Original Article

First Bosnian Study of the Relationship between *APOE* rs7412 and rs429358 Variants and Pregnancy Loss

(*APOE* gene variants / Bosnian women / miscarriage / real-time PCR)

G. ADLER[1], E. MAHMUTBEGOVIC[2], I. UZAR[3], M. A. ADLER[4], N. MAHMUTBEGOVIC[5], A. VALJEVAC[6]

[1]Department of Studies in Antropogenetics and Biogerontology, [3]Department of General Pharmacology and Pharmacoeconomics, Pomeranian Medical University, Szczecin, Poland
[2]Institution of Health Protection of Women and Motherhood Canton Sarajevo, Sarajevo, Bosnia and Herzegovina
[4]Warsaw School of Economics, Warsaw, Poland
[5]Neurology Clinic, Clinical Center of University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[6]Laboratory for Molecular Medicine, Center for Genetics, Medical Faculty, University of Sarajevo, Sarajevo, Bosnia and Herzegovina

Abstract. Due to inconsistent results of *APOE* variants in the survival of pregnancy we investigated the potential relationship of *APOE* rs7412 and rs429358 with pregnancy loss (PL) in Bosnian women. We enrolled 154 women with PL. The minimum week of miscarriage was 6, while the maximum was 28. As a control group, an equal number of mothers with at least one live-born child was included. All women were recruited from the Institution of Health Protection of Women and Motherhood in Sarajevo, Bosnia and Herzegovina. Genotyping was performed by real-time PCR at the Department of General Pharmacology and Pharmacoeconomics, Pomeranian Medical University. The prevalence of genotypes E2/E3, E2/E4, E3/E3, E3/E4, E4/E4 in the group with and without PL were: 14.3 %, 1.3 %, 70.8 %, 12.3 %, 1.3 %, and 13.6 %, 1.3 %, 70.1 %, 14.3 %, 0.7 %, respectively. The frequency of the E4/E4 genotype in women with 1–2 and 3–4 PL compared to women without PL did not differ significantly between those three groups (P value = 0.0712). The frequencies of alleles ε2, ε3, ε4 in the group with and without PL were: 6.8 %, 85.1 %, 8.1 % and 7.5 %, 84.1 %, 8.4 %, respectively, and did not differ significantly. We conclude that our study does not confirm rs7412 and rs429358 as a potential risk factor for PL in the studied group. To elucidate the relationship between PL and variants of the *APOE* gene, studies with a larger sample size and placental histomorphology and genetic diagnosis are required.

Introduction

Pregnancy is a physiological state linked to an increased level of cholesterol, hypercoagulability and thrombosis on the one hand, and decreased fibrinolysis on the other hand. It is estimated that the frequency of pregnancy loss (PL) is about 10–25 % of all clinically recognized pregnancies, wherein the reasons for about 50 % of them are unidentified (Pabinger, 2009; Jaslov et al., 2010; Williams and Broughton Pipkin, 2011).

An increasing body of evidence suggests that PL and recurrent PL (RPL) may be caused by both environmental and genetic factors (Chin et al., 2013; Kusturica et al., 2014; Mahmutbegovic et al., 2017; Sugiura-Ogasawara et al., 2017). In a successful course of pregnancy, among many factors of homeostasis, the balance between inflammatory agents and anti-inflammatory cytokines is essential (Vassiliadis et al., 1998). Baitsch et al. (2011) and Jacobs et al. (2016) drew attention to the role of *APOE* gene variants as a potential marker linked to miscarriages and thrombophilic agent. Several authors report that APOE regulates the mechanisms of cell death by modifying inflammatory responses, and carriers of allele ε4 have reduced concentration of IL-10 in the plasma and attenuated anti-inflammatory activity (Baitsch et al., 2011; Zhang et al., 2011; Jacobs et al., 2016).

Received April 6, 2018. Accepted May 30, 2018.

This work was funded in part by the Pomeranian Medical University, Szczecin, Poland (decision ref. No. WNoZ-307-01/S/13/2017).

