Herbein, Viviana G; Touraine, Renaud; Almawi, Wassim Y; Mahjoub, Touhami

**Source:** American journal of reproductive immunology (New York, N.Y. : 1989); Sep 2013; vol. 70 (no. 3); p. 246-252

**Publication Date:** Sep 2013

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 23521508

Available at [American journal of reproductive immunology \(New York, N.Y. : 1989\)](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

**Abstract:**PROBLEMPlasminogen activator inhibitor type 1 (PAI-1) regulates fibrinolysis, and the common promoter region variants -675G/A (4G/5G) and -844G/A are associated with increased thrombotic risk. Despite evidence linking altered fibrinolysis with adverse pregnancy events, including idiopathic recurrent pregnancy loss (RPL), the contribution of PAI-1 variants to RPL risk remains controversial. We investigated the association between the PAI-1 -844G/A and 4G/5G (-675G/A) variants with altered risk of RPL.METHOD OF STUDYThis was a case-control study involving 304 women with confirmed RPL and 371 age- and ethnically matched control women. PAI-1 genotyping was performed by PCR single-specific primer -675 (G/A) and real-time PCR (-844G/A) analysis.RESULTSMajor allele frequency (MAF) of 4G/5G ( $P < 0.001$ ), but not -844G/A ( $P = 0.507$ ), was higher in RPL cases. PAI-1 4G/5G single-nucleotide polymorphism (SNP) was significantly associated with RPL under additive, dominant, and recessive genetic models; no association of -844G/A with RPL was seen irrespective of the genetic model tested. Taking common -844G/5G haplotype as reference ( $OR = 1.00$ ), multivariate analysis confirmed the association of 4G-containing -844A/4G ( $P < 0.001$ ) and -844G/4G ( $P = 0.011$ ) haplotypes with increased RPL risk.CONCLUSION4G/5G, but not -844G/A, PAI-1 variant is associated with an increased risk of RPL.

**Database:** Medline

## **26. Recurrent pregnancy loss, plasminogen activator inhibitor-1 (-675) 4G/5G polymorphism and antiphospholipid antibodies in Czech women.**

**Author(s):** Subrt, Ivan; Ulcova-Gallova, Zdenka; Cerna, Monika; Hejnalova, Marketa; Slovanova, Jitka; Bibkova, Katarina; Micanova, Zdenka

**Source:** American journal of reproductive immunology (New York, N.Y. : 1989); Jul 2013; vol. 70 (no. 1); p. 54-58

**Publication Date:** Jul 2013

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 23445116

Available at [American journal of reproductive immunology \(New York, N.Y. : 1989\)](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

**Abstract:**PROBLEMThis study compares the frequencies of plasminogen activator inhibitor-1 (-675) 4G/5G polymorphism and its relationship with eight antiphospholipid antibodies (aPLs) in serum of 157 patients with repeated pregnancy loss (RPL).METHOD OF STUDYPAI-1 (-675) 4G/5G polymorphism was determined using standard PCR-RFLP method. Enzyme-linked immunosorbent assay was used for the detection of aPLs against ph-serine, ph-ethanolamine, ph-inositol, ph-DL-glycerol, phosphatidic acid, annexin V, cardiolipin, and beta2-GPI. Allelic frequency and distribution of genotypes were calculated. The prevalence of the risk conferring 4G allele and 4G/4G

homozygous genotype in patients and controls was compared, and the correlation between aPLs positivity and PAI-1 4G/4G genotype was tested by chi-square test. RESULTS Statistically highly significant correlation between RPL and PAI-1 (-675) 4G/4G genotype was found. No correlation between PAI-1 (-675) 4G/5G polymorphism and the presence of antiphospholipid antibodies in RPL patients was observed. CONCLUSION PAI-1 (-675) 4G/4G homozygous genotype increases the risk of RPL independently from the aPLs positivity.

**Database:** Medline

## **27. Genetic association studies of ACE and PAI-1 genes in women with recurrent pregnancy loss: a systematic review and meta-analysis.**

**Author(s):** Su, Mei-Tsz; Lin, Sheng-Hsiang; Chen, Yi-Chi; Kuo, Pao-Lin

**Source:** Thrombosis and haemostasis; Jan 2013; vol. 109 (no. 1); p. 8-15

**Publication Date:** Jan 2013

**Publication Type(s):** Research Support, Non-u.s. Gov't Meta-analysis Journal Article Review

**PubMedID:** 23179239

**Abstract:** A fine balance between coagulation and fibrinolysis is critical in early pregnancy. Plasminogen activator inhibitor-1 (PAI-1) and angiotensin converting enzyme (ACE) are involved in the fibrinolytic process, and several studies have reported the association between their gene polymorphisms and recurrent pregnancy loss (RPL). This study was conducted to investigate the association between PAI-1 and ACE polymorphisms and idiopathic RPL, using meta-analyses. A systematic review of the published literature from the MEDLINE and EMBASE databases before April 2012 was conducted. Of 209 potentially relevant studies, 22 case-control studies comprising a total of 2,820 RPL patients and 3,009 controls were included. Among these studies were 11 reports of PAI-1 4G/5G and 11 of ACE I/D polymorphisms in patients with RPL. A significant association was found with the ACE I/D polymorphism [summary odds ratio 1.29 (95% confidence interval 1.02-1.62)] in studies including more than two recurrent abortions. Subgroup analysis did not show significant associations with RPL in Caucasian and non-Caucasian patients. Meta-analyses of PAI-1 4G/5G polymorphism were not found associations with RPL in studies including more than two or three recurrent abortions, and in studies of Caucasian and non-Caucasian patients. In conclusion, meta-analyses showed a significant association between the ACE I/D polymorphism and idiopathic RPL. High clinical heterogeneity existed among studies of PAI-1 4G/5G, and the aggregated data failed to confer higher susceptibility to idiopathic RPL. More well-designed studies with different ethnic populations are required for future integration.

**Database:** Medline

## **28. Combination of thrombophilic gene polymorphisms as a cause of increased the risk of recurrent pregnancy loss**

**Author(s):** Torabi R.; Zarei S.; Hadavi R.; Jeddi-Tehrani M.; Zeraati H.; Zarnani A.H.; Akhondi M.M.; Shiraz E.S.

**Source:** Journal of Reproduction and Infertility; 2012; vol. 13 (no. 2); p. 89-94

**Publication Date:** 2012

**Publication Type(s):** Article

Available at [Journal of Reproduction & Infertility](#) - from ProQuest (Hospital Premium Collection) - NHS Version

Available at [Journal of Reproduction & Infertility](#) - from PubMed Central

**Abstract:**Background: Recurrent pregnancy loss is (RPL) a heterogeneous condition. While the role of acquired thrombophilia has been accepted as an etiology for RPL, the contribution of specific inherited thrombophilic gene polymorphisms to the disorder has been remained controversial. Methods: One hundred women with a history of two or more consecutive abortions and 100 women with at least two live births and no miscarriages were included in the study and evaluated for the presence of 11 thrombophilic gene polymorphisms (Factor V LEIDEN, Factor V 4070 A/G, Factor V 5279 A/G, Factor XIII 103 G/T, Factor XIII 614 A/T, Factor XIII 1694 C/T, PAI-1 -675 4G/5G, ITGB3 1565 T/C, beta- Fibrinogen -455G/A, MTHFR 677 C/T, MTHFR 1298 A/C) using PCR-RFLP technique. The data were statistically analyzed using Mann-Whitney test and logistic regression model. Results: There was no relation between factor XIII 103G/T gene polymorphism with increased risk of RPL. However, the other 10 gene polymorphisms were found to be associated with increased/decreased risk of RPL. Multiple logistic regression model for analyzing the simultaneous effects of these polymorphisms on the risk of RPL showed that six of these 11 polymorphisms (Factor V 1691G/A, Factor V 5279A/G, Factor XIII 614A/T, beta-Fibrinogen -455G/A, ITGB3 1565T/C, and MTHFR 1298A/C) were associated with RPL. Conclusion: It is possible to calculate the risk of abortion in a patient with RPL by determining only six of the 10 polymorphisms that are individually associated with RPL.

**Database:** EMBASE

## **29. Which thrombophilic gene mutations are important to increase the risk of recurrent pregnancy loss?**

**Author(s):** Zarei S.; Hadavi R.; Jeddi-Tehrani M.; Torabi R.; Zeraati H.; Zarnani A.H.; Akhondi M.M.; Savadi-Shiraz E.

