ISSN:2321-1156

International Journal of Innovative Research in Technology & Science(IJIRTS)

Association Of Maternal ABO Blood Group And Hypertensive Disorders Of Pregnancy

***Dr Sangeeta Mishra**, ****Dr Prasanna Pradhan**,
*Dept of Obstetrics & Gynaecology **Dept. of Pharmacology, VSS Medical College,Burla,Odisha-768017,

Abstract

Objective: To examine the association between ABO blood groups and hypertensive disorders of pregnancy.

Material & Methods: We designed a prospective observational study and risks of hypertensive disorders of pregnancy including pre-eclampsia, and eclampsia were estimated by relative risks for maternal ABO blood group. Using blood group O as a reference, relative risk ratios of hypertensive disorders of pregnancy(Gestational HTN+ pre-eclampsia, and eclampsia) were obtained .A total 4953 singleton pregnant women were recruited over a period of 5 months who had ABO blood testing and follow-up care until delivery in our institution. Outcomes that were studied in relation to maternal blood group included preeclampsia, eclampsia & gestational HTN. The study was duly approved by the institutional ethical committee and appropriate consent was taken from the subjects recruited before they were assigned for the study.

Result: Out of 4953 women, 831 (16.77%),women were diagnosed with Hypertensive disorders of pregnancy. Women with A or AB blood types, but not B, were found at increased risk of Hypertensive disorders of pregnancy compared with O type individuals; relative risk and adjusted relative risks were calculated. Blood group A was found to be highest risk association 2.02 (95% confidence interval (CI), 1.7 to 2.38; P<0.0001) as compared to others. Compared with blood group O, A blood type groups had statistically significant association with hypertensive disorders of pregnancy.

Conclusion: Except one and two nonspecific studies we didn't find any literature regarding the association of risk of ABO phenotype with hypertensive disorders of pregnancy. We found blood group A has the highest risks of hypertensive disorders of pregnancy. This finding may help improve our understanding of the etiology of Hypertensive disorders of pregnancy, which can help to predict the prognosis and decide the management guidelines.

Key word: ABO group, hypertensive disorders,pregnancy,preeclampsia,eclampsia

Introduction

The hypertensive disorders of pregnancy are the leading cause of maternal and perinatal mortality and morbidity internationally[1] Preeclampsia is a severe complication of human pregnancy with overall incidence of 2–10% [2]. It is one of the leading causes of maternal, as well as perinatal morbidity and mortality worldwide. Despite intensive research efforts, the etiology and pathogenesis of preeclampsia are not fully understood. A large number of evidence suggests that an excessive maternal systemic inflammatory response to pregnancy with activation of endothelial cells plays a crucial role in the pathogenesis of the disease[3].

The development of preeclampsia is multifactorial & influenced by both genetic and environmental risk factors.[4] As far as blood group as a factor is concerned, it is exclusively and integrally heritable, genetically determined at conception and remain fixed for life, hence its frequency distribution follows a known pattern governed by gene transmission from generation to generation and varies with the race and geographical distribution of human being[5]. The ABO blood type, an easily accessible factor in patient's genetic make-up has been associated with many diseases[6].

Recent GWAS(Genome-Wide Association studies) have confirmed ABO as a locus for venous thromboembolism (VTE), myocardial infarction (MI), and multiple cardiovascular biomarkers. These studies have shown that carriers of single nucleotide polymorphisms (SNPs) that mark non-O blood group types have higher levels of plasma VWF when compared to O individuals.[7] Similarly, VWF gene is associated with the development and the severity of preeclampsia, and may be a susceptibility factor for preeclampsia[8] According to some studies there is an association between the ABO blood group and DBP.[9] Von Willebrand factor, found higher in non-O (A, B, and AB) compared with O type individuals.[10] VWF may promote platelet aggregation/ adhesion and atheroma leading to endothelial dysfunction, which is known to be involved in the pathogenesis of preeclampsia. Some inflammatory markers, like TNF-alpha and soluble ICAM-1 are upregulated by single nucleotide polymorphism rs651007 at the ABO locus, especially with the 'A' allele.[11,12] As previously mentioned, VWF gene is associated with the development and the severity of preeclampsia.[8] Also

different studies support the association between the ABO blood group system in BP variation.[9] Evidence also suggest association between the ABO blood group and blood pressure among ≥42,000 Belgian men.[13] Kark et al. found there is an association between the ABO blood group A antigen and elevated BP among Males.[14]

Above studies indicate their might be a cross talk between ABO antigen driven mechanism and mechanisms involved in the development of hypertension in hypercoagulable state. So we hypothesize that, is there any relationship between maternal ABO system with development of hypertensive disorder state of pregnancy?