Corresponding author: Grażyna Adler, Department of Studies in Antropogenetics and Biogerontology, Pomeranian Medical University, Żołnierska 48, 71-210 Szczecin, Poland. Phone/Fax: (+48) 914 800 958; e-mail: gra2@op.pl

Abbreviations: B&H – Bosnia and Herzegovina, HWE – Hardy-Weinberg equilibrium, PL – pregnancy loss, RPL – recurrent pregnancy loss.

It is known that in subjects with ε4 alleles compared to subjects with the ε2 and ε3 alleles, higher plasma LDL concentrations are observed. In this context, in early stages of pregnancy the elevated plasma lipid levels may contribute to the thrombus formation by accumulating in the intima of blood vessels, whose endothelial cells have been activated by inflammatory cytokines (Asagri et al., 2013). At a later stage, the formation of thrombus in placenta vessels reduces placental blood flow and oxygen supply to the foetus, leading to the death of the trophoblast cells and PL (Jeddi-Tehrani et al., 2011). On the other hand, it should be noted that cholesterol, as a precursor of steroidogenesis, plays a crucial role in the survival of pregnancy (Frye et al., 2011). The presence of the ε4 allele is linked to decreased affinity of APOE for LDL receptors, which leads to decreased absorption of cholesterol from the bloodstream, and this in turn can lead to disturbances in production of steroid hormones and PL (Ozornek et al., 2010).

As we mentioned above, there are several possible molecular mechanisms for the relationship of the *APOE* variants and pregnancy loss, such as formation of thrombus in the placenta vessels, disturbance in the balance between inflammatory and anti-inflammatory cytokines, and disturbance in steroidogenesis. However, the results on the relationship of *APOE* gene variants and PL in a few European and worldwide populations are contradictory, and the data linked to the consequences of *APOE* variants for PL in the population of Bosnia and Herzegovina (B&H) is non-existent. Therefore, we decided to assess whether the presence of alleles ε2, ε3, ε4 linked to three isoforms of APOE defined as APOE2 (cys112, cys158), APOE3 (cys112, arg158), and APOE4 (arg112, arg158), respectively, may be linked to PL in Bosnian women.

Material and Methods

Subjects

All women were recruited from the Institution of Health Protection of Women and Motherhood in Sarajevo, B&H. The estimated population of Sarajevo is 369,534, while 3,867,055 inhabitants live in B&H, where women constitute about 50 % of the population [http://www.fzs.ba/eng/population.htm, Census 2013th official data. Accessed 15 January 2018]. Twins and women with any serious illness (including hepatic, pulmonary, renal disorders and cancer) were excluded from the study.

According to the definition of the American Society of Reproductive Medicine (ASRM), PL represents spontaneous abortion of an embryo or foetus before the 20th week of pregnancy or a situation when the foetus weighs less than 500 grams or measures less than 25 cm, and RPL when two or more failed pregnancies take place (Practice Committee of the American Society for Reproductive Medicine, 2008).

We recruited 154 women with PL, mean age 33.0 (± 5.4) years, 121 (78.6 %) had at least one live-born child, and all included pregnancies were anembryonic. The minimum week of miscarriage was 6, while the maximum was 28. One hundred and fifty-four healthy controls with no history of PL and at least one live-born child, mean age 31.4 (± 6.7) years, were selected from among local residents using the same exclusion criterion as for patients.

Data of obstetric history, weight, week of miscarriage, and number of successful pregnancies by trimester of PL are shown in Table 1.

All procedures performed in the studies involving human participants were conducted according to the standards of the Declaration of Helsinki (1975, revised 2000). The study was approved by the Local Ethical Commissions: Sarajevo, B&H and Szczecin, Poland (decision ref. Nos. 10-1285-03-14 and KB-0012/175/17, respectively). Informed consent was obtained from all individual participants included in the study.

DNA extraction and genotyping

Genomic DNA from buccal swabs was extracted using QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany), and for genotyping we used the TaqMan SNP Genotyping Assays (Applied Biosystems, Foster City, CA), as we previously reported (Adler et al., 2014, 2017).

