Pomeranian J Life Sci 2025;71(3):1-5 doi: 10.21164/pomjlifesci.1181

Study on Bosnian unexplained abortions (BUNA) and the introgression from Neanderthal Man, rs1042838 of *PGR* gene*

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ABSTRACT

Introduction: In European couples infertility varies 5–24%. The progesterone receptor (PGR) encoded by the *PGR* gene plays a key role in many reproductive pathways. In our study, for the first time among European populations, the potential association of *PGR* rs1042838 with spontaneous abortions (SA), was investigated.
Materials and methods: The TaqMan SNP assay was used in a group of 154 women with SA and 154 controls – mothers with at least 1 live-born child for genotyping the rs1042838 of *PGR* gene.
Results: The prevalence of genotypes GG, GT, TT in women with and without SAs were: 72.8%, 22.7%, 4.5% and 61.0%, 34.4% and 4.6%, respectively (p = 0.080).
Conclusions: Due to the fact that in some populations rs1042838 is rare, its confirmation as a genetic marker of SA requires further studies in larger groups and different populations.
Keywords: pregnancy loss; *PGR* gene; single nucleotide polymorphism.

INTRODUCTION

It is estimated that infertility affects 48.5 mln couples worldwide. One of the causes are spontaneous abortions (SA), which affect an approx. 23 mln couples *per annum*, which in turn constitutes 10–25% of all clinically diagnosed pregnancies [1, 2]. Inclusion of pre-clinical losses, defined as the loss of a pregnancy before diagnosis by ultrasonography (USG), increases result of percentage SA. Moreover, it is suggested that, approx. 50% of SA remain unexplained [3].

Couples, and especially women, may experience a several of emotions due to SA, including: disappointment and sadness, lowered self-esteem, and anxiety. Psychological effects, such as: depression occurrence, flashbacks, substance abuse, and suicide attempts are also reported [4, 5, 6]. Therefore, pregnancy-related complications are a major public health and healthcare challenge.

Among the causes SA, the most often mentioned are: microbial, autoimmune and endocrine factors, as well as anatomical defects of the uterus. Development of high-throughput testing methods and human genome analysis have revealed a new areas of genome linked to its physiological functions or disturbances. For several years, there is a growing body of evidence indicating that a special place in SA is occupied by a genetic factors and the selected gene variants.

The progesterone receptor (PGR) is encoded by the *PGR* gene, located on chromosome 11 and expressed the most in the endometrium, plays an important role in many reproductive pathways, including: oocyte maturation, uterine lining preparation for egg implantation, and pregnancy maintenance at their early stage [7]. The *PGR* gene has 8 exons and 7 introns, located on chromosome 11q22-q23. This gene is extremely polymorphic, and as such includes numerous functional single nucleotide polymorphisms (SNPs). The most common polymorphism is rs1042838 (also known as: 1978G>T, c.3432G>T, Val660Leu). Alongside with the Alu insertion between exons 7 and 8 and the silent rs1042839 substitution in exon 5 (also known as: 2310C>T, H770H), it is referred to as progesterone receptor genes (PROGINS) [8, 9].

The rs1042838 *PGR* belongs to the introgression from Neanderthal Man, and excluding Africans, among contemporary populations of Europeans, Native Americans and Asians living in selected areas, the prevalence of rs1042838 ranges 2–22% [10].

On the one hand, it is suggested that reduced progesterone (PG) secretion may be linked to reproductive problems related to endocrine disorders and the lowers successful implantation probability and early pregnancy maintenance through imbalance of Th1>Th2 cytokines produced by uterine immune cells in response to stress [11]. On the other, rs1042838 carriers show a higher *PGR* mRNA expression, which is linked to a lower SA number and bleeding in the early stage of pregnancy [10, 12]. Additionally, it was shown that orally taken PG reduces SA risk and improves fertility in women who experienced bleeding in early pregnancy and had recurrent miscarriages [13]. Furthermore, vaginal micronized PG may increase the live birth rate for women with a history of 1 or more previous miscarriages and early pregnancy bleeding [14].

Therefore, the aim of the study was to investigate the relationship between the rs1042838G>T *PGR* gene and SA. The study scope has been investigated.

* This study was supported by the Pomeranian Medical University, Department of Studies in Antropogenetics and Biogerontology statutory funds, No. WNoZ-307/S/2023 (G.A.).

MATERIALS AND METHODS

Ethical approval

The study was conducted according to the standards of the Declaration of Helsinki (1975, revised 2000). The protocol was approved by the local Bioethical Committee (decision reference number KB-0012/38/13A-2, Resolution of 25 January 2023). Written, informed consent was obtained from all participants.

