Association between ABO and Rh Blood Groups and Risk of Preeclampsia: A Case-Control Study from Iran

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Abstract

AIM: Preeclampsia (PE) is a major cause of maternal and neonatal morbidity and mortality. There is a genetic component in the development of PE with estimated heritability around 0.47. Several studies have investigated the association between maternal ABO blood groups (OMIM: 110300) and risk of PE, with contradictory results have emerged. Considering that there is no study in this filed from Iranian population, the present case-control study was carried out at Shiraz (south-west Iran).

MATERIAL AND METHODS: In this study 331 women; 121 pregnant with PE and 210 normotensive pregnant women were included. Using blood group O (for ABO blood groups) or Rh+ (for Rh blood groups) as a reference, odds ratios (ORs) and its 95% confidence intervals (95% CI) of PE risk were estimated from logistic regression analysis.

RESULTS: Although the A (OR = 0.67, 95% CI = 0.39-1.17, P = 0.165), B (OR = 0.86, 95% CI = 0.48-1.53, P = 0.615) and AB (OR = 1.14, 95% CI = 0.37-3.45, P = 0.812) phenotypes showed lower risks compared with the O blood group, statistical analysis indicated that there was no significant association between ABO phenotypes and risk of PE. The frequency of Rh- phenotype was higher among PE patients compared with the control group. However, the association was not significant (OR = 1.79, 95% CI = 0.69-4.65, P = 0.229). Adjusted ORs for age of participants and parity did not change the above-mentioned associations.

CONCLUSION: Our present findings indicate that there is no association between ABO and Rh blood groups and risk of PE in Iranian population.

Introduction

Preeclampsia (PE) is a major cause of maternal and neonatal morbidity and mortality in humans. It is characterised by the presence of high blood pressure and proteinuria after the 20th week of pregnancy. It has been reported that PE is one of the top four causes of maternal mortality and morbidity worldwide [1]. For decades many studies investigate the pathogenesis and risk factors of PE with hopes of finding ways for prevention, early detection and effective management. It is well established that there is a genetic component in the development of PE [2-4].

Its heritability was estimated around 0.47 [2]. Genome-wide scans indicate that several chromosomal segments are associated with risk of PE [5, 6]. Consanguineous marriages are associated with increased risk of PE [7], indicating that homozygosity for variant alleles involved in PE.

The ABO blood group was discovered in 1900 by Karl Landsteiner. It is one of best known genetic traits because of its importance in transfusion medicine. In this blood group system, there are four major phenotypic groups named by A, B, AB, and O that result from 3 major alleles (A, B, and O) of the ABO gene (OMIM: 110300). The ABO gene encodes a glycosyltransferase that catalyses the transfer of carbohydrates to the H antigen (FUT1; OMIM: 211100), forming the antigenic structures of the ABO phenotypes. The proteins were encoded by the A and B alleles of ABO catalyse the transfer of different carbohydrates onto the H antigen to form the A or B

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antigens. In the O blood group, the A and B antigens did not produce. The gene encoding ABO blood group was localised on human chromosome 9q34 [8]. The ABO antigens are highly expressed by some human cells and tissues including epithelia, platelets, vascular endothelia and neurones [9, 10]. There is a large body of evidence supporting the notion that ABO antigens are involved in the pathogenesis of various systemic multifactorial traits, including cancers, infectious, neurological and cardiovascular disorders [10-12].

It should be noted that although the exact mechanism of PE pathogenesis remains unknown, it seems that placenta plays the main role. Overall the pathogenesis consists of decreasing placental circulation which causes increasing maternal endothelial dysfunction all of which leads to clinical presentations of preeclampsia such as hypertension and protein urea [13]. It is reported that genes responsible for thrombophilia are associated with an increased risk of preeclampsia [14].

Over many years, studies have investigated the association between maternal ABO blood groups and risk of PE, although contradictory results have emerged [15-21]. Based on our knowledge there is no study in this filed from Iranian population. Therefore present study was carried out.

