ORIGINAL ARTICLE

* The authors contributed equally.

1. Universidad Nacional Mayor de San Marcos, Faculty of Medicine. Medicina y Genética Molecular Materno Perinatal-MEGEMAPE Research Group, Lima, Peru
2. Universidad Nacional Mayor de San Marcos, Faculty of Pharmacy and Biochemistry, Lima, Peru
3. Atrium Health, Concord, North Carolina, USA
4. Universidad de San Martin de Porres, Faculty of Human Medicine, CIGBM, Lima, Peru

a. José Pacheco-Romero: Obstetrician and Gynecologist, Doctor in Medicine; jpachecor@unmsm.edu.pe; ORCID 0000-0002-3168-6717
b. Oscar Acosta: Biologist with specialization in Genetics, Master in Biochemistry; oacostac@unmsm.edu.pe; ORCID 0000-0002-1912-0251
c. Doris Huerta: Biologist, Doctor in Biological Sciences; dhuertac@unmsm.edu.pe; https://orcid.org/0000-0002-0473-8083
d. Marlene Vargas: Medical Technologist, Master in Biochemistry; mvargasc1@unmsm.edu.pe; https://orcid.org/0000-0001-5822-1015
e. Santiago Cabrera: Obstetrician and Gynecologist, Doctor in Medicine; drscabrera@hotmail.com; ORCID 0000-0003-4597-1049
f. Pedro Mascaro: Obstetrician and Gynecologist, Doctor in Medicine; pmascaros@hotmail.com; ORCID 0000-0001-7868-771X
g. Moisés Huamán: Obstetrician and Gynecologist, Doctor in Medicine; moiseshuamang@hotmail.es
h. José Sandoval: Obstetrician and Gynecologist, Doctor in Medicine; jsandovalpar@hotmail.com; ORCID 0000-0002-4073-5699
i. Julio Mateus: Obstetrician and Gynecologist; juliomateus@hotmail.com; ORCID 0000-0001-6886-4807
j. Enrique Gil: Obstetrician and Gynecologist, especialist in Fetal Medicine and Surgery; gilgen1@hotmail.com; ORCID 0000-0001-6515-2599
k. Enrique Guevara: Obstetrician and Gynecologist, Master in Health Services Management; enriqueguevararios@gmail.com; https://orcid.org/0000-0002-6962-2639
l. Ricardo Fujita: Biologist with specialization in Genetics, Doctor in Molecular Genetics; rfujitaa@usmp.pe; https://orcid.org/0000-0002-9617-5109

Funding: The authors received funding from the Universidad Nacional Mayor de San Marcos, as part of 2012-2017 grants from the Vice-Rectorate for Research.

Conflict of interest: The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The article being submitted has not been previously published and has not been previously sent to another journal.

No technology related to artificial intelligence has been used in this research or in the preparation of the article.

Received: 16 August 2024

Accepted: 1 September 2024

Online publication:

Corresponding Author:
Dr. José Pacheco-Romero
Calle Venecia 225 San Borja, Lima, Perú
51 1 372 3555 – Celular: 51 1 999 481 979
jpachecoperu@yahoo.com

Cite as: Pacheco-Romero J, Acosta O, Huerta D, Vargas M, Cabrera S, Mascaro P, Huamán M, Sandoval J, Mateus J, Gil E, Guevara E, Fujita R. Genetic variants and serum ApoA1 and ApoB100 levels in Peruvian pregnant women with severe preeclampsia. Rev peru ginecol obstet. 2024;70(3). Doi: https://doi.org/10.31403/rpgo.v70i2671

Genetic variants and serum ApoA1 and ApoB100 levels in Peruvian pregnant women with severe preeclampsia

Variantes genéticas y niveles séricos de la ApoA1 y ApoB100 en gestantes peruanas con preeclampsia severa

José Pacheco-Romero[1,a*], Oscar Acosta[2,b,*], Doris Huerta[1,c], Marlene Vargas[1,d], Santiago Cabrera[1,e], Pedro Mascaro[1,f], Moisés Huamán[1,g], José Sandoval[1,h], Julio Mateus[3,i], Enrique Gil[1,j], Enrique Guevara[1,k], Ricardo Fujita[4,l]