**Source:** Human Reproduction; 2012; vol. 27

**Publication Date:** 2012

**Publication Type(s):** Conference Abstract

Available at [Human Reproduction](#) - from Oxford Journals - Medicine

Available at [Human Reproduction](#) - from HighWire - Free Full Text

**Abstract:**Introduction: Recurrent pregnancy loss (RPL) is a heterogeneous condition. While the role of acquired thrombophilia has been accepted as an etiology for RPL, the contribution of specific inherited thrombophilic gene polymorphisms to this disorder has remained controversial. Materials and Methods: One hundred women with a history of 2 or more consecutive abortions and 100 women with at least 2 live births and no miscarriages were included in the study and analyzed for the presence of 11 thrombophilic gene polymorphisms (factor V (FV) Leiden, FV 4070 A/G, FV 5279 A/G, factor XIII (FXIII)103 G/T, FXIII 614 A/T, FXIII 1694 C/T, plasminogen activator inhibitor 1 (PAI-1) - 675 4G/5G, integrin beta 3 (ITGB3) 1565 T/C, beta-fibrinogen (BF) -455G/A, methylene tetrahydrofolate reductase (MTHFR) 677 C/T, MTHFR 1298 A/C) using PCR-RFLP technique. The data

was statistically analyzed using Mann-Whitney and logistic regression tests. Results: There was no relation between FXIII 103G/T gene polymorphism with increased risk of RPL. However, the other 10 gene polymorphisms were found to be associated with increased/decreased risk of RPL. Multiple logistic regression model for analyzing the simultaneous effects of these polymorphisms on the risk of RPL showed that among these 11 mutations only six of them (FV Leiden (p-value = 0.016, OR (Odds Ratio) = 6.92 ), FV 5279A/G (p-value <0.001, OR = 2.32 ), FXIII 614A/T (p-value <0.001, OR = 2.76 ), BF -455G/A (p-value = 0.001, OR = 5.21 ), ITGB3 1565T/C (p-value <0.001, OR = 0.13 ), MTHFR 1298A/C (p-value = 0.001, OR = 7.15), remained in the model and were associated with RPL. Conclusion: It is possible to calculate the risk of abortion in an RPL patient by determining only six of the 10 polymorphisms that were individually associated with RPL.

**Database:** EMBASE

### **30. Hereditary thrombophilias in patients with recurrent pregnancy loss**

**Author(s):** Yenicesu O.; Gulerman C.; Ozyer S.; Sarikaya E.; Mollamahmutoglu L.; Cakar E.

**Source:** Human Reproduction; 2012; vol. 27

**Publication Date:** 2012

**Publication Type(s):** Conference Abstract

Available at [Human Reproduction](#) - from Oxford Journals - Medicine

Available at [Human Reproduction](#) - from HighWire - Free Full Text

**Abstract:**Introduction: Recurrent first trimester miscarriage-the loss of two or more consecutive pregnancies at less than 12 weeks' gestation-may have a thrombotic etiology. The genetic thrombophilic mutations have been reported to be associated with recurrent pregnancy loss. The study aims to investigate the prevalence of markers for genetic thrombophilias and to identify the associations of these mutations with recurrent miscarriage. Material and Methods: 802 women with a history of recurrent pregnancy loss were evaluated retrospectively for the presence of Factor V Leiden (FVL), prothrombin (FII) and methylenetetrahydrofolate reductase (MTHFR) 677C/T and 1298A/C mutations, and plasminogen activator inhibitor-1 (PAI-1) -675 4G/5G polymorphisms. Polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) were performed to assess the frequency of genetic risk factors for recurrent pregnancy loss. Results: FVL, prothrombin (FII) and MTHFR 677C/T and 1298A/C homozygote mutations, and plasminogen activator inhibitor-1 (PAI-1) -675 4G/5G polymorphisms were detected in 1%, 0,1%, 11% and 47% of the patients respectively. As heterozygote mutations, results were 14%, 4%, 40% and 43% respectively. Conclusion: In couples with recurrent miscarriage multiple genetic thrombophilic mutations increases the risk of miscarriage in a subsequent pregnancy. So an appropriate clinical evaluation focused on diagnosis and therapy of recurrent pregnancy loss should also consider thrombophilic defects.

**Database:** EMBASE



### **31. Plasminogen activator inhibitor-1, polycystic ovaries and recurrent miscarriage**

**Author(s):** Miller A.; White S.; Regan L.; Aziz M.; Rai R.; Abu-Amro S.; Moore G.

**Source:** BJOG: An International Journal of Obstetrics and Gynaecology; Jun 2012; vol. 119 ; p. 128

**Publication Date:** Jun 2012

**Publication Type(s):** Conference Abstract

Available at [BJOG: An International Journal of Obstetrics & Gynaecology](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

**Abstract:** Polycystic Ovarian Morphology (PCOM) is found in 40% of women with recurrent miscarriage (RM). These women have a significantly lower live birth rate than those with normal ovarian morphology. Women with PCOM have disorder in their fibrinolytic response. This response is governed by a balance between plasminogen activator and plasminogen inhibitors. Studies have reported that both urokinase plasminogen activator and plasminogen activator inhibitor (PAI-1), are associated with repeat polymorphism (5G or 4G), situated at 675 bp in the PAI-1 gene promoter. PAI-1 plasma levels are higher amongst those carrying the 4G/4G polymorphism, when compared to those with the 4G/5G or 5G/5G polymorphism. Objective: To measure the prevalence of the 4G/5G polymorphism in PAI-1 amongst those with PCOM and recurrent miscarriage versus those with recurrent miscarriage and 'normal' ovarian morphology. Methods: Two hundred and ninety women with recurrent miscarriages and PCOM and a matching control group of 257 women with unexplained recurrent miscarriages were recruited to this prospective study at St Mary's hospital recurrent miscarriages clinic. Study group inclusion criteria included the following: PCOM, <40 years, had three consecutive first trimester miscarriages (<12 weeks gestation) Normal uterine anatomy on two dimensional ultrasound and normal peripheral blood karyoty. APA negative and normal factor V genotype. Non-hormonal method of contraception <3 months since the last pregnancy. Results: The prevalence of the 4G/5G polymorphism in PAI-1 was significantly higher (92/192) amongst those with PCOM and recurrent miscarriage versus those with recurrent miscarriage and 'normal' ovarian morphology (71/235;  $P < 0.01$ ). There was no significant difference in the prevalence of the 4G/5G polymorphism between those with 'normal' ovarian morphology and the control group of those with a previous uncomplicated pregnancy. Conclusion: The prevalence of 4G/5G polymorphism in PAI-1 was significantly higher amongst women with PCOM and recurrent miscarriages.

**Database:** EMBASE



**32. The PAI-1 4G/5G polymorphism is not associated with an increased risk of adverse pregnancy outcome in asymptomatic nulliparous women.**

**Author(s):** Said, J M; Tsui, R; Borg, A J; Higgins, J R; Moses, E K; Walker, S P; Monagle, P T; Brennecke, S P

**Source:** Journal of thrombosis and haemostasis : JTH; May 2012; vol. 10 (no. 5); p. 881-886

**Publication Date:** May 2012

**Publication Type(s):** Research Support, Non-u.s. Gov't Multicenter Study Journal Article

**PubMedID:** 22432640

Available at [Journal of thrombosis and haemostasis : JTH](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

Available at [Journal of thrombosis and haemostasis : JTH](#) - from IngentaConnect - Open Access

**Abstract:**BACKGROUND Plasminogen activator inhibitor type 1 (PAI-1) is an important regulator of fibrinolysis. A common deletion polymorphism that results in a sequence of 4G instead of 5G in the promoter region of the gene is associated with a small increase in the risk of venous thromboembolism. Its potential association with adverse pregnancy events remains controversial. OBJECTIVE We aimed to assess the impact of the 4G PAI-1 polymorphism on pregnancy outcomes in women who had no prior history of adverse pregnancy outcomes or personal or family history of venous thromboembolism. PATIENTS/METHODS This study represents a secondary investigation of a prior prospective cohort study investigating the association between inherited thrombophilias and adverse pregnancy events in Australian women. Healthy nulliparous women were recruited to this study prior to 22 weeks gestation. Genotyping for the 4G/5G PAI-1 gene was performed using Taqman assays in an ABI prism 7700 Sequencer several years after the pregnancy was completed. Pregnancy outcome data were extracted from the medical record. The primary outcome was a composite comprising development of severe pre-eclampsia, fetal growth restriction, major placental abruption, stillbirth or neonatal death. RESULTS Pregnancy outcome data were available in 1733 women who were successfully genotyped for this polymorphism. The primary composite outcome was experienced by 139 women (8% of the cohort). Four hundred and fifty-nine women (26.5%) were homozygous for the 4G deletion polymorphism, while 890 (51.4%) were heterozygous. Neither homozygosity nor heterozygosity for the PAI-1 4G polymorphism was associated with the primary composite outcome (homozygous OR = 1.30, 95% CI = 0.81-2.09, P = 0.28, heterozygous OR = 0.84, 95% CI = 0.53-1.31, P = 0.44) or with the individual pregnancy complications. CONCLUSION The PAI-1 4G polymorphism is not associated with an increase in the risk of serious adverse pregnancy events in asymptomatic nulliparous women.