Statistical analysis

All tests were performed using the R CRAN statistical software (version 3.4.2) (R Core Team, 2017). P <

Table 1. Group characteristics according to the trimester of pregnancy loss

	1st trim. N = 118	**2nd trim. N = 21**	**1st + 2nd trim.* N = 15**
Age (years ± SD)	32.8 (± 5.4)	33.5 (± 4.7)	33.3 (± 3.7)
Weight (kg)	74.3 (± 9.5)	72.2 (± 9.8)	73.1 (± 6.7)
No. of pregnancy losses (average/range)	159 (1.3/1–4)	30 (1.4/1–3)	31 (2.1/1–3)
Average week of pregnancy loss (SD)	9.1 (±1.6)	18.1 (±3.7)	13.5 (5.6)
Min. week of miscarriage	6	13	13
Max. week of miscarriage	12	24	28
No. of successful pregnancies (average/ range)	172 (1.5/0–5)	24 (1.1/0–4)	18 (1.2/0–5)

*women with both first and second trimester losses

0.05 was considered statistically significant for all analyses. The function Hardy-Weinberg equilibrium (HWE). χ^2 for three alleles from package *genetics* was performed (Warnes et al., 2013). The distribution of genotypes was determined in women with 1–2 PL and 3–4 PL and without PL, and comparison was made by the Kruskal-Wallis test and Fisher's exact test.

Results

The prevalences of genotypes E2/E3, E2/E4, E3/E3, E3/E4, E4/E4 in the group of women with and without PL were: 14.3 %, 1.3 %, 70.8 %, 12.3 %, 1.3 % and 13.6 %, 1.3 %, 70.1 %, 14.3 %, 0.7 %, respectively, while in none of both groups of women the E2/E2 genotype was noticed. The frequency of alleles ε2, ε3, ε4 in the group of women with and without PL was: 6.8 %, 85.1 %, 8.1 % and 7.5 %, 84.1 %, 8.4 %, respectively (see Table 2). All analysed genotypes in women with and without PL were in agreement with HWE (P value = 0.747 and 0.949, respectively).

The frequency of the E4/E4 genotype in women with 1–2 and 3–4 PL compared to women without PL did not differ significantly between those three groups (P value = 0.0712) (see Table 3).

Discussion

In European populations, the distribution of ε2, ε3 and ε4 alleles of the *APOE* gene ranges from 4.0 % to 13.5 % for ε2, 70.0 % to 89.7 % for ε3 and 6.3 % to 20.8 % for ε4 allele, with the Bosnian population fitting into this pattern perfectly (Adler et al., 2014). The results suggest that the ε2 allele is linked to low reproductive efficiency and the ε3 allele to the high one (Corbo et al., 2004; Li et al., 2014). Jacobs et al. (2016) described the relationship between the presence of the maternal ε2 allele and small for gestational age linked to decreased foetal growth in women with lower circulating cholesterol levels, while Gelfand et al. (2013), linked the ε4 allele to perinatal arterial ischemic stroke. As pregnancy is a hypercoagulable state, it is not surprising that the additive effect of ε4 allele superimposed on this state increases the risk of clotting (Vora et al., 2009; Wintermark et al., 2010). Unfortunately, the relationship of these mechanisms with PL is not entirely clear yet.

Two meta-analyses, both including women with RPL, the first 2090 and the second 975 women, have found an association between the ε4 allele and increased risk of RPL (Meng et al., 2013; Li et al., 2014).