DOI: https://doi.org/10.31403/rpgo.v70i2671

ABSTRACT

Background: Preeclampsia is a multi-organ disease that causes maternal and perinatal morbidity and mortality, with an unclear pathophysiology and without specific prevention methods and/or treatments. Objective: To establish the association between variants -75 G/A in the ApoA1 gene, 2488 C/T in the ApoB100 gene, serum levels of ApoA1 and ApoB100 and severe preeclampsia in Peruvian pregnant women. Methods: Blood samples from pregnant women with severe preeclampsia and healthy women (controls) were processed for DNA extraction and genotyping with the PCR-RFLP technique. In addition, serum was analyzed to quantify ApoA1 and ApoB100. Genotypes and alleles were compared between cases and controls, as well as serum ApoA1 and ApoB100 levels considering genotypes. Results: No significant differences were found between the genotypic and allele frequencies of the -75 G/A variant in the ApoA1 gene and 2488 C/T in the ApoB100 gene of both groups. A significant difference (p=0.039) was found when comparing serum ApoA1 in patients with heterozygous GA genotypes, with lower average levels in severe preeclamptic (161.37 ± 40.21) compared to controls (185.37 ± 35.38). Conclusions: Although no association was found between the variants -75 G/A variants in the APOA1 gene and 2488 C/T in the ApoB100 gene and preeclampsia, however, serum ApoA1 levels were significantly lower in severe preeclamptic women with GA heterozygous genotype than in controls. Thus, we contribute to the understanding of preeclampsia in Peruvian pregnant women.

Key words: Preeclampsia, Pregnant women, Apolipoprotein A-1, Apolipoprotein B-100, Serum, Peru

RESUMEN

Antecedentes. La preeclampsia es una enfermedad multiorgánica que causa morbimortalidad materna y perinatal, con una fisiopatología poco clara y sin métodos de prevención y/o tratamientos específicos. Objetivo. Establecer la asociación entre las variantes -75 G/A en el gen ApoA1, 2488 C/T en el gen ApoB100, los niveles séricos de la ApoA1 y ApoB100 y la preeclampsia severa en gestantes peruanas. Métodos. Se procesaron muestras sanguíneas de gestantes con preeclampsia severa y sanas (controles) para extracción de ADN y genotipado con la técnica PCR-RFLP. Además, se analizó el suero para cuantificar la ApoA1 y ApoB100. Se compararon los genotipos y alelos entre los casos y controles, así como los niveles séricos de ApoA1 y ApoB100 considerando los genotipos. Resultados. No se encontraron diferencias significativas entre las frecuencias genotípicas y alélicas de la variante -75 G/A en el gen ApoA1 y 2488 C/T en el gen ApoB100 de ambos grupos. Se halló una diferencia significativa (p=0,039) al comparar el ApoA1 sérico en pacientes con genotipos heterocigotos GA, siendo los niveles promedio más bajos en preeclámpticas severas (161,37 ± 40,21) respecto a las controles (185,37 ± 35,38). Conclusiones. Si bien no se ha encontrado asociación entre las variantes -75 G/A en el gen APOA1 y 2488 C/T en el gen ApoB100 y la preeclampsia, sin embargo, los niveles séricos de la ApoA1 fueron significativamente menores en las preeclampticas severas con genotipo heterocigoto GA respecto a los controles. De esta manera, se contribuye en la comprensión de la preeclampsia en gestantes peruanas.

Palabras clave. Preeclampsia, Gestantes, Apolipoproteína A-1, Apolipoproteína B-100, Suero, Perú

Introduction

Preeclampsia (PE) is a disease that complicates the pregnant woman with arterial hypertension and vascular compromise of organs and systems. It affects between 2%-8% of pregnant women[1] with greater presence in low- and middle-income countries, up to 12% of pregnant women in Lima, Peru[2]. It contributes significantly to maternal and neonatal morbidity and mortality. It can occur at any time during gestation -usually in the second half of pregnancy- and no treatment or indicators for its prevention have been found so far.