**Database:** Medline

### 33. Recurrent pregnancy loss and its relation to combined parental thrombophilic gene mutations.

**Author(s):** Ozdemir, Oztürk; Yenicesu, Gonca Imir; Silan, Fatma; Köksal, Binnur; Atik, Sinem; Ozen, Filiz; Göl, Mert; Cetin, Ali

**Source:** Genetic testing and molecular biomarkers; Apr 2012; vol. 16 (no. 4); p. 279-286

**Publication Date:** Apr 2012

**Publication Type(s):** Journal Article

**PubMedID:** 22047507

**Abstract:**BACKGROUND AND AIM Recurrent pregnancy loss (RPL) is a heterogeneous disorder that has been associated with antiphospholipid syndrome and other prothrombotic parameters. We aimed to investigate the prevalence of 12 thrombophilic gene mutations in RPL couples in the current results. METHOD In a total of 543 Turkish women with RPL and 327 of their male partners (870 individuals with RPL), and a control group of 106 fertile couples (control) were analyzed for factor V Leiden (FVL), factor V H1299R, factor II prothrombin G20210A, FXIII V34L,  $\beta$ -fibrinogen - 455G>A, plasminogen activator inhibitor-1 (PAI-1), GPIIIa L33P (HPA-1 a/b L33P), methylenetetrahydrofolate reductase (MTHFR) C677T, MTHFR A1298C, ACE I/D, Apo B R3500Q, and Apo E genes. RESULT The overall, heterozygous and/or homozygous point mutations in FVL-FVR2, ApoE2, PAI-1, MTHFR C677T-A1298C, and ACE genes were associated with RPL. There was no meaningful association between RPL and other studied genes. CONCLUSION The homozygosity of 4G in PAI-1 and MTHFR C677T genes in women with RPL, and heterozygosity of FVL, FVR2, ACE, and ApoE2 genes in both parents play crucial role in RPL and should be considered as a risk factor in RPL. Current results showed that RPL is related to combined parental (not only maternal) thrombophilic gene mutations.

**Database:** Medline

### 34. Significance of inherited/acquired thrombophilia in idiopathic recurrent spontaneous abortion: SGRH experience

**Author(s):** Arya V.; Bhargava M.; Majumdar A.

**Source:** Indian Journal of Hematology and Blood Transfusion; Dec 2011; vol. 27 (no. 4); p. 231

**Publication Date:** Dec 2011

**Publication Type(s):** Conference Abstract

Available at [Indian Journal of Hematology and Blood Transfusion](#) - from SpringerLink

Available at [Indian Journal of Hematology and Blood Transfusion](#) - from Europe PubMed Central - Open Access

Available at [Indian Journal of Hematology and Blood Transfusion](#) - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:**Introduction: Pregnancy is a hypercoagulable state and thromboembolism is the leading cause of adverse pregnancy outcomes includes recurrent spontaneous abortions (RSA). In the present study we have tried to evaluate the role of inherited/acquired thrombophilia factors in aetiology of RSA in Indian women. Materials & Methods: A retrospective analysis was done in 45 women with RSA together with 27 healthy fertile controls. Patients were recruited according to the guidelines of RCOG (Royal College of Obstetricians and Gynaecologists). Their demographic profile; clinical presentation and history were duly recorded. EDTA, Citrated and Plain blood samples were used for various investigations. Protein C, Protein S, Antithrombin (AT), APC-R, Lupus Anticoagulant (LAC) and antiphospholipid antibody (APA) assays were performed. Common genetic variants accounting for inherited Thrombophilia such as factor V Leiden (FVL), Prothrombin (G20210A), MTHFR (C677T), GPIIb/IIIa (PLA1/A2) and PAI-1 (4G/5G) were analysed by PCRFLP and ASO-PCR.

Results: Of the evaluated 45 cases and 27 controls, the mean age was 30 and 33 years respectively. Amongst 45 cases, 2.2% (1) had deficiency of protein C and S and 4.4% (2) that of AT. The mean values of protein C, S and AT were 99.4, 89.2 and 106.6 respectively; not significantly different from the control reference values. Six women were weakly positive for the lupus anticoagulant. The mutant T allele of MTHFR and A2 allele of PLA1/ A2 polymorphism were significantly associated with the RSA (P = 0.04, OR: 3.67, CI: 1.01-13.2 and P = 0.05, OR: 6.6, CI: 0.82-52.3 respectively) when compared with the controls. Abnormal APC-R and FVL mutation was found in 2 cases of RSA only; both were of late pregnancy loss. No mutant allele of prothrombin gene was observed either in cases or controls. 4G/5G polymorphism of PLA-1 gene showed no association with RSA (P = 0.101). Conclusions: Screening of pregnant women in early gestation with clinical history of RSA; for protein C, S, AT, LAC and APA together with molecular markers may help in timely and effective management of RSA.

**Database:** EMBASE

### **35. Analysis of plasminogen activator inhibitor-1, integrin beta3, beta fibrinogen, and methylenetetrahydrofolate reductase polymorphisms in Iranian women with recurrent pregnancy loss.**

**Author(s):** Jeddi-Tehrani, Mahmood; Torabi, Raheleh; Zarnani, Amir H; Mohammadzadeh, Afsane; Arefi, Soheila; Zeraati, Hojjat; Akhondi, Mohammad M; Chamani-Tabriz, Leili; Idali, Farah; Emami, Shaghayegh; Zarei, Saeed

**Source:** American journal of reproductive immunology (New York, N.Y. : 1989); Aug 2011; vol. 66 (no. 2); p. 149-156

**Publication Date:** Aug 2011

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 21241403

Available at [American journal of reproductive immunology \(New York, N.Y. : 1989\)](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

**Abstract:**PROBLEMTo identify the associations of the plasminogen activator inhibitor-1 (PAI-1) -675 4G/5G, beta fibrinogen (BF) -455G/A, integrin beta 3 (ITGB3) 1565T/C, and methylenetetrahydrofolate reductase (MTHFR) 677C/T and 1298A/C polymorphisms with recurrent pregnancy loss (RPL).METHOD OF STUDYPolymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) were performed to assess the frequency of five candidate genetic risk factors for RPL, and the frequencies of the polymorphisms were calculated and compared between case and control groups.RESULTSThe BF -455G/A, MTHFR 677C/T, and 1298A/C polymorphisms were found to be positively, and ITGB3 1565T/C polymorphism negatively, associated with RPL. Homozygosity but not heterozygosity for PAI-1 -675 4G/5G polymorphism was significantly higher in patients with RPL than in the control group. The presence of both mutations of MTHFR genes highly increased the risk of RPL.CONCLUSIONThe data highlight the importance of thrombophilia screening in patients with RPL.

**Database:** Medline

### **36. Polymorphism 4G/5G in plasminogen activator inhibitor type 1 as a factor for early recurrent pregnancy loss development**

**Author(s):** Ivanov P.D.; Komsa-Penkova R.; Tsvyatkovska T.; Ivanov I.; Konova E.; Kovacheva K.; Simeonova M.; Tanchev S.

**Source:** Journal of Thrombosis and Haemostasis; Jul 2011; vol. 9 ; p. 101

**Publication Date:** Jul 2011

**Publication Type(s):** Conference Abstract

Available at [JOURNAL OF THROMBOSIS AND HAEMOSTASIS](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

Available at [JOURNAL OF THROMBOSIS AND HAEMOSTASIS](#) - from IngentaConnect - Open Access

**Abstract:**Background: A different pathologic mechanism between early and late pregnancy loss development was supposed, correspondingly to the diverse blood flow conditions in endometrium before and after placenta development. Aim: We presumed hypofibrinolytic polymorphism 4G/5G (PL 4G/ 5G), genotype 4G/4G in plasminogen activator inhibitor type 1 (PAI- 1) as a possible factor increasing the risk for development of very early recurrent pregnancy loss (RPL) in arterial-like conditions in the primary intervillous space. Methods: PL 4G/5G as well as Factor V Leiden (FVL), prothrombin (FII) gene mutation 20210 G>A and polymorphism 677 C>T in methylentetrahydrofolat reductase (MTHFR) gene was investigated in 102 women with two or more RPL before 10 weeks of gestation and in 95 healthy women with at least one uncomplicated full-term pregnancy and no history of vascular diseases. Results: A significant difference in the prevalence of PL 4G/5G was found between patients and controls (42.2% vs. 25.3%, OR: 2.16, 95% CI: 1.13-4.15, P = 0.019). The difference remains still significant after the adjustment for FVL, FII 202010 G>A and 677 C>T in MTHFR (the prevalence of PL 4G/5G alone was 43.3% and 23.6% respectively in patients and controls, OR: 2.47, 95% CI: 1.01- 5.59, P = 0.026). Conclusions: The found association between PL 4G/5G and RPL encourages the incorporation of this polymorphism into the spectrum of thrombophilic factors which should be analysed in women with reproductive failure before 10 weeks of gestation. In order to prevent uteroplacental microthrombosis development and poor fetal outcome, an implication of prophylactic anticoagulant treatment in further pregnancy should be considered.

