1. INTRODUCTION

Pregnancy is a physiological state that predisposes to hypercoagulability and thrombosis. Due to thrombosis changes in the blood flow (venous stasis), changes in the vascular wall (hypotonia, endothelial damage) and increased levels of coagulation factors such as: VII, VIII, X, XII as well as decreased activity levels of natural anticoagulants, protein C and S, which increase the risk of venous thromboembolism in women with a thrombophilia even further are observed. Pregnancy loss (PL) can be caused due to diverse factors with thrombophilia being one of them (1).

According to definition, miscarriage is every unwanted pregnancy loss until the age of 24 weeks of pregnancy, while according to epidemiological definition, miscarriage is considered as extrusion of the fetus weighting less than 500 grams, or less than 25 cm, which matches to the 20 to 22 week pregnancy (2). Routine gynecological, endocrine and cytogenetic diagnostics could not clarify the reason up to 40% of cases of pregnancy losses worldwide. Recently, the heritable factors of thrombophilia that may predispose to obstetrical complications attract a great attention. In recent studies it was found that -675 ID, 4G/5G PAI-1 polymorphism, as referred to a new thrombophilic factor may increase the pregnancy loss, and knowledge of its variants may improve the predictive ability (3,4). The -675 ID, 4G/5G PAI-1 polymorphism consisting of a single insertion/deletion of a guanine base at position 675 in the promoter region of PAI-1 gene gives rise to 2 alleles 4G and 5G which differ in their regulation of the concentration of plasminogen activator inhibitor-1 gene (PAI-1) (5, 6).

Individuals who are homozygous 4G have higher concentrations of PAI-1 than those who are homozygous 5G, and individuals who are heterozygous 4G/5G, which have intermediate levels of PAI-1 (7). Some studies have reported that the increases in PAI-1...
serum level lead to a thrombotic tendency (8-10). Furthermore, PAI-1 plays crucial role in the process of fibrinolysis and any changes in concentrations and activity may cause thrombotic changes in the utero-placental unit.

2. AIM

The aim of our study was to investigate the relationship between -675 ID, 4G/5G PAI-1 gene polymorphism and pregnancy loss in European women and women elsewhere in the world.

Statistical analysis

Significance of PAI-1 alleles frequency differences between women with pregnancy loss and control group (without pregnancy loss) was assessed using Fisher’s exact test in Statistics 12 software package (StatSoft, Tulsa, OK, USA). P value <0.05 was considered as statistically significant.

By the end of June 2017, PubMed and Scopus electronic databases were searched. The objective was to identify case-control studies on the association between frequency of 4G allele of PAI-1 gene polymorphism and pregnancy loss, using the following search terms: pregnancy loss, miscarriage, genetic risk of thrombophilia, rs1799889 PAI-1 gen, 4G/5G PAI-1 gene polymorphism, PAI-1 gene locus 4G/5G polymorphism. The following data were extracted for each study included in systematic review: authors (reference number), country/area, total number of women, number of women with and without pregnancy loss for each population, distribution of genotypes and alleles in women with and without PL. Reports in English and Bulgarian language were taken into consideration.

The geographical regions excluding Korea and the Gaza Strip: 1- Bulgaria (13), 2- Czech Republic (14), 3- Germany (16), 4- Germany (17), 5- Bosnia and Herzegovina (11), 6- Serbia (23), 7- Bulgaria (12). Note that data 1-4, 7 but not 5 and 6 are for recurrent PL.

3. RESULTS

Our results, PubMed and Scopus databases posted as of 30/06/2017, and literature research yielded a dataset containing data from 17 populations belonging to 12 countries (see Table 1). The total number of women across all 17 populations was 3209 and 2423 in the study and control group, respectively.

4. DISCUSSION

It is estimated that the frequency of pregnancy loss is about 10-25% of all clinically recognized pregnancies, wherein the reasons about 50% of all miscarriages are unidentifiable causes (28, 29).

The pregnancy loss is considered as a multifactorial disease occurring as the result of external factors, many variants of genes among which are mentioned responsible for hemostatic disorders and endothelial dysfunction and behavioral risk factors. Recently, the polymorphism -675 ID, 4G/5G of PAI-1 gene, linked with hemostasis and endothelial function is eagerly studied in the context of PL and recurrent PL in Europe and worldwide (Figure 1 and Figure 2). The Figure 1 shows the frequency of 4G allele of PAI-1 gene in some populations of European women with and without pregnancy loss (controls).