Although personal factors associated with the risk of PE are known, such as maternal age over 35 years, primigravida, multiple pregnancy, history of personal or family PE, obesity, diabetes, arterial hypertension, renal disease or autoimmune disease, it is considered that genomic variants in preeclampsia could play an important role in the susceptibility of a pregnant woman to suffer from it. These include DNA single nucleotide polymorphisms (SNPs) -involved in angiogenesis, inflammation and immune response- or copy number variations, deletions or duplications of important DNA segments in placental development and function[3-5].

On the other hand, maternal serum lipid levels appear to change throughout pregnancy in pregnant women with hypertensive disease, and this is more significant in women with preeclampsia[6].

Apolipoprotein A1 (Apo A1) is the main protein component of high-density lipoproteins (HDL). It is a multifunctional protein involved in cholesterol transport and regulation of inflammatory and immune responses[7], inhibiting oxidation of low-density lipoproteins (LDL) and elimination of toxic phospholipids. Research suggests that Apo A1 levels in pregnant women may increase in late gestation in both blood and placental tissues, especially in those with preeclampsia[2,8].

Apolipoprotein B100 (apo-B100) is a protein involved in the circulation of cholesterol in the body as a form of low-density lipoprotein (LDL). Mutations in the gene that directs the production of apolipoprotein B100 can cause conditions such as familial hypercholesterolemia[9].

Methods

The present study is an associative, observational design type cases (severe preeclampsia) and controls (without preeclampsia), conducted between 2017 and 2019. The women were pregnant women in the third trimester attended at the Hospital Docente Madre-Niño San Bartolomé and at the Instituto Nacional Materno Perinatal, public institutions of reference in the city of Lima, belonging to the Peruvian Ministry of Health.

A pregnant woman was defined as having preeclampsia when she presented blood pressure >140/90 mmHg and proteinuria ≥300 mg/24h. Severe preeclampsia was considered when there was also evidence of dysfunction of other maternal organs, such as acute kidney injury (creatinine ≥90 µmol/L; 1 mg/dL), hepatic involvement (elevated transaminases) with or without right upper quadrant or epigastric abdominal pain, neurologic complications (such as eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomas), hematologic complications (thrombocytopenia <150,000/µL, disseminated intravascular coagulation, hemolysis), or uteroplacental dysfunction (fetal growth restriction, umbilical artery Doppler wave abnormalities, or fetal death)[10].

Sampling was non-probabilistic (by convenience). Inclusion criterion for the case group were age ≥18 years with a diagnosis of severe preeclampsia in the second half of pregnancy and confirmed by clinical and laboratory data. Pregnant women without proteinuria or with chronic hypertension, diabetes, other medical conditions or with incomplete information were excluded. The inclusion criteria for the control group were age ≥18 years, apparently healthy pregnant woman, without preeclampsia and without relevant diseases.

The research protocol and informed consent were approved by the Ethics Committee of the Faculty of Medicine of the Universidad Nacional Mayor de San Marcos, Lima, Peru, and the Ethics Committees of the participating hospitals. Informed consent was obtained from the pregnant women and data were collected in a clinical record.

Blood samples were extracted in Vacutainer tubes (3 mL), kept refrigerated and transferred to the laboratory for DNA extraction with commercial kits and separation of blood serum for biochemical evaluation of ApoA-1 and ApoB-100 levels by ELISA.

The DNA obtained was processed by PCR-RFLP technique to determine the genotypes and alleles of the -75/GA polymorphisms in the ApoA-1 gene and 2488C/T (XbaI) in the ApoB-100 gene, with specific primers and digestion with MspI and XbaI restriction enzymes, respectively, according to pre-established protocols[2].

Allelic and genotypic frequencies were calculated according to the Hardy-Weinberg equilibrium hypothesis. To establish the association between genotypes, alleles and severe preeclampsia, the chi-square test or Fisher's exact test was performed considering a $p < 0.05$. In addition, the risk was established by odds ratio (OR). Calculations of the mean and standard deviation of ApoA-1 and ApoB-100 data in cases and controls were performed, comparing them with the Student's t-test for independent samples. IBM SPSS v25 IBM statistical software and population genetics packages were used.