Material and Methods

Study design

The present case-control study was conducted at Hafez Hospital (Shiraz, Iran) by reviewing medical files for pregnant women. PE was defined as pregnancy-induced hypertension (systolic blood pressure > 140 mmHg and diastolic blood pressure > 90 mm Hg) plus significant proteinuria (repeatedly ≥ 0.3 g/l or ≥ 0.5 g/24 hours or dipstick ≥+ representing values ≥ 0.3 g/l) after 20 weeks of gestational age in an earlier normotensive woman. The controls were pregnant women presented for delivery, with blood pressure values < 139/89 mmHg and no proteinuria recorded during the antenatal visits or at the time of delivery. Women with a twin pregnancy were excluded from PE and control groups. This study included 331 women; 121 pregnant with PE and 210 normotensive pregnant women. The ABO and Rh phenotypes were determined by standard serology methods.

Because Iranian population is one of the most heterogeneous populations [22-24], we select our participants (patients and controls) from Persian (Caucasians) Muslims living in Shiraz (Fars Province, South-West Iran).

Statistical analysis

For the control group, the observed frequencies of the ABO phenotypes were assessed for Hardy-Weinberg equilibrium using the χ^2 statistic [25]. To analyse differences between cases and controls, we used t-test (for continuous variables), logistic regression (for categorical variables). Using blood group O (for ABO blood groups) or Rh$^+$ (for Rh blood groups) as a reference, odds ratios (ORs) and its 95% confidence intervals (95% CI) of PE risk were estimated from logistic regression analysis. Also, logistic regression models were used to ORs adjusted for potential confounding factors. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA; version 11.5). Values of P<0.05 were considered as statistically significant.

Results

Table 1 shows selected characteristics factors in study groups. There was significant difference between cases and control group for age (t = 4.7, df = 329, P < 0.001). It should be noted that there was no association between parity and PE (OR = 0.76, 95% CI: 0.48-1.20, P = 0.241).

Table 1: Selective characteristic and blood groups among healthy pregnant women controls and preeclamptic patients

Characteristic	Controls	Cases	Results of comparison
Number	210	121	-
Age (years)	27.4 ± 5.6*	30.5 ± 6.1	P < 0.001
Systolic BP (mmHg)	109.9 ± 7.8	154.7 ± 17.4	P < 0.001
Diastolic BP (mmHg)	71.2 ± 7.1	97.6 ± 9.5	P < 0.001
Parity			
Nulliparity	110 (52.4 %)	73 (60.3 %)	P = 0.282
Other parities	95 (45.2 %)	48 (39.7 %)	
Missing	5 (2.4 %)	0	
ABO blood groups			
O	93 (44.3 %)	61 (50.4 %)	P = 0.536
A	63 (30.0 %)	28 (23.1 %)	
B	46 (21.9 %)	26 (21.5 %)	
AB	8 (3.8 %)	6 (5.0 %)	
Rh Blood Groups			
Rh$^+$	201 (95.7 %)	112 (92.6 %)	P = 0.223
Rh$^-$	9 (4.3 %)	9 (7.4 %)	

* Expressed as mean ± standard deviation (SD).

Table 1 also shows the prevalence of the ABO and Rh phenotypes in PE patients and healthy control pregnant women. The phenotypic frequencies of the ABO were in accordance with Hardy–Weinberg equilibrium in control group (χ^2 = 1.47, df = 1, P = 0.223). Although the A (OR = 0.67, 95% CI = 0.39-1.17, P = 0.165), B (OR = 0.86, 95% CI = 0.48-1.53, P = 0.615) and AB (OR = 1.14, 95% CI = 0.37-3.45, P = 0.812) phenotypes showed lower risks compared with the O blood group, statistical analysis indicated that there was no significant association between ABO phenotypes and risk of PE. To further evaluate the possible influence of difference of age of participants

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and parity between the patient and control groups, as two confounding factors on the relationship between ABO blood groups and risk of PE, multiple logistic regression analysis was used. After adjustment for age of participants and parity, the same result was revealed (Table 2). Our present finding of no association between ABO blood groups and risk of PE is consistent with some reports [16, 17]. It should be noted that some researchers find the significant association between ABO blood groups and risk of PE [15, 18-21, 27].