**Database:** EMBASE

### **37. Polymorphisms of plasminogen activator inhibitor-1, angiotensin converting enzyme and coagulation factor XIII genes in patients with recurrent spontaneous abortion.**

**Author(s):** Aarabi, Mahmoud; Memariani, Toktam; Arefi, Soheila; Aarabi, Mohsen; Hantoosh Zadeh, Sedigheh; Akhondi, Mehdi A; Modarressi, Mohammad H

**Source:** The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians; Mar 2011; vol. 24 (no. 3); p. 545-548

**Publication Date:** Mar 2011

**Publication Type(s):** Journal Article

**PubMedID:** 20822334

**Abstract:**We investigated polymorphisms of plasminogen activator inhibitor-1 (PAI-1), angiotensin converting enzyme (ACE ) and coagulation factor XIII (FXIII) genes and their association with recurrent spontaneous abortion (RSA) in Iranian patients and normal healthy controls. Ten (18.5%) patients were homozygote (4G/4G) for PAI-1 polymorphism, in contrast with two (2%) controls ( $p = 0.001$ ). Patients with homozygote 4G mutation were significantly more prone to RSA in contrast to others (odds ratio: 11.0, 95% CI: 2.3-52.4). Nineteen (30.2%) patients and 25 (26.6%) controls were homozygote (DD) for ACE polymorphism. We observed only two patients and one control with homozygosity (34leu) for FXIII polymorphism. 4G/4G polymorphism for PAI-1 gene could be a thrombophilic mutation leading to abortion in Iranian population.

**Database:** Medline

### **38. Use of low molecular-weight heparin and natural progesterone for the prevention of recurrent pregnancy complications (pre-eclampsia, pregnancy loss, placental abruption) in women with metabolic syndrome**

**Author(s):** Radulovich T.B.; Perederyaeva E.B.; Makatsaria A.D.

**Source:** Thrombosis Research; Feb 2011; vol. 127

**Publication Date:** Feb 2011

**Publication Type(s):** Conference Abstract

**Abstract:**Objective: The study of obstetric and perinatal outcomes in women with metabolic syndrome and complicated pregnancy history. Methods: 52 patients aged 22 to 43 years with metabolic syndrome who had the fetal loss syndrome, severe pre-eclampsia, placental abruption in previous pregnancies. Testing for hereditary and acquired forms of thrombophilia. Results: In the study group the multigenic defects were verified in 100% of cases; the feature of multigenic defects is that the 4G/5G polymorphism of plasminogen activator inhibitor-1 gene was found in 92.3% of cases, the 4G/4G phenotype of the gene PAI-1 was verified in 61.5% of cases. The polymorphism in the tissue-type plasminogen activator I/D gene, in the angiotensin-converting enzyme I/D gene, in the fibrinogen 455G/A gene, mutations of methylenetetrahydrofolate reductase C677T were found in 65.4%, 48.1%, 55.8%, 55.8% respectively. Acquired antiphospholipid antibodies were verified in 15.4% of cases. All women received antithrombotic therapy from the fertile cycle involved low molecular-weight heparin (Enoxaparin sodium, daily dose 0.4-0.8 ml), vitamins B, folic acid and natural progesterone for indications. Antithrombotic therapy was controlled by thrombophilia markers (D-Dimer) and the anti-Xa test. Pregnancy was achieved in 100%. There were not recurrent fetal loss, severe pre-eclampsia, placental abruption in the study group. Live births was in all cases. Conclusions: There is genetic hypofibrinolysis and acquired form of thrombophilia in patients with metabolic syndrome and complicated pregnancy history. It may play an important part in impaired invasion cytotrophoblast and impaired placental development. Timely antithrombotic prophylaxis may be a key of successful outcome of pregnancy.

**Database:** EMBASE

**39. Polymorphisms in NOS3, ACE and PAI-1 genes and risk of spontaneous recurrent miscarriage in the Gaza Strip.**

**Author(s):** Al Sallout, Rami J; Sharif, Fadel A

**Source:** Medical principles and practice : international journal of the Kuwait University, Health Science Centre; 2010; vol. 19 (no. 2); p. 99-104

**Publication Date:** 2010

**Publication Type(s):** Journal Article

**PubMedID:** 20134171

Available at [Medical principles and practice : international journal of the Kuwait University, Health Science Centre](#) - from Free Medical Journals . com

**Abstract:**OBJECTIVEThis study was conducted to investigate the correlation between spontaneous recurrent miscarriage (RM) and common polymorphisms in angiotensin-converting enzyme (ACE), plasminogen activator inhibitor 1 (PAI-1) and endothelium-derived nitric oxide synthase 3 (NOS3) genes among women experiencing RM in the Gaza Strip.METHODSThe presence of these genetic profiles was determined for 100 women who had had at least 3 constitutive abortions and 100 controls without any history of abortion using molecular biological techniques.RESULTSThe ACE D/D polymorphism was present in 49% of the study population and in 54% of the controls ( $p = 0.479$ ). Similarly, there was no significant difference detected in the distribution of polymorphisms for PAI-1, with the 4G/4G genotype present in the study group and in controls ( $p = 1.00$ ). NOS3 4a/4a was present in 4% of the study group and in none of the 100 controls ( $p = 0.123$ ). In this study, we also discovered a new variant in the NOS3 gene which was named 4c allele and was encountered in 1 patient and in 1 control subject.CONCLUSIONThere was no significant association between ACE I/D, PAI-1 4G/5G and NOS3 4a/4b and the occurrence of first-trimester RM. In-depth investigation of the association of NOS3 4a/4a with RM is strongly recommended.

**Database:** Medline

**40. Angiotensin-converting enzyme D/I and plasminogen activator inhibitor-1 4G/5G gene polymorphisms are associated with increased risk of spontaneous abortions in polycystic ovarian syndrome.**

**Author(s):** Sun, L; Lv, H; Wei, W; Zhang, D; Guan, Y

**Source:** Journal of endocrinological investigation; Feb 2010; vol. 33 (no. 2); p. 77-82

**Publication Date:** Feb 2010

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 19636212

**Abstract:**BACKGROUND Polycystic ovary syndrome (PCOS) is a main cause of infertility, particularly in high-risk settings such as spontaneous abortions (SAB). We aimed to evaluate the effect of genetic polymorphisms in ACE and plasminogen activator inhibitor-1 (PAI-1) on the occurrence of SAB in PCOS. METHODS One hundred and forty-two PCOS patients (83 women have a history of one or more unexplained SAB, 59 women have successfully live births) and 107 healthy controls matched for age and body mass index were included in the study. Levels of PAI-1, LH, FSH, testosterone, fasting glucose and insulin were measured. ACE deletion (D)/insertion (I) and PAI-1 4G/5G gene polymorphisms were performed. RESULTS The D/D and/or 4G/4G genotype frequency, the D or 4G allelic frequency, the combination of the ACE D/D and PAI-1 4G/5G, D/I and 4G/4G genotypes of PCOS patients with SAB women were statistically higher than non-SAB group ( $p < 0.05$ ). The 4G/4G or D/D genotype of PCOS with SAB patients had significantly higher PAI-1 levels than non-SAB women. CONCLUSION The ACE D/I and PAI-1 4G/5G gene polymorphisms might represent risk factor in PCOS with SAB. Homozygosity for ACE D or PAI-1 4G polymorphisms as well as compound carrier status are significant positive explanatory variable for PCOS patients with SAB, which may result in increased PAI-1 concentrations and hypofibrinolysis and contribute to early pregnancy loss.

**Database:** Medline

**41. Are polymorphisms in the ACE and PAI-1 genes associated with recurrent spontaneous miscarriages?**

**Author(s):** Goodman, Chelsi; Hur, Jee; Goodman, Cyle S; Jeyendran, Rajasingham S; Coulam, Carolyn

**Source:** American journal of reproductive immunology (New York, N.Y. : 1989); Dec 2009; vol. 62 (no. 6); p. 365-370

**Publication Date:** Dec 2009

**Publication Type(s):** Journal Article

**PubMedID:** 19821806

Available at [American Journal of Reproductive Immunology](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

**Abstract:**PROBLEM To determine whether the ACE D/D genotype or the combination of PAI-1 4G/4G and ACE D/D genotypes may serve as a risk factor for recurrent pregnancy loss. METHOD OF STUDY Buccal swabs were obtained from 120 women experiencing recurrent pregnancy loss and from 84 fertile control women. DNA was extracted from the buccal swab samples using the Qiagen DNA Mini Kit (Qiagen), followed by multiplex polymerase chain reaction (PCR). PCR products were analyzed for the ACE gene polymorphism, which consists of the insertion or deletion (I/D) of a 287-bp fragment in intron 16, and the PAI-1 4G/4G genotype. RESULTS No significant differences in specific ACE gene mutations were observed when patients experiencing recurrent miscarriage were compared with control women. When the frequencies of homozygous mutations for ACE D/D and PAI-1 4G/4G were compared between recurrent aborters and controls, again no significant differences in the prevalence of the combination of these gene mutations were



noted.**CONCLUSION**Homozygosity for the D allele of the ACE gene and the combination of the D/D genotype with two 4G alleles of the PAI-1 promoter gene are not associated with a significant increase in the risk of recurrent miscarriage.