Results

The number of participating pregnant women was 52 with severe preeclampsia (cases) and 40 without preeclampsia (controls), with a mean age of 28 years for both groups (28.8 years + 7.4 standard deviation in severe preeclampsia versus 28.1 + 6.7 SD in controls).

Table 1 shows the results for the genes evaluated. When comparing patients with severe preeclampsia and controls, no significant differences were found in the genotypic and allelic frequencies of the -75 G/A variant in the ApoA1 gene and 2488 C/T in the ApoB100 gene, indicating that there was no association and that the variants evaluated were not at risk.

Table 2 shows the serum ApoA1 and ApoB100 levels according to genotypes in patients with severe preeclampsia and controls. No significant

Table 1. Variants in ApoA1 and ApoB100 genes in patients with severe preeclampsia and controls, Lima, Peru.

		Severe preeclampsia	Controls		
Gene, variant	Genotypes and alleles	n (%)	n (%)	OR (95% CI)	p^a
ApoA1 -75 G/A	GG	13 (25.0)	11 (27.5)	Reference	0.916
	GA	27 (51.9)	19 (47.5)	1.202 (0.445-3.251)	
	AA	12 (23.1)	10 (25.0)	1.015 (0.318-3.244)	
	G	53 (51.0)	41 (51.3)	Reference	0.913
	A	51 (49.0)	39 (48.7)	1.012 (0.565-1.812)	
ApoB100 2488 C/T (XbaI)	X-X- (CC)	28 (53.9)	24 (60.0)	Reference	0.478
	X- X+ (CT)	14 (26.9)	12 (30.0)	1.001 (0.389-2.571)	
	X+X+ (TT)	10 (19.2)	4 (10.0)	2.143 (0.595-7.717)	
	X- (C)	70 (67.3)	60 (75.0)	Reference	0.330
	X+ (T)	34 (32.7)	20 (25.0)	1.457 (0.760-2.794)	

[a] According to chi-square test or Fisher's exact test. The genotypic frequencies of ApoA1 -75 G/A in pregnant women with severe preeclampsia and controls are in Hardy-Weinberg equilibrium

Table 2. Serum ApoA1 and ApoB100 levels according to genotypes in patients with severe preeclampsia and controls, Lima, Peru.

		Severe preeclampsia n=52	Controls n=40	
Marker	Genotypes	X ± SD mg/dL serum	X ± SD mg/dL serum	p^a
ApoA1	GG	188.23 ± 45.20	175.91 ± 41.62	0.494
	GA	161.37 ± 40.21	185.37 ± 35.38	0.039 *
	AA	166.83 ± 39.55	167.00 ± 41.51	0.992
	Total, patients	169.35 ± 42.05	178.18 ± 38.45	0.298
ApoB100	X-X- (CC)	43.21 ± 18.29	41.33 ± 16.30	0.728
	X- X+ (CT)	44.21 ± 15.53	44.58 ± 16.06	0.816
	X+X+ (TT)	43.80 ± 15.96	46.25 ± 13.96	0.886
	Total, patients	43.60 ± 16.85	42.80 ± 15.75	0.815

*[a] According to Student's t-test for independent samples. * p<0.05, significant difference. X ± SD = Mean ± standard deviation*

differences were found in serum ApoB100 averages overall and with genotypes for the 2488 C/T (XbaI) polymorphism. According to the GG and AA homozygous genotypes for the -75 G/A polymorphism, ApoA1 levels showed no differences between cases and controls. However, a significant difference (p=0.039) was found when comparing mean serum ApoA1 in the GA heterozygous genotype, with lower mean ApoA1 levels in severe preeclamptic pregnant women (161.37 ± 40.21) compared to controls (185.37 ± 35.38).

Discussion

Hypertensive disorders of pregnancy is one of the leading causes of maternal and perinatal morbidity and mortality worldwide. The underlying mechanisms of PE ocurrence remain unclear and there are no specific prevention methods and/or treatments.

In the pathogenesis of PE, it is considered that a superficial invasion of the trophoblast causes inadequate remodeling of the spiral arteries, producing maternal endothelial dysfunction due to the imbalance between angiogenic and antiangiogenic factors that would lead to the clinical disorder[10].