Table 2: Association between ABO and Rh blood groups and risk of preeclampsia

Phenotypes	Crud OR			Adjusted OR*		
	OR	95% CI	P	OR	95% CI	P
ABO blood groups						
O	1.0	-	-	1.0	-	-
A	0.67	0.39-1.17	0.165	0.71	0.40-1.28	0.263
B	0.86	0.48-1.53	0.615	0.86	0.47-1.59	0.644
AB	1.14	0.37-3.45	0.812	0.86	0.26-2.86	0.811
Non-O	0.78	0.49-1.22	0.282	0.78	0.49-1.26	0.326
Rh blood groups						
Rh⁺	1.0	-	-	1.0	-	-
Rh⁻	1.79	0.69-4.65	0.229	1.64	0.61-4.42	0.322

*Adjusted ORs for the age of participants and parity.

On the other hand, the Rh⁻ phenotype showed the higher risk for PE compared with the Rh⁺ phenotype. However, the association was no significant (OR = 1.79, 95% CI = 0.069-4.65, P = 0.229). Adjusted OR for the age of participants and parity did not change the above-mentioned association (Table 2). This finding is not consistent with previous reports [19].

Discussion

It has been reported that the A [20], AB [15, 18, 19, 27] and O [21] blood groups were the risk factor for PE. It is suspected that PE may result from changes in ischaemic vascular function [26] which can be influenced by ABO blood groups [27]. It should be noted that previous studies exploring ABO blood groups in women with PE revealed a great controversy between published studies [15-21]. While some studies reported the associations of ABO blood groups with PE [15, 18-20, 27], other studies failed to reach similar conclusions [16, 17]. Previously it has been reported that several genetic polymorphisms showed dissimilar associations with multifactorial complex traits among different ethnic groups [28-32]. Finally, it should mention that small sample size in studies and ethnicity are potential sources of heterogeneity between studies.

References

1. Payne B, Magee LA, von Dadelszen P. Assessment, surveillance and prognosis in pre-eclampsia. Best Pract. Res. Clin. Obstet. Gynaecol. 2011;25:449-462. https://doi.org/10.1016/j.bpobgyn.2011.02.003 PMid:21459048

2. Nilsson E, Salonen Ros H, Cnattingius S, Lichtenstein P. The importance of genetic and environmental effects for pre-eclampsia and gestational hypertension: a family study. BJOG. 2004;111:200-206. https://doi.org/10.1111/j.1471-0528.2004.00042x.x PMid:14961879

3. Thorup J, Nordenskjöld A, Hutson JM. Genetic and environmental origins of hypospadias. Curr Opin Endocrinol Diabetes Obes. 2014;21:227-232. https://doi.org/10.1097/MED.0000000000000063 PMid:24722170

4. Petry CJ, Beardsall K, Dunger DB. The potential impact of the fetal genotype on maternal blood pressure during pregnancy. J Hypertens. 2014;32:1553-1561. https://doi.org/10.1097/HJH.0000000000000212 PMid:24842698

5. Laivuori H, Lahermo P, Ollikainen V, Widen E, Haiva-Mallinen L, Sundstrom H, Laitinen T, Kaaja R, Ylikorkala O, Kere J. Susceptibility loci for preeclampsia on chromosomes 2p25 and 9p13 in Finnish families. Am J Hum Genet. 2003;72:168-177. https://doi.org/10.1086/345311 PMid:12474145 PMCid:PMC378622