**Database:** Medline

#### **42. Plasminogen activator inhibitor-1 4G/5G gene polymorphism in women with fetal loss.**

**Author(s):** Ghosh, Kanjaksha; Shetty, Shrimati; Vora, Sonal

**Source:** International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics; Nov 2009; vol. 107 (no. 2); p. 159-160

**Publication Date:** Nov 2009

**Publication Type(s):** Journal Article

**PubMedID:** 19628210

Available at [International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

**Database:** Medline

#### **43. Early pregnancy loss in celiac women: The role of genetic markers of thrombophilia.**

**Author(s):** Ciacci, C; Tortora, R; Scudiero, O; Di Fiore, R; Salvatore, F; Castaldo, G

**Source:** Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver; Oct 2009; vol. 41 (no. 10); p. 717-720

**Publication Date:** Oct 2009

**Publication Type(s):** Journal Article

**PubMedID:** 19395327

**Abstract:****BACKGROUND**Adverse pregnancy outcomes are more frequent in celiac than in non-celiac women.**AIMS**To investigate a possible role of genetic prothrombotic variants in early pregnancy loss of celiac women.**METHODS**Thirty-nine celiac women who had experienced early pregnancy losses (at least two losses within the first 3 months of pregnancy), and 72 celiac women with a history of one or more normal pregnancies and no pregnancy loss (controls) entered the study, at the moment of diagnosis for celiac disease. A clinical history was obtained from each woman. DNA from leukocytes was tested for: factor V Leiden (mutation G1691A), factor V R2 (H1299R), factor II (G20210A), methylenetetrahydrofolate reductase (MTHFR) (C677T and A1298C), beta-fibrinogen (-455 G>A), PAI-1 alleles 4G/5G, factor XIII (V34L), and HPA-1 (L33P).**RESULTS**Age at diagnosis was significantly higher ( $p=0.002$ ) in the celiac women with pregnancy losses than in controls. Of the gene variants studied, the allelic frequency of 4G variant of PAI-1, and the frequency of mutant genotypes were significantly more frequent in the group of celiac women with early pregnancy loss ( $p=0.00003$  and  $0.028$ , respectively). Surprisingly, the beta-fibrinogen -455 G>A genotype distribution (but not the allelic frequency of the variant allele) significantly differed between the two groups, since variant genotypes were more frequent in the control group ( $p=0.009$ ).**CONCLUSION**The 4G variant of the PAI-I gene may predispose to miscarriage a subset of celiac women; these data should be verified on larger populations.

**Database:** Medline



#### **44. Comparison of thrombophilic gene mutations among patients experiencing recurrent miscarriage and deep vein thrombosis**

**Author(s):** Coulam C.B.; Wallis D.; Weinstein J.; Dasgupta D.S.; Jeyendran R.S.

**Source:** American Journal of Reproductive Immunology; 2008; vol. 60 (no. 5); p. 426-431

**Publication Date:** 2008

**Publication Type(s):** Article

**PubMedID:** 18803625

Available at [American Journal of Reproductive Immunology](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

**Abstract:**Problem: Inherited thrombophilia has been shown to be a risk factor for cardiovascular disease including deep venous thrombosis as well as reproductive disorders including recurrent pregnancy loss. We have previously reported three out of the 10 thrombophilic mutations studied, plasminogen activator inhibitor-1 (PAI-1) 4G/5G, factor XIII V34L, and homozygous MTHFR C667T, correlated significantly with recurrent pregnancy loss compared with controls. This study was undertaken to compare the frequencies of nine inherited thrombophilias among women with a history of recurrent pregnancy loss with individuals experiencing deep venous thrombosis and fertile controls. Method o study: Six hundred thirty-four participants including 550 women with a history of recurrent pregnancy loss, 43 individuals with deep vein thrombosis and 41 fertile women without a history of recurrent miscarriage. All participants had buccal swabs taken for DNA analyses of nine gene polymorphisms including factor V G1691A, factor V H1299R (R2), factor II Prothrombin G20210A, factor XIII V34L, beta-fibrinogen -455G>A, PAI-1 4G/5G, human platelet antigen 1 a/b (L33P), MTHFR C677T, MTHFR A1298C. Frequencies of thrombophilic gene polymorphisms were compared among the three populations studied. Results: Individuals with a history of DVT had a significantly higher frequency of all of the polymorphisms studied compared with women experiencing a history of recurrent pregnancy loss and the fertile controls. The frequencies of mutations for V34L and PAI-1 4G/5G were significantly increased among women experiencing recurrent pregnancy loss compared with controls. The most prevalent polymorphisms were factor XIII V34L and PAI-1 4G/4G for both individuals with a history of deep vein thrombosis and recurrent pregnancy loss compared with controls. Conclusion: Screening for risk factors for inherited thrombophilia with only polymorphisms for factor V von Leiden, factor II prothrombin and MTHFR may be missing the more prevalent identifiers of jeopardy. © Journal compilation © 2008 Blackwell Munksgaard.

**Database:** EMBASE

#### **45. Comparison of the plasminogen activator inhibitor-1 4G/5G gene polymorphism in females with venous thromboembolism during pregnancy or spontaneous abortion**

**Author(s):** Schenk J.F.; Stephan B.; Zewinger S.; Speer T.; Pindur G.

**Source:** Clinical Hemorheology and Microcirculation; 2008; vol. 39 (no. 1); p. 329-332

**Publication Date:** 2008

**Publication Type(s):** Conference Paper

**PubMedID:** 18503142

**Abstract:**Genetic polymorphisms in plasminogen activator inhibitor-1 gene-675 4G/5G (PAI-1 4G/5G) are claimed to contribute to an increased risk of venous thromboembolism. Inherited thrombophilia, on the other hand, is associated with the occurrence of spontaneous abortions. The objective of this study was, to explore the significance of genetic polymorphisms of PAI-1 4G/5G with particular emphasis on 4G alleles in pregnant women suffering from venous thromboembolism or early spontaneous abortion, respectively. Therefore genetic PAI-1 4G/5G polymorphisms were studied in 108 pregnant females suffering from venous thromboembolism (n=69) or from spontaneous abortion (<20 week, n=39), respectively. Healthy volunteers (n=238) were taken as controls. The frequencies of 4G alleles (4G/4G or 4G/5G genotypes) of PAI-1 were significantly higher in venous thromboembolism (OR: 3.40, p=0.0088) and slightly higher, but not significantly, in abortions (RR: 2.33; p=0.1162) compared to controls. The incidence of 4G-carriers in females with abortion was 0.68 (-32%) compared to women suffering from venous thromboembolism alone. We conclude from these data, that the occurrence of PAI-1 4G/4G or 4G/5G genotypes, respectively, is clinically significant for the pathogenesis of venous thromboembolism in pregnancy but not for early abortion. © 2008 - IOS Press and the authors. All rights reserved.

**Database:** EMBASE

#### **46. Fibrinolytic defects and recurrent miscarriage: A systematic review and meta-analysis**

**Author(s):** Sotiriadis A.; Makrigiannakis A.; Stefanos T.; Paraskevaidis E.; Kalantaridou S.N.

**Source:** Obstetrics and Gynecology; May 2007; vol. 109 (no. 5); p. 1146-1155

**Publication Date:** May 2007

**Publication Type(s):** Review

**PubMedID:** 17470597

Available at [Obstetrics and gynecology](#) - from Ovid (LWW Total Access Collection 2015 - Q1 with Neurology)

**Abstract:**OBJECTIVE: To systematically review evidence of the association between fibrinolytic defects and recurrent miscarriage. DATA SOURCES: MEDLINE, EMBASE, and references of retrieved articles (last update September 2006) were used. METHODS OF STUDY SELECTION: Studies comparing the prevalence of fibrinolytic defects in patients with recurrent miscarriage and control women were reviewed. Of 111 potentially relevant studies, data from 14 were integrated with meta-analytic techniques and were presented as odds ratios (ORs). TABULATION, INTEGRATION, AND RESULTS: Plasminogen activator inhibitor-1 4G/5G polymorphism (OR 1.65, 95% confidence interval [CI] 0.92-2.95) and increased plasminogen activator inhibitor activity were not significantly associated with recurrent miscarriage, although the latter showed profound heterogeneity across studies. Although factor XII C46T polymorphism is not associated with recurrent miscarriage (OR 1.07, 95% CI 0.52-2.22), factor XII deficiency is significantly associated (five studies, 1,096 women; OR 18.11, 95% CI 5.52-59.39), with minimal heterogeneity across studies. Factor XIII Val34Leu and Tyr204Phe polymorphisms were not associated with recurrent miscarriage (OR 1.24, 95% CI 0.46-3.34 and OR 2.61, 95% CI 0.45-15.16, respectively). There were no eligible studies found for the rest

of the factors searched (urokinase-type plasminogen activator, tissue-type plasminogen activator, kallicrein,  $\alpha_2$ -antiplasmin,  $\alpha_2$ -macroglobulin, thrombin-activated thrombolysis inhibitor, and factor XI). Only a small minority of studies ascertained miscarriage according to specific criteria, and none of the studies provided equal examination for confounders in cases and controls. **CONCLUSION:** Factor XII deficiency is associated with recurrent miscarriage. Data on the other factors either fail to show association or are quite limited. © 2007 The American College of Obstetricians and Gynecologists.