Table 1. Distribution of PAI-1 gene polymorphism

![Table 1](Image)

![Figure 1](Image)
The highest frequency of the 4G allele in women without pregnancy loss was in Korean women, 59.3%, while intermediate values was in Indian, Iranian (two consecutive groups) and Tunisian populations: 47.5%, 43.3%, 44.8% and 38%, respectively (18-20, 22, 24). Also, it should be noted, that other Iranian author, Poursadegh reports frequency of the 4G allele, 42.0% (19).

Among populations outside Europe, the statistically significant association between 4G allele and pregnancy loss in Iranian (two groups) and Tunisian women was found (p<0.001; p<0.05; p<0.001, respectively) (20, 21, 25). However, in another group of Iranian women, there was no association between the presence of 4G allele and pregnancy loss (19). Additionally, several studies also state that 4G allele did not affect pregnancy loss in Korean, Egyptian, Indian and Palestinian women (p>0.05) (15, 18, 22, 24).

In presented results the fact, that the frequency of 4G allele in European populations compared to non European populations is higher, draws attention. Furthermore, there is a disagreement as to the association 4G allele with pregnancy loss. We asked ourselves the question, whether the countries where the allele frequency is higher, the statistically significant relationship between 4G allele and pregnancy loss more often occurs (see Figure 3).

Based on presented results we deduce that, the high frequency of 4G allele in population, is not unambiguously linked with the risk of pregnancy loss.

5. CONCLUSION

Both in Europe and elsewhere in the world, the high frequency of 4G allele in population, is not unambiguously linked with the risk of pregnancy loss.

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• Declaration of interests The authors declare no potential conflict of interests.
REFERENCES

1. Hyde KJ, Schust DJ. Genetic considerations in recurrent pregnancy loss. Cold Spring Harb Perspect Med. 2015; 5: a023119.

2. WHO recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Acta Obstet Gynecol Scand. 1997; 56(3): 247-253.

3. Snehlata Pandey, Archana Pandey, UK Chauhan, Arvind Tripathi, Jitendra Tripathi, Sanjeev Dubey, et al. Recurrent pregnancy loss and association of MTHFR, PAI-1 and ACE gene polymorphisms in women. 2015; 1(4): 50-55.

4. Su MT, Lin SH, Chen YC, Kuo PL. Genetic association studies of ACE and PAI-1 genes in women with recurrent pregnancy loss: a systematic review and meta-analysis. 2013; 109(1): 8-15.

5. Nordt TK, Lohrmann J, Bode C. Regulation of PAI-1 expression by genetic polymorphism. Impact on atherogenesis. Thromb Res. 2001; 103 Suppl 1: S1-5.

6. Eriksson P, Kallin B, van’t Hooft FM, Bavenholm P, Hamsten A. Allele-specific increase in basal transcription of the plasminogen-activator inhibitor 1 gene is associated with myocardial infarction. 1995; 92(6): 1851-1855.

7. Dawson S, Hamsten A, Wiman B, Henney A, Humphries S. Genetic variation at the plasminogen activator inhibitor-1 locus is associated with altered levels of plasma plasminogen activator-inhibitor-1 activity. Arterioscler Thromb. 1991; 11(1): 183-190.

8. Francis CW. Plasminogen activator inhibitor-1 levels and polymorphisms Arch Pathol Lab Med. 2002; 126(11): 1401-1404.

9. Sartori MT, Danesin C, Saggiorato G, Tormene D, Simioni G, Kapsimali V, et al. Association between the plasminogen activator type 1 gene and deep vein thrombosis in patients with inherited thrombophilia. Clin Appl Thromb Hemost. 2003; 9(4): 299-307.

10. Tsantes AE, Nikolopoulos GK, Bagos PG, Rapti E, Mantzios G, Kapsimali V, et al. Association between the plasminogen activator inhibitor-1 4G/5G polymorphism and venous thrombosis. A meta-analysis. 2007; 97(6): 907-913.

11. Mahmutbegovic E, Skonieczna-Zydecka K, Valjevac A, Mahmutbegovic N, Pawinska-Matecka A, Czerska E, et al. Lack of association between I/D ACE and -675 ID 4G/5G PAI-1 polymorphisms in women. 2015; 1(4): 50-55.

12. Ivanov P, Komsa-Penkova R, Konova E, Gecheva S, Ivanov I, Kovacheva K, et al. Combined thrombophilic factors among women with late recurrent spontaneous abortions. Akush Ginekol. (Sofia). 2011; 50(3): 8-12 (in Bulgarian).

13. Ivanov P, Komsa-Penkova R, Ivanov I, Konova E, Kovacheva K, Simeonova M, et al. Plasminogen activator inhibitor type 1 activity in women with unexplained very early recurrent pregnancy loss. Akush Ginekol. (Sofia). 2010; 49(5): 3-8 (in Bulgarian).

