Association Between - 675 ID, 4G/5G PAI-1 Gene Polymorphism and Pregnancy Loss: A Systematic Review

Grazyna Adler1, Emir Mahmutbegovic2, Amina Valjevac3, Mateusz A Adler4, Nevena Mahmutbegovic2, Krzysztof Safranow4, Ewa Czerska5, Anna Pawinska-Matecka5, Iwona Ciechanowicz5, Damir Marjanovic9,10

1Department of Studies in Anthropogenetics and Biogerontology, Pomeranian Medical University, Szczecin, Poland
2Institution of Health Protection of Women and Motherhood Canton Sarajevo, Sarajevo, Bosnia and Herzegovina
3Laboratory for Molecular Medicine, Center for Genetics, Medical Faculty, University of Sarajevo, Sarajevo, Bosnia and Herzegovina
4Warsaw School of Economics, Warsaw, Poland
5Neurology Clinic, Clinical Center of University of Sarajevo, Sarajevo, Bosnia and Herzegovina
6Department of Biochemistry and Medical Chemistry, Pomeranian Medical University, Szczecin, Poland
7Central Laboratory, Regional Hospital, Szczecin, Poland
8Pomeranian Medical University, Szczecin, Poland
9International Burch University, Bosnia and Herzegovina
10Institute for Anthropological Research, Zagreb, Croatia

Corresponding author: Grazyna Adler, Associate Professor, Department of Studies in Anthropogenetics and Biogerontology, Pomeranian Medical University, ul. Żołnierska 49, 78-111 Szczecin, Poland, ORCID ID: http://www.orcid.org: 0000-0001-8792-553X. E-mail: gra2@op.pl

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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 cytogentic 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 endothelial plasminogen activator inhibitor 1 gene 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 (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, rs1799869 PAI-1 gene, 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.


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).


Figure 1. Frequency of 4G allele PAI-1 gene in European women, with and without PL. 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.
Based on presented results we deduce that, the high frequency of 4G allele in women without pregnancy loss was in Korean women, 58.9%, and the lowest in Egyptian, Iranian (two consecutive groups) and Tunisian 13.1%, 14.5%, 20.5% and 16.7%, respectively (15, 18-22, 25). Intermediate values of frequency 4G allele were observed in Indian women and women from the Gaza Strip, 46.5% and 40.0%, respectively (18, 24). Also, it should be noted, that other Iranian author, Poursadegh reports frequency of the 4G allele, 42.0% (19).

The highest frequency of the 4G allele in women with pregnancy loss was in Korean women, 59.3%, while intermediate values was in Indian, Iranian (in two consecutive groups) and Palestinian women: 47.5%, 43.3%, 44.8% and 38%, respectively (18-20, 22, 24). Also, it should be noted, that other Iranian author, Torabi reports frequency of the 4G allele 24.5% [21]. The lowest frequency of 4G allele was in Tunisian and Egyptian women, 33.2% and 22.1%, respectively (15, 25).

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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