**Database:** EMBASE

#### **47. Multiple thrombophilic gene mutations rather than specific gene mutations are risk factors for recurrent miscarriage**

**Author(s):** Coulam C.B.; Roussev R.; Jeyendran R.S.; Fishel L.A.

**Source:** American Journal of Reproductive Immunology; May 2006; vol. 55 (no. 5); p. 360-368

**Publication Date:** May 2006

**Publication Type(s):** Article

**PubMedID:** 16635210

Available at [American journal of reproductive immunology \(New York, N.Y. : 1989\)](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

**Abstract:** Problem: Recurrent miscarriage is a heterogeneous condition. While the role of acquired thrombophilia has been accepted as an etiology of recurrent miscarriage, the contribution of specific inherited thrombophilic genes to this disorder has remained controversial. We compared the prevalence of 10 thrombophilic gene mutations among women with a history of recurrent miscarriages and fertile control women. Method of study: A total of 150 women with a history of two or more recurrent pregnancy losses and 20 fertile control women with no history of pregnancy losses had buccal swabs taken for DNA analyses of 10 gene mutations [factor V G1691A, factor V H1299R (R2), factor V Y1702C, factor II prothrombin G20210A, factor XIII V34L, b-fibrinogen - 455G>A, PAI-1 4G/5G, HPA1 a/b (L33P), MTHFR C677T, MTHFR A1298C]. The prevalence of these mutations was compared between women experiencing recurrent miscarriage and controls. Results: No differences in the frequency of specific gene mutations were detected when women with recurrent miscarriage were compared with control women. However, the prevalence of homozygous mutations and total gene mutations among patients with recurrent miscarriage was significantly higher than among controls. Homozygous mutations were found in 59% of women with a history of recurrent pregnancy loss contrasted to 10% of control women. More than three gene mutations among the 10 genes studied were observed in 68% of women with recurrent miscarriage and 21% of controls. Conclusion: Inherited thrombophilias are associated with recurrent miscarriage. This association is manifest by total number of mutations rather than specific genes involved. © 2006 Blackwell Munksgaard.

**Database:** EMBASE

**48. Plasminogen activator inhibitor activity, 4G5G polymorphism of the plasminogen activator inhibitor 1 gene, and first-trimester miscarriage in women with polycystic ovary syndrome**

**Author(s):** Glueck C.J.; Sieve L.; Zhu B.; Wang P.

**Source:** Metabolism: Clinical and Experimental; Mar 2006; vol. 55 (no. 3); p. 345-352

**Publication Date:** Mar 2006

**Publication Type(s):** Article

**PubMedID:** 16483878

**Abstract:**We assessed whether hypofibrinolytic plasminogen activator inhibitor 1 (PAI-1 activity) showed an independent association with first-trimester miscarriage in the 430 women with polycystic ovary syndrome (PCOS) who had previous pregnancies (from a cohort of 967 women with PCOS). Prospectively, we hypothesized that Glucophage (Bristol-Myers Squibb, Princeton, NJ) promotes successful live births in women with PCOS by lowering PAI-1 activity before conception and maintaining further reductions of PAI-1 activity during the first trimester of pregnancy. We also assessed whether PAI-1 activity levels were independently related to PAI-1 genotype and to modifiable risk factors body mass index (BMI), insulin, and triglyceride. By stepwise logistic regression, with the dependent variable being previous pregnancy outcomes at 3 levels (live birth pregnancies only [n = 208]; both  $\geq 1$  live birth and  $\geq 1$  first-trimester miscarriage [n = 111]; or first-trimester miscarriages only [n = 71]) and explanatory variables PAI-1 genotype, PAI-1 activity, insulin, homeostasis model assessment of insulin resistance, BMI, and triglyceride, PAI-1 activity was positively associated with first-trimester miscarriage ( $P = .004$ ). For each 5 IU/mL increment in PAI-1 activity, the risk being in an adverse first-trimester miscarriage category increased (odds ratio, 1.12; 95% confidence interval, 1.04-1.20). Prospectively, from pretreatment to the last preconception visit on Glucophage, in 30 women who subsequently had live births, PAI-1 activity fell 44%, but rose 19% in 23 women with first-trimester miscarriage ( $P = .03$ ). In the 30 women with live birth pregnancies, median PAI-1 activity fell continuously from pretreatment through the first trimester (from 16.8 to 6.7 IU/mL), whereas PAI-1 activity was either unchanged or rose in women with first-trimester miscarriage. Of the 921 women with PCOS who had 4G5G data, 718 (78%) had 4G4G-4G5G genotypes vs 87 (69%) of 126 normal female controls ( $\chi^2 = 4.95$ ,  $P = .026$ ). The 4G allele frequency was 53% in women with PCOS vs 46% in controls ( $\chi^2 = 4.3$ ,  $P = .04$ ). Of the 866 women with PCOS who had PAI-1 activity data, by stepwise regression, positive independent determinants of PAI-1 activity included BMI (partial  $R^2 = 10.6\%$ ,  $P < .0001$ ), insulin (partial  $R^2 = 2.8\%$ ,  $P < .0001$ ), triglyceride (partial  $R^2 = 1.1\%$ ,  $P = .0009$ ), and the 4G4G-4G5G genotype (partial  $R^2 = 1\%$ ,  $P = .0011$ ). The PAI-1 gene 4G polymorphism is more common in women with PCOS than in normal women and, in concert with obesity, hyperinsulinemia, and hypertriglyceridemia, contributes to treatable, hypofibrinolytic, miscarriage-promoting, high PAI-1 activity. Preconception and first-trimester decrements in PAI-1 activity on Glucophage are associated with live births, whereas increments or no change in PAI-1 activity despite Glucophage appears to be associated with first-trimester miscarriage. © 2006 Elsevier Inc. All rights reserved.

**Database:** EMBASE

#### **49. Plasminogen activator inhibitor-1: A review**

**Author(s):** Pihusch M.; Holler E.; Pihusch V.

**Source:** LaboratoriumsMedizin; Dec 2005; vol. 29 (no. 6); p. 403-411

**Publication Date:** Dec 2005

**Publication Type(s):** Review

**Abstract:** Plasminogen activator inhibitor-1 (PAI-1) is the most potent inhibitor of both tissue type (t-PA) and urokinase type plasminogen activator (u-PA) and thus regulates fibrinolysis as well as proteolysis, cell migration, and tumor cell invasiveness. Stimulated by cytokines, lipopolysaccharide, very low density lipoproteins, and transforming growth factor beta-1 (TGF beta-1), PAI-1 also influences inflammation, metabolic disorders, and fibrotic diseases. PAI-1 is produced in liver cells, adipocytes, smooth muscle cells, and platelets. In pathological conditions, increased PAI-1 levels mainly result from release by endothelial cells or tumor cells. Elevation of PAI-1 activity is described to be associated with pregnancy complications like recurrent miscarriage, pregnancy-induced hypertension, and preeclampsia. Spontaneous abortion seems to be related to the 4G/4G genotype of the polymorphism in the PAI-1 promoter. Women with polycystic ovarian syndrome, which is associated with anovulatory infertility, also show significantly higher PAI-1 levels than healthy controls. Increased PAI-1 levels are found in a number of malignancies and might give information about prognosis and preferential response to certain therapies especially in patients with primary breast cancer. By influencing extracellular matrix turnover, PAI-1 seems to play a role in fibrotic disorders including nephropathy, chronic lung diseases, cardiac fibrosis, and liver fibrosis. Upregulated by inflammatory mediators, PAI-1 levels are increased in sepsis, trauma, surgery, and a variety of diseases associated with inflammatory reactions. PAI-1 is suggested to play a functional role in host response to trauma. Inflammatory states are also found in the pathogenesis of atherosclerosis and the metabolic syndrome. Vascular diseases as well as insulin resistance leading to metabolic state are associated with both elevated PAI-1 levels and the 4G/5G polymorphism of the PAI-1 promoter. The 4G/4G and 4G/5G genotypes were observed to be more frequent in patients with obesity, myocardial infarction, and venous thromboembolism. PAI-1 thus represents an important non-invasive diagnostic criterion in a number of diseases and might reveal new therapeutic strategies. © 2005 by Walter de Gruyter.