The disease may appear suddenly and the warning of impending severe preeclampsia may be a sustained systolic blood pressure of 160 mmHg or more, a new and persistent increase in creatinine (90 micromol/L or more, 1 mg/100 mL or more), increased alanine transaminase (more than 70 IU/L, or twice the upper limit of the normal range) or decreased platelet count (less than 150.000/microliter), as well as compromised fetal health[11].

Lipoproteins are complex particles with a central core containing cholesterol and triglyceride esters surrounded by free cholesterol, phospholipids and apolipoproteins, elements that facilitate the formation and work of lipoproteins. The functions of apolipoproteins are: 1) to play a structural role, 2) to act as ligands for lipoprotein receptors, 3) to guide the formation of lipoproteins, and 4) to act as activators or inhibitors of enzymes involved in lipoprotein metabolism[12]. The protein fraction of lipoproteins consists of several apolipoproteins and enzymes whose functions are lipid transport and metabolism[13].

Lipoprotein metabolism is regulated and controlled by specific apolipoproteins (apo-), which make up various types of lipoproteins[14]. They regulate protein metabolism by transporting and redistributing lipids to cells and tissues[15]. Apo B-100 represents the circulating Apo B particles in the body and is an LDL. The Apo B-100/Apo A-1 ratio has been proposed as a reliable parameter to predict atherosclerosis and fatal cardiovascular disease events linked to lipid alterations[16].

A change in the Apo B/Apo A-1 ratio has been associated with an increased risk of preeclampsia[17]. Preeclamptic patients have been reported to have significantly lower Apo A-1 levels and a higher Apo B-100/Apo A-1 ratio, considering them as useful markers[18]. However, discrepancies can be found in the literature on the relationship between Apo A-1/Apo B-100 levels and preeclampsia.

In a previous study of various genetic polymorphisms in the Peruvian population, including the genotypes and alleles of the Apo A-1 and Apo B-100 genes, as in the present study, no significant differences were found between pregnant women with severe preeclampsia and those without preeclampsia[2]. However, when comparing pregnant women with severe preeclampsia and controls without eclampsia, a significant difference (p=0.039) in mean serum ApoA1 levels was found in those with heterozygous GA genotype for the -75 G/A polymorphism. Specifically, mean ApoA1 levels in severe preeclamptic were lower compared to controls.

The -75 G/A variant (rs670) in the promoter region of the ApoA1 gene has an effect on transcriptional activity, mainly due to the presence of the A allele, associated with a decrease in this activity and in ApoA1 synthesis[19,20]. In the trend of our results, it has been shown that heterozygosity in polymorphisms in the promoter region, including the -75 G/A, results in significant reduction of gene expression, and therefore in decreased levels of ApoA1 and other biochemical markers such as HDL-c[21].

ApoA1 expression has been reported to be elevated in plasma and placenta of preeclamptic women in midgestation compared with controls without preeclampsia. ApoA1 concentration has also been associated with systolic pressure, but

during late gestation. In addition, the transcriptional activity of the ApoA1 gene can be regulated by the PPARγ, protein, influencing, among other aspects, trophoblast functions[8]. All this shapes the importance of ApoA1 in preeclampsia and other related conditions and/or diseases, due to its multifunctionality and therapeutic potential[22].

The variability among populations and allelic frequencies in the promoter region of the gene can differentially modulate the expression of the ApoA1 gene. In this regard, different variants in the ApoA1 gene have been evaluated in North America, including -75 G/A, and specific hereditary patterns have been observed in Asian subgroups, with frequencies different from those of European origin, suggesting that ethnicity may influence the expression of the ApoA1 gene[23]. This aspect is important according to the results of the present study, where genes, biochemistry, genetic ancestry, among the main factors, may complement each other to influence the development of preeclampsia, considering that the patients come from the city of Lima, Peru, whose inhabitants are characterized by a high Amerindian component[24].

In Latin America, and particularly in Peru, there are studies on genetic variants and preeclampsia that aim to contribute to the pathophysiology of the disease. However, they are still insufficient, since other factors such as epigenetics, biochemical markers, among others, should be considered, complemented with clinical studies and the use of new massive technologies for data collection and analysis[2,25,26].