Patients and method

We performed a prospective analysis of all consecutive pregnant women who attended our antenatal clinic between Nov 2012 and Sept 2013. A total of 4953 patients were recruited over a period of 5 months .Inclusion criteria were singleton pregnancies who sought their first antenatal care at GA12 weeks, and who underwent ABO blood typing along with other basic antenatal care laboratory investigations in our institution. Only Pts belonging to places within 100 km radius from the study area with complete address and contact details were included.But those, who had known underlying disease or condition that could affect the pregnancy outcomes (i.e. chronic hypertension, overt diabetes, renal or collagen vascular disease, hyperthyroidism, smoking or congenital fetal anomalies), Rh-negative blood type and incomplete clinical data and history are excluded from the study.

Data were collected regarding maternal age, parity, body mass index at first visit, ABO blood group, GA at delivery, route of delivery, neonatal birth weight and adverse pregnancy outcomes. ABO blood group was determined by a standard blood group serology analysis. Proteinuria estimated by using dipstick method. Blood samples were obtained from all patients (1 ml from each). The samples were tested immediately following collection. Hb, TPC,DC, TLC, BT,CT other routine investigation like LFT,RFT, Sr.Uric acid , Sr Na+,K+ , RBS/FBS were carried out at RDC in our college.

Evaluation of hypertensive disorder of pregnancy: The Working Group classification of hypertensive disorders complicating pregnancy [15] was used.

Gestational hypertension

- Systolic BP ≥140 or diastolic BP ≥90 mm Hg for first time during pregnancy
- No proteinuria
- BP returns to normal before 12 weeks postpartum
- Final diagnosis made only postpartum

Preeclampsia

- BP ≥140/90 mm Hg after 20 weeks' gestation
- Proteinuria ≥300 mg/24 hours or ≥1+ dipstick

Eclampsia syndrome: Seizures that cannot be attributed to other causes in a woman with preeclampsia Study protocol was approved by Institutional ethics committee for human. Informed consent was taken from each patient.

Statistical Analysis:

Due to absence of both A and B antigens, O blood type was used as the reference group. The relative risks (RRs) and Adjusted relative risk with 95% confidence intervals (CIs) of the Hypertensive disorders of pregnancy in A, B and AB blood were calculated. P-value <0.05 was considered statistically significant.

Results

We investigated a total sample of 4953 after adjusting dropout rate to initial sample size. The population of different blood group types represent the national population standard after excluding Rh negative blood types. As shown in Table-1,Out of total 4953 samples blood group O represent 38% , A,B&AB represent 23%,32% &7% respectively. As O blood groups are not exposed to any of the A & B antigen that was taken as control. Incidence and Relative risk of exposed group A,B &AB were compared with control and intergroup comparison along with their relative risk were calculated accordingly.

Table-1-Total sample size and patient taken

Table-1		
Blood Group	**Sample size at the start**	**Drop-out adjusted sample**
A (Exposed gr. antigen A)	1025	1139 (23%)
B (Exposed gr. antigen B)	1426	1585 (32%)
AB(Exposed Antigen A& B)	312	347 (7%)
O (Unexposed control)	1694	1882 (38%)
Total	4457	4953 (100%)

In this study we found a total number of 831 cases positive for hypertensive disorder of pregnancy. Surprisingly we found a higher number (213/527) of Gestational hypertension cases in blood group O population(Table-2). On the contrary we found a higher incidence of preeclampsia and eclampsia cases in A type individuals. Another study is required to justify this association .But as opposed to above finding the overall incidence rate of Hypertensive disorder of pregnancy cases are highest (349/1139) in A type individuals as compared to (285/1882) O blood group population.