6. Arngrimsson R, Siguroardottir S, Frigge ML, Bjarnadottir RI, Jonsson T, Stefansson H, Baldursdottir A, Einarsdottir AS, Palsson B, Snorradottir S, Lachmeijer AMA, Nicolae D, Kong A, Bragason BT, Gulcher JR, Geirsson RT, Stefansson K. A genome-wide scan reveals a maternal susceptibility locus for pre-eclampsia on chromosome 2p13. Hum Mol Genet. 1999;8:1799-1805. https://doi.org/10.1093/hmg/8.9.1799 PMid:10441346

7. Anvar Z, Namavar-Jahromi B, Saadat M. Association between consanguineous marriages and risk of pre-eclampsia. Arch Gynecol Obstet. 2011;283 Suppl 1:5-7. https://doi.org/10.1007/s00404-010-1528-8 PMid:20517614

8. Ferguson-Smith MA, Aitken DA, Turleau C, de Grouchy J. Localisation of the human ABO: Np-1: AK-1 linkage group by regional assignment of AK-1 to 9q34. Hum Genet. 1976;34: 35-43. https://doi.org/10.1007/BF00284432 PMid:184030

9. Storry JR, Olsson ML. The ABO blood group system revisited: a review and update. Immnunochemistry. 2009;25:48-49.

10. Liumbruno GM, Franchini M. Beyond immunohaematology: the role of the ABO blood group in human diseases. Blood Transfus. 2013;11:491-499. PMid:24120598 PMCid:PMC3827391

11. He M, Wolpin B, Rexrode K, Manson JE, Rimm E, Hu FB, Qi L. ABO blood group and risk of coronary heart disease in two prospective cohort studies. Arterioscler Thromb Vasc Biol. 2012;32:2314-2320. https://doi.org/10.1161/ATVBAHA.112.248757 PMid:22895671 PMCid:PMC3488453

12. Liumbruno GM, Franchini M. Hemostasis, cancer, and ABO blood group: the most recent evidence of association. J Thromb Thrombolysis. 2014;38:160-166. https://doi.org/10.1007/s11239-013-1027-4 PMid:24233389

13. Naljayan MV, Karumanchi SA. New developments in the pathogenesis of preeclampsia. Adv Chronic Kidney Dis. 2013;20:265-270. https://doi.org/10.1053/j.ackd.2013.02.003 PMid:23928392 PMCid:PMC4107338

14. Wang X, Bai T, Liu S, Pan H, Wang B. Association between thrombophilia gene polymorphisms and preeclampsia: a meta-analysis. PLoS One. 2014;9:e100789. https://doi.org/10.1371/journal.pone.0100789 PMid:24967675 PMCid:PMC4072713

15. Spinillo A, Capuzzo E, Baltaro F, Piazzi G, Iasci A. Case-control study of maternal blood group and severe preeclampsia. J Hum Hypertens. 1995;9:623-625. PMid:8523376

16. Witsenburg C, Rosendaal F, Middeldorp J, Van der Meer FJ, Scherjon SA. Factor VIII levels and the risk of pre-eclampsia, HELLP syndrome, pregnancy related hypertension and severe intrauterine growth retardation. Thromb Res. 2005;115:387-392. https://doi.org/10.1016/j.thromres.2004.09.009 PMid:15733972

17. Clark P, Walker I, Govan L, Wu O, Greer IA. The GOAL study: a prospective examination of the impact of factor V Leide and

_____

ABO(H) blood groups on haemorrhagic and thrombotic pregnancy outcomes. Br J Haematol. 2008;140:236-240. PMid:18028481

18. Hiltunen LM, Laivuori H, Rautanen A, Kaaja R, Kere J, Krusius T, Paunio M, Rasi V. Blood group AB and factor V Leiden as risk factors for pre-eclampsia: a population-based nested case-control study. Thromb Res. 2009;124:167-173. https://doi.org/10.1016/j.thromres.2008.11.012 PMid:19110300

19. Lee BK, Zhang Z, Wikman A, Lindqvist PG, Reilly M. ABO and RhD blood groups and gestational hypertensive disorders: a population based cohort study. BJOG. 2012;119:1232-1237. https://doi.org/10.1111/j.1471-0528.2012.03421.x PMid:22734590