14. Subrt I, Ulcova-Gallova Z, Cerna M, Hejnalova M, Slovanova J, Bikkova K, et al. Recurrent pregnancy loss, plasminogen activator inhibitor-1 (-675) 4G/5G polymorphism and antiphospholipid antibodies in Czech women. Am J Reprod Immunol. 2013; 70(1): 54-58.

15. Elmahgoub IR, Afify RA, Abdel Aal AA, El-Sherbiny WS. Prevalence of coagulation factor XIII and plasminogen activator inhibitor-1 gene polymorphisms among Egyptian women suffering from unexplained primary recurrent miscarriage. J Reprod Immunol. 2014; 103: 18-22.

16. Wolf CE, Haubelt H, Pauer HU, Hinney B, Krome-Cesar C, Legler TJ, et al. Recurrent pregnancy loss and its relation to FV Leiden, FII G20210A and polymorphisms of plasminogen activator and plasminogen activator inhibitor. Pathophysiol Haemost Thromb. 2003; 33(3): 134-137.

17. Buchholz T, Lohse P, Rogenhofer N, Kosian E, Pihusch R, Thaler CJ. Polymorphisms in the ACE and PAI-1 genes are associated with recurrent spontaneous miscarriages. Hum Reprod. 2003; 18(11): 2473-2477.

18. Parveen F, Tuteja M, Agrawal S. Polymorphisms in MTHFR, MTHFD, and PAI-1 and recurrent miscarriage among North Indian women. Arch Gynecol Obstet. 2013; 288(5): 1171-1177.

19. Poursadegh Zonouzi A, Charzapazeh N, Ghobian S, Sadaghian MM, Farzadi L, Ghassemzadeh A, et al. The association between thrombophilic gene mutations and recurrent pregnancy loss. J Assist Reprod Genet. 2013; 30(10): 1353-1359.

20. Khosravi F, Zarei S, Ahmadvand N, Akbarzadeh-Pasha Z, Sadavi E, Zarnani AH, et al. Association between plasminogen activator inhibitor 1 gene mutation and different subgroups of recurrent miscarriage and implantation failure. J Assist Reprod Genet. 2014; 31(1): 121-124.

21. Torabi R, Zarei S, Zeraati H, Zarnani AH, Akhondi MM, Dadivi R, et al. Combination of thrombophilic gene polymorphisms as a cause of increased the risk of recurrent pregnancy loss. J Reprod Infertil. 2012; 13(2): 89-94.

22. Kim JJ, Choi YM, Lee SK, Yang KM, Paik EC, Jeong HJ, et al. The PAI-1 4G/5G and ACE I/D polymorphisms and risk of recurrent pregnancy loss: a case-control study. Am J Reprod Immunol. 2014; 72(6): 571-576.

23. Dordevic V, Gvozdenov M, Pruner I, Kovac M, Tomic B, Stankovic M, et al. The prevalence of PAI-1 4G/5G Polymorphism in women in fetal loss-first data for a Serbian population. J Med Biochem. 2014; 33(2): 203-207.

24. Al Sallout RJ, Sharif PA. Polymorphisms in NOS3, ACE and PAI-1 genes and risk of spontaneous recurrent miscarriage in the Gaza Strip. Med Princ Pract. 2010; 19(2): 99-104.

25. Magdoud K, Herbepin VG, Touraine R, Almawi WY, Mabjoub T. Plasminogen activator inhibitor 1 4G/5G and -844G/A variants in idiopathic recurrent pregnancy loss. Am J Reprod Immunol. 2013; 70(3): 246-252.

26. Ozdemir O, Yenicesiu G, Silan F, Koksal B, Atik S, Ozen F, et al. Recurrent pregnancy loss and its relation to combined parental thrombophilic gene mutations. Genet Test Mol Biomarkers. 2012; 16(4): 279-286.

27. Salazar Garcia MD, Sung N, Mullenix TM, Dambaeva S, Beaman K, Gilman-Sachs A, et al. Plasminogen Activator Inhibitor-1 4G/5G Polymorphism is Associated with Reproductive Failure: Metabolic, Hormonal, and Immune Profiles. Am J Reprod Immunol. 2016; 76(1): 70-81.

28. Zinaman MJ, Clegg DE, Brown CC, O’Connor J, Selevan SG. Estimates of human fertility and pregnancy loss. Fertil Steril. 1996; 65(3): 503-509.

29. Jassow CR, Carney JL, Kutteh WH. Diagnostic factors identified in 1020 women with two versus three or more recurrent pregnancy losses. Fertil Steril. 2010; 93(4): 1234-1243.