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Title:

Is there any relationship between ABO/Rh blood group and patients with pre-eclampsia?

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Abstract

Objectives: The purpose of the present study was to evaluate the association between pre-eclampsia and blood groups in a group of pregnant women hospitalized in a University Hospital in Porto Alegre, Brazil -Hospital São Lucas (HSL)/PUCRS.

Study design: Our sample consisted of 10.040 pregnant women admitted to the maternity department of HSL between 2005 and 2010. The patients were reviewed retrospectively for inclusion. Medical records of 414 women were diagnosed as preeclampsia/eclampsia and were identified 9611 women to the control group. The patients were divided into two groups: the group with preeclampsia/eclampsia and the control group, and their blood groups were considered. Data were analyzed using SPSS for Windows version 17.0. Categorical data were summarized by counts and percentages, with the statistical significance evaluated by the Chi-square test. The null hypothesis was rejected when $p<0.05$.

Main outcome measures: Maternal parameters were compared between control group and pre-eclampsia, respectively, Systolic Blood Pressure (117±19,98 *vs.* 165±19,99); Diastolic Blood Pressure (73±14,23 *vs.* 106±14,24) and maternal weight at booking (73± 33 *vs.* 83± 33). For all data: mean+SD; $P<0.05$. In relation to blood groups, firstly they were stratified by Rh and ABO phenotypes, separately. After that the groups were stand together

Results: No differences in blood group distribution were observed between controls and pre-eclampsia for any analysis. ($p>0.05$).

Conclusions: When we adopted stricter criteria for pre-eclampsia and a large sample from the same region we noted that the results did not show any association between blood groups and the development of pre-eclampsia.

Keywords: Hypertension, Pregnancy-Induced; ABO Blood-Group System; Rh Blood-Group System; Immunological; Prenatal Care

Introduction

The ABO and Rh-Blood Group System are genetically determined and remain the most important blood groups systems clinically [1, 2]. The presence of D antigen confers Rh positive (Rh+), and the absence, Rh negative (Rh-). Furthermore pre-eclampsia is a major contributor to maternal and perinatal morbidity and mortality worldwide [3, 4]. These conditions are related to a poor extravillious trophoblast invasion and inadequate remodeling of maternal spiral arteries [5]. The disease mechanisms are thought to be multifactorial involving immunological, genetic factors, and may be related to blood clotting cascade [6-9], and associated with thrombosis of the placental vasculature and thrombophilia [10].

Despite several studies have examined the association between ABO /Rh systems and pre-eclampsia no consensus exists in relation to the true association between pre-eclampsia and blood groups or to which specific blood group pre-eclampsia is related to, and what the magnitude of the association [11]. Dienst *et al*., was the first to suggest that isoimmunization to the A or B antigen was a cause of pre-eclampsia [12]. This finding was supported by Pike and Dickins who reported a significant excess of group O in pre-eclamptic women [13] which was not found by Clark *et al*., [14]. Also, ABO blood group has been associated with several thrombotic disease states; for instance, blood group non-O increased risk for venous thrombosis [15, 16] and ABO locus O^1 allele reduced risk for myocardial infarction [17]. Two systematic reviews and meta-analysis of studies analysing ABO blood group system in patients with pre-eclampsia was performed in 2008 and 2013. In the first one no significant association was found [11] however in the later review, the analyses revealed an association between AB blood group and pre-eclampsia [18], as reported in a large study in 2012 [19]. Also, many authors reported these associations over the last century; eventually they were related only to one allele, or even only to Rhesus group [1,20-24]. Nevertheless, the association is not seen in all studies and there are very few large population-based studies [25,26]. Finally to the best of our knowledge there are not studies presenting how pre-eclampsia and ABO/Rh systems are related in a Brazilian population. Thus the purpose of the present study was to evaluate this association in a group of pregnant women hospitalized University Hospital in Porto Alegre, Brazil -Hospital São Lucas (HSL)/PUCRS.

Methods

Pre-eclampsia was defined as high blood pressure (≥ 140/90 mmHg) accompanied by proteinuria ≥ 300 mg/24h urine, after the twentieth week of pregnancy, and Eclampsia as the presence of seizures, coma or both not related to other changes in the central nervous system during

pregnancy or postpartum in women with pre-eclampsia [27]. Maternal blood group was coded as A, B, O, AB and Rh (+/-). Our sample consisted of 10.040 pregnant women admitted to the maternity department of São Lucas Hospital between 2005 and 2010. The patients were reviewed retrospectively for inclusion. Medical records of 414 women were diagnosed as preeclampsia/eclampsia and were identified 9611 women to the control group. The patients were divided into two groups: the group with preeclampsia/eclâmpsia and the control group and their blood groups were considered. Data were analyzed using SPSS for Windows version 17.0. Continuous variables are presented as mean ± standard deviation (SD) and tested by Student's t test. Categorical data were summarized by counts and percentages, with the statistical significance evaluated by the Chi-square test. The null hypothesis was rejected when $P<0.05$.