The limitations of the present investigation may be the sample size, the study of other genetic variants and different biochemical markers, aspects that should be considered in subsequent studies.

In conclusion, although no association was found between preeclampsia and the polymorphisms -75 G/A in the APOA1 gene and 2488 C/T in the ApoB100 gene, however, with respect to serum ApoA1 and APOB100 levels, a significant difference was found when comparing the average serum ApoA1 in the GA heterozygous genotype among patients, with lower ApoA1 levels in severe preeclampsia compared to controls. Thus, we are contributing to the understanding of the factors involved in the development of preeclampsia in Peruvian pregnant women.

References

1. ACOG. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020 Jun;135(6):e237-e260. doi: 10.1097/AOG.0000000000003891
2. Pacheco-Romero J, Acosta Conchucos O, Huerta Canales D, Cabrera Ramos S, Vargas Chávez M, Mascaro Sánchez P; for the MEGEMAPE Research Group. Genetic markers for preeclampsia in Peruvian women. Colomb Med (Cali). 2021 Feb 26;52(1):e2014437. doi: 10.25100/cm.v52i1.4437
3. Tyrmi JS, Kaartokallio T, Lokki AI, Jääskeläinen T, Kortelainen E, Ruotsalainen S; et al; FINNPEC Study Group, FinnGen Project, and the Estonian Biobank Research Team. Genetic Risk Factors Associated With Preeclampsia and Hypertensive Disorders of Pregnancy. JAMA Cardiol. 2023 Jul 1;8(7):674-83. doi: 10.1001/jamacardio.2023.1312
4. Kovacheva VP, Eberhard BW, Cohen RY, Maher M, Saxena R, Gray KJ. Preeclampsia Prediction Using Machine Learning and Polygenic Risk Scores From Clinical and Genetic Risk Factors in Early and Late Pregnancies. Hypertension. 2024 Feb;81(2):264-72. doi: 10.1161/HYPERTENSIONAHA.123.21053
5. Melton PE, Johnson MP, Gokhale-Agashe D, Rea AJ, Ariff A, Cadby G, et al. Whole-exome sequencing in multiplex preeclampsia families identifies novel candidate susceptibility genes. J Hypertens. 2019 May;37(5):997-1011. doi: 10.1097/HJH.0000000000002023
6. Liu L, Zhang X, Qin K, Xu C, Ruan F, Liu Y, Zhao H, et al. Characteristics of Serum Lipid Metabolism among Women Complicated with Hypertensive Disorders in Pregnancy: A Retrospective Cohort Study in Mainland China. Obstet Gynecol Int. 2024 Feb 14;2024:9070748. doi: 10.1155/2024/9070748
7. Georgila K, Vyrla D, Drakos E. Apolipoprotein A-I (ApoA-I), Immunity, Inflammation and Cancer. Cancers (Basel). 2019 Aug 1;11(8):1097. doi: 10.3390/cancers11081097
8. Liu Z, Pei J, Zhang X, Wang C, Tang Y, Liu H, Yu Y, Luo S, Gu W. APOA1 Is a Novel Marker for Preeclampsia. Int J Mol Sci. 2023 Nov 15;24(22):16363. doi: 10.3390/ijms242216363
9. Andersen LH, Miserez AR, Ahmad Z, Andersen RL. Familial defective apolipoprotein B-100: A review. J Clin Lipidol. 2016 Nov-Dec;10(6):1297-302. doi: 10.1016/j.jacl.2016.09.009
10. Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet. 2019 May;145 Suppl 1(Suppl 1):1-33. doi: 10.1002/ijgo.12802. Erratum in: Int J Gynaecol Obstet. 2019 Sep;146(3):390-391. doi: 10.1002/ijgo.12892
11. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management. NICE guideline [NG133] Published: 25 June 2019. Last Updated: 17 April 2023. https://www.nice.org.uk/guidance/ng133/chapter/Recommendations#management-of-pre-eclampsia
12. Feingold KR. Introduction to Lipids and Lipoproteins. [Updated 2024 Jan 14]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK305896/

13. Errico TL, Chen X, Martin Campos JM, Julve J, Escolà-Gil C, Blanc-Vaca F. Mecanismos básicos: estructura, función y metabolismo de las lipoproteínas plasm. Clín Invest Arteriosclerosis. abril-junio 2013;25(2):98.103. DOI: 10.1016/j.arteri.2013.05.003

14. Mahley RW, Innerarity TL, Rall Jr SC, Weisgraber KH. Plasma lipoproteins: apolipoprotein structure and function. J Lipid Res. 1984 Dec 1;25(12):1277-94. PMID: 6099394.