20. Phaloprakarn C, Tangjitgamol S. Maternal ABO blood group and adverse pregnancy outcomes. J Perinatol. 2013;33:107-111. https://doi.org/10.1038/jp.2012.73 PMid:22678143

21. Elmugabil A, Rayis DA, Ahmed MA, Adam I, Gasim GI. O Blood Group as Risk Factor for Preeclampsia among Sudanese Women. Open Access Maced J Med Sci. 2016; 4(4):603-606. https://doi.org/10.3889/oamjms.2016.108 PMid:28028398 PMCid:PMC5175506

22. Rafiee L, Saadat I, Saadat M. Glutathione S-transferase genetic polymorphisms (GSTM1, GSTT1 and GSTO2) in three Iranian populations. Mol Biol Rep. 2010;37:155-158. https://doi.org/10.1007/s11033-009-9565-8 PMid:19430957

23. Saadat M. Distribution of ACE insertion/deletion (I/D) polymorphism in Iranian populations. Mol Biol Res Commun. 2015;4:63-66. PMid:27843997 PMCid:PMC5019291

24. Fallahzadeh-Abarghooei L, Zahedi T, Mirabedi F, Saadat M. Alleleic prevalence of intron 3 insertion/deletion genetic polymorphism of DNA double-strand break repair gene XRCC4 in four Iranian populations. Egypt J Med Hum Genet. 2015;16:215-218. https://doi.org/10.1016/j.ejmhg.2015.02.004

25. Saadat M. Estimation of allelic frequencies for ABO and Rh blood groups. Egypt J Med Hum Genet. 2016;16:205-206.

https://doi.org/10.1016/j.ejmhg.2015.01.001

26. Roberts JM, Hubel CA. The two stage model of preeclampsia: variations on the theme. Placenta. 2009;30 Suppl A:S32-37.

27. Than NG, Romero R, Meiri H, Erez O, Xu Y, Tarquini F, Barna L, Szilagyi A, Ackerman R, Sammar M, Fule T, Karaszi K, Kovalszky I, Dong Z, Kim CJ, Zavodszky P, Papp Z, Gonen R. PP13, maternal ABO blood groups and the risk assessment of pregnancy complications. PLoS One. 2011;6:e21564. https://doi.org/10.1371/journal.pone.0021564 PMid:21799738 PMCid:PMC3143125

28. Saadat M. Apolipoprotein E (APOE) polymorphisms and susceptibility to breast cancer: A meta-analysis. Cancer Res Treat. 2012;44:121-126. https://doi.org/10.4143/crt.2012.44.2.121 PMid:22802750 PMCid:PMC3394861

29. Saadat M. Haplotype analysis of XRCC1 (at codons 194 and 399) and susceptibility to breast cancer, a meta-analysis of the literatures. Breast Cancer Res Treat. 2010;124:785-791. https://doi.org/10.1007/s10549-010-0895-y PMid:20411322

30. Saadat M, Ansari-Lari M. Polymorphism of XRCC1 (at codon 399) and susceptibility to breast cancer, a meta-analysis of the literatures. Breast Cancer Res Treat. 2009;115:137-144. https://doi.org/10.1007/s10549-008-0051-0 PMid:18481169

31. Loh M, Koh KX, Yeo BH, Song CM, Chia KS, Zhu F, Yeoh KG, Hill J, Iacopetta B, Soong R. Meta-analysis of genetic polymorphisms and gastric cancer risk: Variability in associations according to race. Eur J Cancer. 2009;45:2562-2568. https://doi.org/10.1016/j.ejca.2009.03.017 PMid:19375306

32. Saadat M. Genetic polymorphisms of glutathione S-transferase T1 (GSTT1) and susceptibility to gastric cancer: a meta-analysis. Cancer Sci 2006;97:505-509. https://doi.org/10.1111/j.1349-7006.2006.00207.x PMid:16734729

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