**Database:** EMBASE

**50. Polymorphisms in the ACE and PAI-1 genes are associated with recurrent spontaneous miscarriages**

**Author(s):** Buchholz T.; Rogenhofer N.; Kosian E.; Thaler C.J.; Lohse P.; Pihusch R.

**Source:** Human Reproduction; Nov 2003; vol. 18 (no. 11); p. 2473-2477

**Publication Date:** Nov 2003

**Publication Type(s):** Article

**PubMedID:** 14585904

Available at [Human reproduction \(Oxford, England\)](#) - from Oxford Journals - Medicine

**Abstract:**Background: Successful pregnancies require fine tuning of fibrinolytic activities in order to secure fibrin polymerization and stabilization of the placental basal plate as well as to prevent excess fibrin deposition in placental vessels and intervillous spaces. Fibrinolysis is tightly regulated by plasminogen activator inhibitor-1 (PAI-1). Endothelial PAI-1 synthesis is induced by angiotensin II, which is generated by angiotensin I-converting enzyme (ACE). Methods: We studied the ACE deletion (D)/insertion (I) polymorphism and the PAI-1 4G/5G polymorphism in women with recurrent spontaneous miscarriages (RM). Both polymorphisms have been shown to be associated with ACE and PAI-1 expression levels respectively. A study group of 184 patients with a history of two or more consecutive unexplained spontaneous miscarriages was compared with a control group of 127 patients with uneventful term deliveries and no history of miscarriages. Results: Our findings show: (i) homozygosity for the D allele of the ACE gene, which results in elevated PAI-1 concentrations and hypofibrinolysis, is associated with an elevated risk of RM; (ii) the combination of the D/D genotype with two 4G alleles of the PAI-1 promoter, which further increases PAI-1 plasma levels, is significantly more frequent in RM patients compared with controls. Conclusions: Based on these results, we recommend the incorporation of these two polymorphisms into the spectrum of thrombophilic mutations which should be analysed in individuals with recurrent spontaneous miscarriages. Patients homozygous for both the ACE D and PAI-1 4G alleles may benefit from the application of low molecular weight heparin as early as possible in the pregnancy in order to prevent uteroplacental microthromboses.

**Database:** EMBASE

**51. Plasminogen activator inhibitor 1 4G/5G polymorphism and coagulation factor XIII Val34Leu polymorphism: impaired fibrinolysis and early pregnancy loss.**

**Author(s):** Dossenbach-Glaninger, Astrid; van Trotsenburg, Michael; Dossenbach, Martin; Oberkanins, Christian; Moritz, Anne; Krugluger, Walter; Huber, Johannes; Hopmeier, Pierre

**Source:** Clinical chemistry; Jul 2003; vol. 49 (no. 7); p. 1081-1086

**Publication Date:** Jul 2003

**Publication Type(s):** Journal Article

**PubMedID:** 12816904

Available at [Clinical chemistry](#) - from HighWire - Free Full Text

Available at [Clinical chemistry](#) - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:**BACKGROUND A successful outcome of pregnancy depends on proper placental formation. In the very beginning of this process, trophoblast invasion and fibrin deposition into the wall of the decidual veins play an important part. Two polymorphisms, coagulation factor XIII (FXIII) Val34Leu and plasminogen activator inhibitor 1 (PAI-1) 4G/5G, interfere with fibrin cross-linking and regulation of fibrinolysis and may therefore contribute to early pregnancy loss. METHODS We enrolled 49 unrelated Caucasian women with a history of two consecutive or three to six nonconsecutive early pregnancy losses and 48 unrelated parous healthy controls without a history of pregnancy loss and evaluated them for the following genetic variants: the factor V Leiden and prothrombin G20210A gene mutations, the methylenetetrahydrofolate reductase C677T and A1298C polymorphisms, and the PAI-1 4G/5G and FXIII Val34Leu polymorphisms. RESULTS For the isolated occurrence of PAI-1 4G/5G or FXIII Val34Leu, we found no statistically significant difference between cases and controls. For homozygosity of either or compound carrier status of both mutations, the overall relative risk for early pregnancy loss was significantly increased (odds ratio = 2.4; 95% confidence interval, 1.1-5.5; P = 0.032). We observed no statistically relevant association of any of the other tested mutations with early pregnancy loss. CONCLUSION Homozygosity for PAI-1 4G or FXIII 34Leu polymorphisms as well as compound carrier status is associated with early pregnancy loss.

**Database:** Medline

## 52. Genetic hypofibrinolysis in complicated pregnancies.

**Author(s):** Glueck, C J; Kupferminc, M J; Fontaine, R N; Wang, P; Weksler, B B; Eldor, A

**Source:** Obstetrics and gynecology; Jan 2001; vol. 97 (no. 1); p. 44-48

**Publication Date:** Jan 2001

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 11152905

Available at [Obstetrics and gynecology](#) - from Free Medical Journals . com

Available at [Obstetrics and gynecology](#) - from Ovid (Journals @ Ovid) - London Health Libraries

**Abstract:**OBJECTIVETo assess the hypofibrinolytic 4G/4G mutation of the plasminogen activator inhibitor (PAI-1) gene as a possible factor contributing to severe preeclampsia, abruptio placentae, fetal growth restriction, and stillbirth.METHODSWe compared 94 women from a previous report who had obstetric complications to 95 controls with normal pregnancies matched for ethnic background and age. We collected blood and extracted DNA after delivery. All subjects had been tested for thrombophilic mutations factor V Leiden, C677T mutation in the methylenetetrahydrofolate reductase gene, and the G20210A mutation in the prothrombin gene. In the present study we tested for the hypofibrinolytic 4G/4G mutation in the PAI-1 gene.RESULTSWomen who had obstetric complications were more likely than controls to be 4G/4G homozygotes, 32% (30 of 94) women versus 19% (18 of 95) controls, odds ratio (OR) and 95% confidence intervals (CI) 2.0 (1.02, 3.9). Mutations in the PAI-1 gene were independently associated with obstetric complications (OR 1.56, 95% CI 1.005, 2.43). Heterozygosity for the factor V Leiden mutation was more common in the 30 women who had PAI-1 4G/4G than in the 18 4G/4G controls (33% versus 0%, Fisher P =.008). Seventy-six percent of women had some form of thrombophilia or hypofibrinolysis compared with 37% of controls (Fisher P <.001).CONCLUSIONSWomen with severe preeclampsia, abruptio placentae, fetal growth restriction, and stillbirth had increased incidence of the hypofibrinolytic 4G/4G mutation of the PAI-1 gene that is frequently associated with the thrombophilic factor V Leiden mutation, further predisposing them to thrombosis.

**Database:** Medline

## 53. The 4G/4G polymorphism of the hypofibrinolytic plasminogen activator inhibitor type 1 gene: an independent risk factor for serious pregnancy complications.

**Author(s):** Glueck, C J; Phillips, H; Cameron, D; Wang, P; Fontaine, R N; Moore, S K; Sieve-Smith, L; Tracy, T

**Source:** Metabolism: clinical and experimental; Jul 2000; vol. 49 (no. 7); p. 845-852

**Publication Date:** Jul 2000

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 10909993

**Abstract:**The specific aim of the current study of 133 women with at least 1 pregnancy and measures of hypofibrinolytic and thrombophilic gene mutations was to determine retrospectively whether the mutations were associated with adverse pregnancy outcomes including prematurity, miscarriage, stillbirth, intrauterine growth retardation (IUGR), eclampsia, and abruptio placentae. Four gene mutations (factor V Leiden, methylenetetrahydrofolate reductase [MTHFR], prothrombin, and 4G/5G polymorphism of the plasminogen activator inhibitor type 1 [PAI-1] gene) were assessed by polymerase chain reaction (PCR). One hundred twenty-two women were genotyped for all 4 genes and divided into gene mutation (n = 68) and non-gene (n = 54) groups. The gene mutation group included those with at least 1 thrombophilic mutation (heterozygous for factor V Leiden, heterozygous for prothrombin, and homozygous for MTHFR), or hypofibrinolysis with homozygosity



for the 4G polymorphism of the PAI-1 gene. The non-gene mutation group included those with no mutation for all 4 genes (wild-type normal) or who were wild-type normal for the prothrombin and factor V Leiden mutations and heterozygous for MTHFR and/or 4G/5G for the PAI-1 gene, neither heterozygosity associated with coagulation abnormalities. The 68 women with gene mutations, versus 54 in the non-gene mutation group, has more prematurity (10% v 4%,  $\chi^2 = 5.4$ ,  $P = .021$ ), more IUGR (3% v 0%,  $P = .035$ ), and more total complications of pregnancy (37% v 21%,  $\chi^2 = 11.6$ ,  $P = .001$ ). The number of pregnancies ( $P = .0001$ ) and 4G/4G polymorphism of the PAI-1 gene ( $P = .029$ ) were positively associated with complications of pregnancy by stepwise logistic regression when the age, number of pregnancies, and all 4 gene mutations were the explanatory variables. Heritable hypofibrinolysis, mediated by 4G/4G homozygosity for the PAI-1 gene, is an independent significant, potentially reversible risk factor for pregnancy complications, probably acting through thrombotic induction of placental insufficiency.