In our study the distribution of ε4 allele found in women with PL was 8.1 % (N = 154) and was comparable to Ozdemir's results for Caucasians women with RPL, included in a meta-analysis by Meng et al., 7.9 % (N = 3246) (Ozdemir et al., 2012; Meng et al., 2013). In the presented study we did not confirm the possible link of ε4 allele to PL, while Ozdemir et al. (2012) found such a relationship in their group of women. Higher ε4 allele distribution, 11.4 % (N = 136) and 12.3 % (N = 69), was reported in Turkish and American women with

Table 2. Distribution of allele and genotype frequencies of the APOE gene in women with and without PL

	Women with PL, N (%)	Women without PL, N (%)	P value	OR (95% CI)
Genotypes				
E2/E2	0 (0)	0 (0)	ND	ND
E2/E3	19 (12.3)	21 (13.6)	0.866	0.892 (0.432–1.831)
E2/E4	2 (1.3)	2 (1.3)	1	1 (0.072–13.956)
E3/E3	112 (72.8)	108 (70.1)	0.705	1.135 (0.672–1.992)
E3/E4	19 (12.3)	22 (14.3)	0.738	0.845 (0.412–1.721)
E4/E4	2 (1.3)	1 (0.7)	1	2.009 (0.1104–119.451)
Alleles				
ε2	21 (6.8)	23 (7.5)	0.871	0.900 (0.450–1.792)
ε3	262 (85.1)	259 (84.1)	1	1 (0.649–1.540)
ε4	25 (8.1)	26 (8.4)	1	0.959 (0.544–1.691)

*ND – not determined

Table 3. Carrier of allele in women with miscarriage by the number of PL and women without PL

Carrier of alleles (from genotypes)	Women with 1–2 or 3–4 PL (N)		Sum	Women without PL (N)	P value	OR (95% CI)
ε2 carrier (E2/E3, E2/E4)	19	2	21	23	0.871	0.899 (0.450–1.792)
ε3 carrier (E2/E3, E3/E3, E3/E4)	136	14	150	151	1.000	0.746 (0.107–4.489)
ε4 carrier (E2/E4, E3/E4, E4/E4)	22	1	23	25	0.875	0.906 (0.465–1.759)

RPL, respectively (Goodman et al., 2009; Meng et al., 2013). In both studies the ε4 allele was a risk factor for RPL.

Similar values were reported in Czech women with PL and RPL, 10.8 % (N = 334) and 11.8 % (N = 76), respectively (Rynekrova et al., 2012). However, in that case, the relationship between the ε4 allele and PL and RPL was not found. With the higher distribution of ε4 allele (17.8 %), Korkmazer et al. (2013) did not confirm the association of *APOE* with RPL in Turkish women as well. However, it should be noted that the group with RPL consisted of only 45 women.

Studies on the relationship of ε4 allele with RPL were also carried out in non-Caucasian populations, such as two Iranian populations reported by Asagri et al. (2013) and Poursadegh Zonouzi et al. (2014), in both of which data support the association of the ε4 allele with RPL.

APOE plays a crucial role in atherosclerosis and neurogenic disorders by participating in the lipid metabolism and mechanisms of cell death and by modifying the inflammatory response (Danesh et al., 2004). The ε4 allele of *APOE* gene is linked to low IL-10 concentrations, which has been shown to be crucial for successful pregnancy (Chaouat et al., 1996; Tziakas et al., 2006). On the one hand, the proinflammatory status linked to *APOE* variants may explain the relationship between the ε4 allele and RPL; on the other hand, the lower concentrations of APOE in the plasma with consequential lower tissue levels may also cause reproductive disturbances.

Yalcintepe et al. (2015) reported very interesting results, where ε2 and ε4 (both $P < 0.0001$) alleles had higher frequency in spontaneously aborted foetal materials in comparison to their mothers. In this context, it would be interesting to conduct research on a larger sample size, including both parents and the placental histomorphology diagnosis of the lost pregnancy. Unfortunately, only one such report exists.

Conclusions

Overall, the current study is the first report on the relationship of *APOE* rs7412 and rs429358 variants and PL in Bosnian women. Our results indicate that the *APOE* variants do not contribute to PL risk in this population. We concluded that subsequent studies with a larger sample size and the placental histomorphology and genetic diagnosis are required to elucidate the mechanisms underlying the relationship between PL pathogenesis and variants of the *APOE* gene.

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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