Results

Maternal parameters were compared between control group and pre-eclampsia, respectively, Systolic Blood Pressure (117 ± 19,98 *vs.* 165 ± 19,99); Diastolic Blood Pressure (73 ± 14,23 *vs.* 106 ± 14,24); Weight at the end of pregnancy (73,4 ± 33,03 *vs.* 83,11 ± 33,08). For all data: mean+SD; $p<0.05$. In relation to blood groups, firstly we stratified by Rh (Figure Aa) and ABO (Figure Ab) phenotypes. After that we stand together both blood systems (Figure B). No differences in blood group distribution were observed between controls and pre-eclampsia ($p > 0.05$).

Discussion

The current study tried to refute reported correlation between blood groups and pre-eclampsia/eclampsia using a large cohort in a Southern Brazilian population. Previous studies that report a positive relationship between blood groups and pre-eclampsia were conducted in different countries which have different characteristics of the blood phenotypes and used different criteria do characterize pre-eclampsia. Thus this association might be investigated with conflicting results [11, 18]. For example, in Iraq, there was a significant decrease in group O type in patients with pre-eclampsia compared to healthy controls [22] and in Colombia patients with Rh(-) were eleven times more likely to develop pre-eclampsia compared with the Rh(+) factor [23]. Spinillo *et al.*, in 1995, in Italy and Hiltunen *et al.*, in 2009, in Finland indentified blood group AB as a risk factor for severe pre-eclampsia [24,28]. Also, Sezik et al., in 2002, in Turkey, showed that almost half of the patients with the blood group O Rh(-) had HELLP syndrome in a severe pre-eclampsia population [1].

In discussing some of the biometric problems involved in establishing associations between blood groups and diseases, Dr J.A. Fraser Roberts, in 1955 stresses the large number of cases

required and the importance of adopting rigid and precisely defined criteria [29]. Early studies in the fifties, who tried to demonstrate such a comparison, did not use the criterion of pre-eclampsia but considered pregnancy toxaemic or non-toxaemic, and the diagnosis of toxaemia was made by the presence of the least two of the following after 28th week of pregnancy: blood pressure ≥140/90 mmHg; clinical oedema; albuminuria not due to infection.

Then, when we adopt stricter criteria for pre-eclampsia and a large sample from the same region we note that the results showed no relationship between blood groups and the development of pre-eclampsia. Probably the association found in others studies may be related to another risk factor involved in physiopathology of the disease as obesity, cardiovascular, hypertensive disorders and/or also vascular injuries.

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References

[1] M. Sezik, H. Toyran, and E.G. Yapa, Distribution of ABO and Rh blood groups in patients with HELLP syndrome, Arch. Gynecol. Obstet. 267 (2002) 33-36.

[2] O.O. Omotade, A.A. Adeyemo, C.M. Kaiode, S.L. Falade, S. Ikpeme, Gene frequencies of ABO and Rh (D) blood group alleles in a healthy infant population in Ibadan, Nigeria, West Afr. J. Med.18 (1999) 294-297.

[3] K.S. Khan, D. Wojdyla, L. Say, A.M. Gülmezoglu, P.F. Van Look, WHO analysis of causes of maternal death: a systematic review, Lancet. 367 (2006) 1066-1074.

[4] A.V. Chobanian, G.L. Bakris, H.R. Black, W.C. Cushman, L.A. Green, J.L. Izzo Jr, D.W. Jones, B.J. Materson, S. Oparil, J.T. Wright Jr, et al, The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC-7 report, JAMA. 289 (2003) 2560-2572.

[5] I.A. Brosens, W.B. Robertson and H.G. Dixon, The role of the spiral arteries in the pathogenesis of preeclampsia, Obstet Gynecol Annu. 1 (1972) 177-191.

[6] J.I. de Vries, G.A. Dekker, P.C. Huijgens, C. Jakobs, B.M. Blomberg, H.P. van Geijn, Hyperhomocysteinaemia and protein S deficiency in complicated pregnancies, Br J Obstet Gynaecol. 104 (1997) 1248-1254.

[7] G.A. Dekker, J.I. de Vries, P.M. Doelitzsch, P.C. Huijgens, C. Jakobs, B.M. Blomberg, H.P. van Geijn, Underlying disorders associated with severe early-onset preeclampsia, Am J Obstet Gynecol. 173 (1995) 1042-1048.

[8] D.A. Clark, Cytokines and pregnancy, Curr Opin Immunol. 1 (1989) 1148-1152.