15. Oram JF, Yokoyama S Apolipoprotein-mediated removal of cellular cholesterol and phospholipids. J Lipid Res. 1996 Dec;37(12):2473-91. PMID: 9017501.

16. Castillo Arocha I, Armas Rojas NB, Dueñas Herrera A, González Greck OR, Arocha Mariño C, Castillo Guzmán A. Riesgo cardiovascular según tablas de la OMS, el estudio Framingham y la razón apolipoproteína B/apolipoproteína A1. Rev Cubana Invest Biomed. December 2010;29(4):479-88

17. Serrano NC, Guio-Mahecha E, Quintero-Lesmes DC, Becerra-Bayona S, Paez MC, et al. Lipid profile, plasma apolipoproteins, and pre-eclampsia risk in the GenPE case-control study. Atherosclerosis. 2018 Sep;276:189–94. doi:10.1016/j.atherosclerosis.2018.05.051

18. Timur H, Korkut Daglar H, Kara O, Kirbas A, Inal HA, Gencosmanoglu Turkmen G, Yilmaz Z, Elmas B, Uygur D. A study of serum Apo A-1 and Apo B-100 levels in women with preeclampsia. Pregnancy Hypertens. 2016 Apr;6(2):121-5. DOI: 10.1016/j.preghy.2016.04.003

19. Smith JD, Brinton EA, Breslow JL. Polymorphism in the human apolipoprotein A-I gene promoter region: association of the minor allele with decreased production rate in vivo and promoter activity in vitro. J Clin Invest. 1992;89:1796–800. doi: 10.1172/JCI115783

20. Al-Bustan S, Al-Serri A, Annice B, Alnaqeeb M, Ebrahim G. Re-sequencing of the APOAI promoter region and the genetic association of the -75GA Apo polymorphism with increased cholesterol and low-density lipoprotein levels among a sample of the Kuwaiti population. BMC Med Genet. 2013;14:90. doi: 10.1186/1471-2350-14-90

21. Matsunaga A, Sasaki J, Han H, Huang W, Kugi M, Koga T, Ichiki S, Shinkawa T, Arakawa K: Compound heterozygosity for an apolipoprotein A1 gene promoter mutation and a structural nonsense mutation with apolipoprotein A1 deficiency. Arterioscler Thromb Vasc Biol. 1999 Feb;19(2):348–55. doi: 10.1161/01.atv.19.2.348

22. Cochran BJ, Ong KL, Manandhar B, Rye KA. APOA1: A protein with multiple therapeutic functions. Curr Atheroscler Rep. 2021 Feb;23(3):11. https://doi.org/10.1007/s11883-021-00906-7

23. Henkhaus RS, Dodani S, Manzardo AM, Butler MG: APOA1 gene polymorphisms in the South Asian immigrant population in the United States. Indian J Hum Genet. September 2011;17(3):194–200. DOI:10.4103/0971-6866.92103

24. Sandoval J, Salazar-Granara A, Acosta O, Castillo-Herrera W, Fujita R, Pena S, Santos F. Tracing the Genomic Ancestry of Peruvians Reveals a Major Legacy of Pre-Columbian Ancestors. J Hum Genet. 2013;58(9):627–34. https://doi.org/10.1038/jhg.2013.73

25. Qi J, Wu B, Chen X, Wei W, Yao X. Diagnostic biomolecules and combination therapy for pre-eclampsia. Reprod Biol Endocrinol. 2022;20:136. https://doi.org/10.1186/s12958-022-01003-3

26. Michita RT, Kaminski VL, Chies JAB. Genetic Variants in Preeclampsia: Lessons From Studies in Latin-American Populations. Front Physiol. 2018;9:1771. doi: 10.3389/fphys.2018.01771