**Database:** Medline

**54. Plasminogen activator inhibitor activity: an independent risk factor for the high miscarriage rate during pregnancy in women with polycystic ovary syndrome.**

**Author(s):** Glueck, C J; Wang, P; Fontaine, R N; Sieve-Smith, L; Tracy, T; Moore, S K

**Source:** Metabolism: clinical and experimental; Dec 1999; vol. 48 (no. 12); p. 1589-1595

**Publication Date:** Dec 1999

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 10599993

**Abstract:** In 41 women with at least one pregnancy drawn from a group of 149 (108 never-pregnant) women with polycystic ovary syndrome (PCOS), our specific aim was to determine whether hypofibrinolysis mediated by high plasminogen activator inhibitor activity (PAI-Fx) is an independent risk factor for miscarriage. The 41 women had 77 total pregnancies with 34 miscarriages (44%) and 42 live births (55%). There were 12 women with at least one pregnancy, at least one miscarriage, and no live births (16 pregnancies and 16 miscarriages). There were 15 women with at least one pregnancy, no miscarriages, and at least one live birth (25 pregnancies and 28 live births). Of 12 women with only miscarriages and no live births, 67% had PAI-Fx greater than 16.4 U/mL (normals' 95th percentile), versus 29% of 15 women with no miscarriages and all live births ( $\chi^2 = 3.8$ ,  $P = .052$ ). By stepwise logistic regression, the number of pregnancies ( $P = .0001$ ) and PAI-Fx ( $P = .016$ ) were significant positive explanatory variables for the number of miscarriages. Age, 4G/5G polymorphisms of the PAI gene, factor V Leiden, methylenetetrahydrofolate reductase (MTHFR) gene mutations, androstenedione, testosterone, sex hormone-binding globulin, the Quetelet index, and fasting serum insulin and glucose were not significant variables in the logistic regression model. In a separate stepwise logistic regression, three nonoverlapping groups of women (12 with  $\geq 1$  pregnancy,  $\geq 1$  miscarriage, and 0 live births, 10 with  $\geq 1$  pregnancy,  $\geq 1$  miscarriage, and  $\geq 1$  live births, and 15 with  $\geq 1$  pregnancy, 0 miscarriages, and  $\geq 1$  live births) were the dependent variables. PAI-Fx was positively associated ( $P = .05$ ) with the group with the worst pregnancy outcome ( $\geq 1$  pregnancy,  $\geq 1$  miscarriage, and 0 live births). The 41 women with PCOS and at least one pregnancy were more likely than healthy normal controls to have heterozygosity and homozygosity for the 4G/5G polymorphism of the PAI-1 gene ( $P = .028$ ), but did not differ from normals for factor V Leiden ( $P > .10$ ) or MTHFR ( $P > .09$ ) mutations. PAI-Fx is a predominant independent significant positive reversible risk factor for miscarriage in women with PCOS.

**Database:** Medline

**55. Use of a low-molecular weight heparin (enoxaparin) or of a phenformin-like substance (moroxydine chloride) in primary early recurrent aborters with an impaired fibrinolytic capacity.**

**Author(s):** Gris, J C; Neveu, S; Tailland, M L; Courtieu, C; Marès, P; Schved, J F

**Source:** Thrombosis and haemostasis; Mar 1995; vol. 73 (no. 3); p. 362-367

**Publication Date:** Mar 1995

**Publication Type(s):** Comparative Study Randomized Controlled Trial Clinical Trial Journal Article

**PubMedID:** 7667816

**Abstract:**An impaired fibrinolytic capacity, defined as an insufficient venous occlusion-induced shortening of the plasma euglobulin clot lysis time, is a common feature in women suffering from primary early recurrent unexplained miscarriages. We investigated the therapeutic effect of a low-molecular-weight heparin and of a phenformin-like substance. In a prospective, randomized trial, 30 consecutive patients initially received either enoxaparin, 20 mg per day during one month, or moroxydine chloride, 1200 mg per day during one month. In case of fibrinolytic status normalization, they were treated during 6 months by the beneficial treatment which was planned to be continued during eventual pregnancies. Patients with hypofibrinolysis persistence received the alternative treatment during another month and a new evaluation was performed. No treatment was given when a persistent abnormal response to the venous occlusion test was evidenced. In case of positive response, the treatment was continued during 6 months. The primary study end-points consisted of any of the following: effect of the treatments on the fibrinolytic response; number of patients becoming pregnant during the 6 months following the last venous occlusion test; number of full-term pregnancies. Concerning the effects on the fibrinolytic system, 20 out of 29 women responded to the first or second-line enoxaparin treatment whereas only 1 woman out of 19 responded to moroxydine chloride ( $p = 0.00002$ ). Concerning the effects on fertility, responders to LMWH were more likely to initiate a new pregnancy than non-responders (16/20 vs 2/10,  $p = 0.002$ ). In patients conceiving, LMWH responders were more likely to obtain live births than nonresponders (13/16 vs. 0/2,  $p = 0.02$ ). (ABSTRACT TRUNCATED AT 250 WORDS)

**Database:** Medline

## Strategy 380279

#	Database	Search term	Results
1	Medline	exp "PLASMINOGEN ACTIVATOR INHIBITOR 1"/	8246
2	Medline	("PAI 1").ti,ab	10014
3	Medline	("PLASMINOGEN ACTIVATOR 7373 INHIBITOR 1").ti,ab	
4	Medline	(1 OR 2 OR 3)	13800
5	Medline	(4G).ti,ab	2536
6	Medline	(homozygos*).ti,ab	8899
7	Medline	(4 AND 5 AND 6)	55
8	Medline	(4 AND 5)	778
9	Medline	(miscarriage OR "spontaneous abortion").ti,ab	14507
10	Medline	exp "ABORTION, SPONTANEOUS"/	34757
11	Medline	(9 OR 10)	41954
12	Medline	(8 AND 11)	60
13	Medline	("four gene" OR "4 gene").ti,ab	4678
14	Medline	(4 AND 11 AND 13)	1
15	EMBASE	("PAI 1").ti,ab	14024
16	EMBASE	exp "PLASMINOGEN ACTIVATOR INHIBITOR 1"/	16071
17	EMBASE	("PLASMINOGEN ACTIVATOR 9079 INHIBITOR 1").ti,ab	
18	EMBASE	(15 OR 16 OR 17)	21660

19	EMBASE	(4G).ti,ab	3709
20	EMBASE	("four gene" OR "4 gene").ti,ab	5441
22	EMBASE	("4 G").ti,ab	8973
23	EMBASE	(19 OR 20 OR 22)	18035
24	EMBASE	(homozygos*).ti,ab	11519
25	EMBASE	exp HOMOZYGOSITY/	63149
26	EMBASE	(24 OR 25)	65897
27	EMBASE	(miscarriage OR "spontaneous abortion").ti,ab	22610
28	EMBASE	exp "SPONTANEOUS ABORTION"/	37158
29	EMBASE	("early pregnancy loss").ti,ab	1299
30	EMBASE	(27 OR 28 OR 29)	43771
31	EMBASE	(18 AND 23 AND 26 AND 30)	22
32	EMBASE	(18 AND 23 AND 30)	68
33	Medline	((future OR subsequent) ADJ2 pregn*).ti,ab	4565
34	Medline	(4 AND 5 AND 33)	0
35	Medline	exp "ABORTION, SPONTANEOUS"/pc	2515
36	Medline	(4 AND 5 AND 35)	1
37	Medline	exp PREGNANCY/	827301
38	Medline	(4 AND 5 AND 37)	84
39	EMBASE	exp PREGNANCY/	686259
40	EMBASE	(18 AND 23 AND 39)	116

41	EMBASE	*"PLASMINOGEN ACTIVATOR 5034 INHIBITOR 1"/	
42	EMBASE	(39 AND 41)	80
43	Medline	(1 AND 37)	278