[9] M.J. Kupferminc, A. Eldor, N. Steinman, A. Many, A. Bar-Am, A. Jaffa, G. Fait, J.B. Lessing, Increased frequency of genetic thrombophilia in women with complications of pregnancy, N Engl J Med. 340 (1999) 9-13.

[10] L. Robertson, O. Wu, P. Langhorne, S. Twaddle, P. Clark, G.D. Lowe, I.D. Walker, M. Greaves, I. Brenkel, L. Regan, I.A. Greer, Thrombophilia in pregnancy: a systematic review, Br J Haematol. 132 (2006) 171-196.

[11] P. Clark and O. Wu, ABO(H) blood groups and pre-eclampsia. A systematic review and meta-analysis, Thromb Haemost. 100 (2008) 469-474.

[12] A. Dienst, Zentralbl Gynäkol. 29 (1905) 353 (as cited by Ottenberg R. The etiology of eclampsia. Historical and critical notes. JAMA 81 (1923) 295-297).

[13] L.A. Pike and A.M. Dickins, ABO Blood Groups and Toxaemia of Pregnancy, British Medical Journal. 2 (1954) 321-323.

[14] P. Clark, I.D. Walker, L. Govan, O. Wu, I.A. Greer, The GOAL study: a prospective examination of the impact of factor V Leiden and ABO(H) blood groups on haemorrhagic and thrombotic pregnancy outcomes, Br J Haematol. 140 (2008) 236-240.

[15] H. Jick, D. Slone, B. Westerholm, W.H. Inman, M.P. Vessey, S. Shapiro, G.P. Lewis, J. Worcester, Venous thromboembolic disease and ABO blood type. A cooperative study, Lancet. 1 (1969) 539-542.

[16] V.M. Morelli, M.C. De Visser, H.L. Vos, R.M. Bertina, F.R. Rosendaal, ABO blood group genotypes and the risk of venous thrombosis: effect of factor V Leiden, J Thromb Haemost. 3 (2005) 183-185.

[17] N. von Beckerath, W. Koch, J. Mehilli, O. Gorchakova, S. Braun, A. Schömig, A. Kastrati, ABO locus O1 allele and risk of myocardial infarction, Blood Coagul Fibrinolysis. 15 (2004) 61-67.

[18] P.N. Alpoim, M. de Barros Pinheiro, D.R. Junqueira, L.G. Freitas, M. das Gracas Carvalho, A.P. Fernandes, et al, Preeclampsia and ABO blood groups: a systematic review and meta-analysis, Mol Biol Rep. 40 (2013) 2253-2261

[19] B.K. Lee , Z. Zhang , A. Wikman, P.G. Lindqvist, M. Reilly, ABO and RhD blood groups

and gestational hypertensive disorders: a population-based cohort study, BJOG. 119 (2012) 1232-1237.

[20] D. May, Letter: Maternal blood group A and pre-eclampsia, Br Med J. 4(1973) 738.

[21] C. Hoff and C. Bixler, Maternofetal ABO antigenic dissimilarity and pre-eclampsia, Lancet 1 (1984) 729-730.

[22] N. Amin, S. Tahir, N. Abadi, K. Kubba, Association of blood groups with preeclamptic toxemia, Med Sci Res. 17 (1989) 861-862.

[23] A. Olaechea and H. Julián, Factor RH(-) en preeclampsia, Rev Colomb Obstet Ginecol. 42 (1991) 51-53.

[24] L.M. Hiltunen, H. Laivuori, A. Rautanen, R. Kaaja, J. Kere, T. Krusius, M. Paunio, V. Rasi, Blood group AB and factor V Leiden as risk factors for pre-eclampsia: a population-based nested case-control study, Thromb Res. 124 (2009) 167-173.

[25] E. Nurk, G.S. Tell, H. Refsum, P.M. Ueland, S.E. Vollset, Factor V Leiden, pregnancy complications and adverse outcomes: the Hordaland Homocysteine Study, QJM. 99 (2006) 289-298.

[26] E.R. Morrison, Z.H. Miedzybrodzka, D.M. Campbell, N.E. Haites, B.J. Wilson, M.S. Watson, M. Greaves, M.A. Vickers, Prothrombotic genotypes are not associated with pre-eclampsia and gestational hypertension: results from a large population-based study and systematic review, Thromb Haemost. 87 (2002) 779-785.

[27] Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 183 (2000) S1-S22.

[28] A. Spinillo, E. Capuzzo, F. Baltaro, G. Piazzi, A. Iasci, Case-control study of maternal blood group and severe pre-eclampsia, J Hum Hypertens. 9 (1995) 623-625.

[29] J.A. Roberts, Discussion on the ABO blood group and disease, Proc R Soc Med. 48 (1955) 143-144.