Study population and sample collection

This is a continuation of the project from 2017 in which we collected buccal swabs from 308 Bosnian women from the general population of Sarajevo; 154 with and 154 with no history of SA. All women were of Bosnian origin and were enrolled from the Institution of Health Protection of Women and Motherhood in Sarajevo, B&H [15].

Inclusion criteria were: women with 1 or more SA were selected as a study group, and women without SA and with at least 1 live-born child, as a control group. Women with a history of immunological, thyroid diseases, neoplastic process, and active infectious or inflammatory diseases were excluded.

Data collection tools

DNA from buccal swabs was extracted using QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). The extraction was performed according to the manufacturer's instructions, and DNA samples were stored at +4°C for further analyses. The *PGR* genotyping was performed using StepOneTM real-time PCR System (Roche Diagnostics, Warsaw, Poland), TaqPath ProAmp Master Mix and commercial pre-designed TaqMan® SNP Genotyping Assay: C_7493568_30 (Thermo Fisher Scientific, Waltham, MA, USA), according to the manufacturer's instruction. Samples were first heated at 95°C for 10 min, before amplification as follows: 40 cycles of 2-step PCR at 95°C for 15 s and 60°C for 1 min. Approximately 10% of the samples were genotyped in duplicate to monitor genotyping quality and the same results were obtained. The data were analyzed with Taq Man Genotyper Software v. 1.0.1.

Statistical analysis

All tests were performed using the R CRAN statistical software – version 3.4.2 (R Core Team, 2017). The *PGR* genotype and allele frequencies were determined by direct counting. The differences in genotype and allele distributions between women with and without SA from studied populations were evaluated using chi-square (χ^2) test. Statistical significance was considered for $p < 0.05$.

RESULTS

The mean age of Bosnian women with and without SA was 33.0 (± 5.4) and 31.4 (± 6.7) years, respectively. In women with SA, there were 457 pregnancies, of which 193 ended with SA, and 50 with an induced abortion (IA). Assuming that all IAs end in live births, the percent of women with SA is 42.2%. However, if they all end with SA, the percent of women with SA is 53.2%. Data on age, body weight and obstetric history by SA trimester were presented in Table 1.

TABLE 1. Women characteristics by loss trimester

Characteristic	I trimester n = 118	II trimester n = 21	I + II trimester n = 15
Age, years (±SD)	32.8 (±5.4)	33.5 (±4.7)	33.3 (±3.7)
Body weight, kg (±SD)	74.3 (±9.5)	72.2 (±9.8)	73.1 (±6.7)
Number of successful pregnancies (average/range)	172 (1.5/0–5)	24 (1.1/0–4)	18 (1.2/0–5)
Nuumber of spontaneous abortions (average/range)	159 (1.3/1–4)	30 (1.4/1–3)	31 (2.1/1–3)
Min.–max. week of spontaneous abortions	6–12	13–24	13–28
Average week of spontaneous abortions (±SD)	9.1 (±1.6)	18.1 (±3.7)	13.5 (±5.6)

I and II trimester loss combined; SD – standard deviation

DISCUSSION

The aim of the study was to investigate the relationship between the rs1042838G>T *PGR* gene and SA. Unfortunately, all the results published in the last 10 years concern populations outside of Europe, namely, Canadian and Han Taiwanese women [16, 17]. It is important because the differences in the minor allele frequency (MAF) of *PGR* are observed between geographic locations and human populations. The worldwide MAF, rs1042838: T is 7.1%. The highest frequency is reported in Europeans (17.3%), moderate in Americans (13.9%), and the lowest in Africans and East Asians (1%), according to 1000 Genomes_30x. Among the Europeans, the highest allele T frequency is in Sardinians (26%) (who are considered Italian), as a separate population they represent an important European population isolate [18].

The age of Han Taiwanese women with and without SA was 31.0 (±5.0) and 29.8 (±4.9) years, respectively [17]. While, the mean age of Canadian women at the time of the study was not given, only the mean age at the time of pregnancy, which was 31.4 (±6.1) years [16]. In Canadian women with SA, there were 1.379 pregnancies, of which 1.027 (75%) ended with SA; for Taiwanese women, such information was not provided.

Populations of Han Taiwanese and Canadian women with 2–3 SA and Bosnians with 1–4 were included.

The genotype and allele frequencies distribution and case-control associations in Bosnian, Han Taiwanese, and Canadian women were presented in Table 2.