Table-2.Total no of patients in different blood group

Table-2					
	A	**B**	**AB**	**O**	**Total**
GH	156	124	34	213	527
Preeclampsia	162	28	4	44	238
Eclampsia	31	7	0	28	66
Total	349	159	38	285	831

We calculated a total incidence per thousand of population for the positive cases in each group. As per Table-3, the incidence of hypertensive disorders are highest (306.4) in A type individuals as compared to other groups. Incidence among the control was found to be only 151.4. (Chart-1)

Chart-1-Incidence among exposed and non-exposed

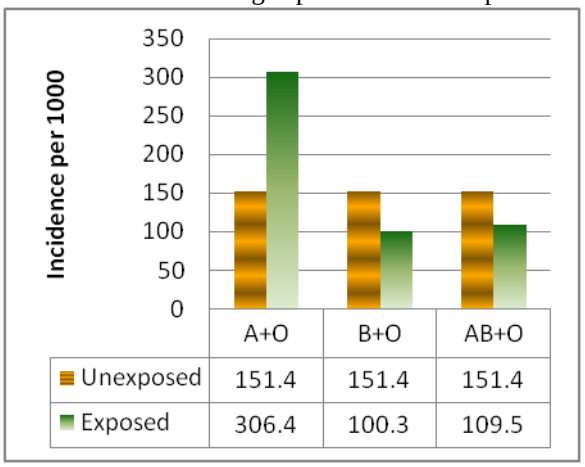

Table-3 Incidence among different groups and RR

Table-3						
Group	**Exposure**	**Population**	**Disease developed**	**Incidence/ 1000**	**Relative Risk**	**Confidence interval**
A	Yes (A)	1139	349	306.4	2.02 P≤ 0.0001	1.76-2.38
	No (O)	1882	285	151.4		
B	Yes (B)	1585	159	100.3	0.66 P≤ 0.0001	0.55-0.79
	No (O)	1882	285	151.4		
AB	Yes (AB)	347	38	109.5	0.723 P=0.0461	0.52-0.994

Similarly relative risk was calculated for all exposed group. We found a relative risk of 2.02 (P≤0.0001,CI: 1.76-2.38) for A as compared to control. The relative risks of B 0.66 (P≤0.0001, CI: 0.55-0.79) and AB was 0.723 (P=0.0461,CI: 0.52-0.994) .It signifies there is risk association of 102% of hypertensive disorders in pregnant woman when they are exposed to A type antigen as compared to other groups.(Table-4)

Table-4

Table-4				
	A	**B**	**AB**	**O**
RR as compared to unexposed	2.02	0.693	0.723	-
	P ≤0.0001	P≤ 0.0001	P=0.0461	-

We also calculated the intergroup relative risk A as compared to B and AB before and after the adjusting the population. We calculated the adjusted relative risk applying the incidence rate of unadjusted individual population to adjusted population. (Table-5)

Table-5			
Incidence among unadjusted population			
Exposure group	**population**	**Total positive cases**	**% of positive cases**
A+O	3021	634	20.98
B+O	3467	444	12.8
AB+O	2229	323	14.49
Incidence among adjusted population			
Exposure group	**Population**	**Total positive cases**	**% of positive cases**
A+O	2476(1238+1238)	566	22.85
B+O	2476(1238+1238)	311	12.56
AB+O	2476(1238+1238)	322	13

Population A was found to be an increased association risk (RR=1.63,ARR=1.81) with hypertensive disorders of pregnancy as compared to B ,also A type population has increased association risk(RR=1.44,ARR=1.75) as compared to B. We didn't find a significant association of AB as compared to B. (Table-6)

Table-6- Adjusted and un adjusted relative risk

Table-6		
Relative risk	**Unadjusted**	**Adjusted**
A to B	1.6387(P ≤0.0001)	1.81(P ≤0.0001)
AB to B	1.13(P=0.06)	1.03(P=0.63)
A to AB	1.44(P ≤0.0001)	1.75(P ≤0.0001)

In summary the risk of association with A type individual with hypertensive disorders of pregnancy is highly significant both as compared to unexposed group($P \leq 0.0001$) and B group population ($P \leq 0.0001$).B and AB group population are significantly ($P \leq 0.0001$) not associated with hypertensive disorders of pregnancy as compared to unexposed whereas there is no significant association of AB (P=0.06,0.63) as compared to B in both unadjusted and adjusted group of population.