TABLE 2. Rs1042838 *PGR* allele and genotype frequencies distribution and case-control associations

Population with/without SA, n	PGR rs1042838	Women		χ^2 (df)	p	OR	References
		with	without SA				
	Genotype, n (%)						
	GG	112 (72.7)	94 (61)	5.255 (2)	0.072	1.798 (1.085–3.009)	this study
	GT	35 (22.7)	53 (34.4)				
	TT	7 (4.6)	7 (4.6)				
	Allele, n (%)						
	G	259 (84.1)	241 (78.2)	3.069 (1)	0.080	1.467 (0.977–2.217)	
	T	49 (15.9)	67 (21.8)				
Canadians, 227/129	Genotype, n (%)						
	GG	176 (78.0)	92 (71.0)	1.786 (2)	0.409	1.414 (0.844–2.354)	[16]
	GT	46 (20.0)	34 (26.0)				
	TT	5 (2.0)	3 (2.0)				
	Allele, n (%)						
	G	398 (87.7)	218 (84.5)	1.158 (1)	0.282	1.305 (0.837–2.019)	
	T	56 (12.3)	40 (15.5)				
Han Taiwanese, 121/179	Genotype, n (%)						
	GG	116 (95.9)	179 (100)	7.497 (2)	**0.006**	NA	[17]
	GT	5 (4.1)	0				
	TT	0	0				
	Allele, n (%)						
	G	237 (97.9)	358 (100)	5.168 (1)	**0.006**	NA	
	T	5 (2.1)	0				

χ^2 – chi-square value; 95%CI – 95% confidence interval; df – degrees of freedom; OR – odds ratio; p – p-value; statistically significant p-values ($p < 0.05$) are bolded; NA – non available; SA – spontaneous abortions

In Bosnian women with 1–2 or 3–4 losses, distribution of genotypes GG, GT and TT was as follows: 101 (72.7%), 31 (22.3%), 7 (5.0%) and 11 (73.3%), 4 (26.7%) and none, respectively. While, distribution of alleles G and T in the corresponding groups was: 233 (83.8%), 45 (16.2%) and 26 (86.7%), 4 (13.3%), respectively. The carriage of genotype nor allele was not significantly more frequent in Bosnian women with 1–2 SA compared to 3–4 SA, p = 0.647; OR (95%CI) = 1.209 (0.307–3.887) and p = 0.886; OR (95%CI) = 0.821 (0.228–2.254), respectively. Allele and genotype frequencies distribution by loss number was presented in Table 3.

The molecular factors and mechanisms resulting in SA or preterm birth have been of great interest for several decades. There are publications on the relationship of rs1042838 *PGR* with pre-eclampsia, premature birth, endometrial and breast cancer, unfortunately, publications on the relationship of SA with rs1042838 are rare [16, 17, 18, 19, 20, 21, 22]. Moreover, all the results published in the last 10 years concern populations outside Europe, namely, Han Taiwanese and Canadian women [16, 17]. Therefore, we decided to investigate the relationship between the rs1042838G>T *PGR* gene and SA in Bosnian women.

In our study the rarer T allele frequency was 15.9%, and distribution of genotypes GG, GT and TT: 72.7%, 22.7% and 4.6% in women with SA, while in women without SA in the corresponding groups allele frequency was 21.8 % and genotypes 61%, 34.4% and 4.6%. Both, allele and genotypes, distribution in women with and without SA did not differ significantly, (p = 0.080 and p = 0.072, respectively). We have also examined allele and genotype frequency distributions in subgroups with

TABLE 3. Allele and genotype frequencies distribution by loss number in Bosnian women

rs1042838 PGR	Number of SA 1–2, n (%) or 3–4, n (%)		χ^2 (df)	p	OR (95%CI)
Genotype, n (%)					
GG	101 (72.7)	11 (73.3)	0.870 (2)	0.647	1.209 (0.307–3.887)
GT	31 (22.3)	4 (26.7)			
TT	7 (5.0)	0			
Allele, n (%)					
G	233 (83.8)	26 (86.7)	0.021 (1)	0.886	0.821 (0.228–2.254)
T	45 (16.2)	4 (13.3)			

χ^2 – chi-square value; 95%CI – 95% confidence interval; df – degrees of freedom; OR – odds ratio; p – p-value; SA – spontaneous abortions

1–2 and 3–4 SA in Bosnian women. Still, a significant relationship between *PGR* rs1042838 and the number of SA had not been observed, (p = 0.886 for 1–2 SA and p = 0.647 for 3–4 SA).

The results published by Su et al., in population Han Taiwanese women with SA indicate that the frequency of the rarer allele rs1042838T was very low, 2.1%, which is consistent with its' prevalence in Asian populations. What is more, of the 179 women in the control group, none carried the rare allele. The authors found that the difference between the groups was statistically significant (p = 0.006), and thus suggested that the T allele of the *PGR* gene may be associated with miscarriages in this population [17]. Moreover, the authors observed a significant difference between representation of GG, GT and TT genotypes in women with SA: 95.9%, 4.1% and none vs women without SA, which all was homozygote GG, (p = 0.006).

While, in the Canadian population, Hanna et al. examined the frequency of allele rs1042838T, which in women with and without SA was 12.3% vs 15.5%, respectively. There was no statistically significant difference between the groups (p = 0.282), and the association of the T allele with SA in this population was excluded. The same was true for the genotypes, where GG, GT and TT in the corresponding groups were: 78%, 20% and 2% vs 71%, 26% and 2%, respectively (p = 0.409) [16].

Unfortunately, both publications on Han Taiwanese and Canadian population do not allow to conclude on the relationship between the rs1042838 of the *PGR* gene and SA. Although the difference in the MAF between the group of Han Taiwanese women with SA and the group of women without SA was statistically significant (p = 0.006), the very low frequency of the T allele suggests conducting broader study on a larger group.

Admittedly, we found one more, earlier (2004) publication, by Schweikert et al., where rs1042838 also was analyzed. Moreover, the authors analyzed rs552916 (also known as 1031G>C) and rs3740753 (also known as 344S>T) in exon 1, and rs1042839 in exon 5, in a group of German women with and without SA [23]. In this study the authors suggested, that tested variants may be associated with SA. However, it should be noted that despite examining a larger number of variants, the limitations of the conclusions drawn lie in the small group number of women with and without SA, 42 vs 40, respectively. Moreover, authors suggested that in 33 of 42 women with SA, the examination revealed factors that might have contributed to SA, such as: hyperandrogenemia, hyperprolactinemia, elevated hormone levels and positive autoantibody tests.

Comparative studies of the genome of NM and Modern Man – MM (*Homo sapiens*) have shown the presence of numerous introgressions from NM (INM) in individuals living in contemporary populations. Among INM one can include rs1042838 *PGR* that has been identified in sequenced Neanderthal genomes and introduced into the modern human gene pool.

It is suggested that the rs1042838 *PGR* gene is linked to phenotypic traits such as having more offspring/siblings, higher rates of early pregnancy loss and premature birth (before 37 weeks of gestation or before 259 days of gestation counting from the date of the last menstruation) [10, 12]. Moreover, it is claimed that modern INM rs1042838 carriers-man have higher *PGR* expression, and that carriers-women have fewer SA and bleeding in the early stages of pregnancy, implying the *PGR* variants may be protective for pregnancy. Zeberg et al. suggested that selected variants of *PGR* may be conducive to pregnancies. That would explain their relationship with increased fertility, and the increase in their prevalence in modern populations [10]. Apart Africans populations, INM is present in ca. 20% subjects of modern populations. On the other hand, Li et al. indicate a possible relationship between rs1042838 of the *PGR* gene and premature birth, but consider this fact as a physiological compromise between SA and live birth born prematurely [12].

As we mentioned above, *PGR* has undergone evolutionary changes that have resulted in clinical implications for modern populations. Li et al. suggested *PGR* as a possible candidate gene due to collected evidence of evolutionary constraint, suggesting important implications for reproductive capacity [12]. It is also important to note that many other gene variants and their interrelationships may play a role during pregnancy and may be potential candidates for determining the success of a pregnancy or the risk of SA. In recent years, more and more attention has been paid to the genotyping of paternal material. Testing the rs1042838 of *PGR* among couples or fetuses could contribute to the confirmation or exclusion of a specific variant as a risk factor of SA [24, 25, 26].

Due to the tested variant rarity in many populations, studies on groups with larger numbers are necessary. In order to account for the interactions, testing other genes variants should also be considered. Furthermore, studies in different populations should be conducted, as it is difficult to conclude whether rs1042838 of the *PGR* gene may be a risk modifier in different populations and ethnic groups, e.g. those that have a unique population structure or are characterized by strictly endogamous tribes.

CONCLUSION

In conclusion, the involvement of rs1042838 of the *PGR* gene in SA has not been fully confirmed.

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