Discussion & Conclusion

We found a direct association of degree of RR with hypertensive disorders of pregnancy in A blood groups. Although we found that A blood type is significantly associated with hypertensive disorders of pregnancy; however, the incidence of Gestational hypertension are maximum with O blood groups whereas incidence of preeclampsia and eclampsia are highest seen in A type individuals. Knowing the risk of specific type blood groups with hypertensive disorders may be clinically useful because it may play preventive and curative role in maternal and neonatal prognosis as well as pregnancy management.

Out of several hypotheses for the observed relationship between ABO blood types and preeclampsia, one mechanism may be due to an effect of von Willebrand factor, which was found higher in non-O (A, B, and AB) compared with O type individuals.10 Evidence suggests that von Willebrand factor can promote platelet aggregation/ adhesion and atherosis formation leading to endothelial dysfunction, which is known to be involved in the pathogenesis of preeclampsia.16,17 Other mechanisms may also get involved. But in our study, we found only an increased risk of hypertensive disorders of pregnancy in women with A blood types, but not B and AB type pregnancies. Some inflammatory markers, like tumor necrosis factor-alpha and soluble intercellular adhesion molecule 1 were identified to be upregulated at the ABO locus through polymorphism, especially with the A allele.11,12 As these markers are associated with preeclampsia,18,19 we can say this can be one possible mechanism.

Findings from this study, support the hypothesis that genetic factors related to the distribution of some blood groups may play a role in the development of hypertensive disorder of pregnancy. A significant association was found between the ABO blood group and hypertensive disorder of pregnancy. We observed women with A blood types have significantly higher risk (63%-81%) of hypertensive disorder of pregnancy as compared to 'B' type individuals & 102% Increased risk as compared to O individuals. Women with A blood types, but not B & AB, has significantly higher risk of hypertensive disorder of pregnancy as compared to O type individuals.

Several studies have described the associations between particular ABO phenotypes and pregnancy complications. In a study on British women with A blood type researchers found 2.7 fold risk of preeclampsia compared with O type individuals.20 Similarly other studies found an increased risk of preeclampsia by 2.1- to 3.1-folds in Italian and Finnish gravidas with AB blood type compared with O type women.21,22

In our study, we found that A blood type is significantly associated with hypertensive disorders of pregnancy; however, the incidence of Gestational hypertension are maximum with O blood groups whereas incidence of preeclampsia and eclampsia are highest seen in A type individuals. But the role of blood groups in hypertensive disorders of pregnancy cannot be concluded without a proper investigation of paternal blood group and its association. Also we didn't adjust the age sex and parity which may be the potential confounders. As a preliminary study we found a potential association which needs to be further investigated along with the paternal blood group and the pathogenesis mechanisms that leads to development of Hypertensive disorders of pregnancy.

Acknowledgments

We are thankful to Dr Nihar ranjan Mishra & Dr Pravat Mallik who helped us to collect the follow up data by coordinating ASHA,ANM,MPHW other local volunteers.We are also thankful to professors &unit heads of Obs & Gynaec dept. who helped us in patient recruitment.

References

[1] Roberts JM, Pearson G, Cutler J, Lindheimer M. Summary of the NHLBI Working Group on Research on Hypertension During Pregnancy. Hypertension 2003;41:437-45

[2] Duckitt K, Harrington D. Risk factors for preeclampsia at antenatal booking: systematic review of controlled studies. Br Med J 2005; 330: 565.

[3] Redman CW, Sacks GP, Sargent IL. Preeclampsia: an excessive maternal inflammatory response to pregnancy. Am J Obstet Gynecol 1999; 180: 499–506.

[4] Roberts JM, Gammill HS. Preeclampsia: recent insights. Hypertension 2005; 46: 1243–1249.

[5] Mourant A.E., Kopec A.C. and Domaniewska-Sobczak K., Blood groups and diseases, Oxford University Press, Oxford **(1978)**

[6] Dave V.P., Kaul D. and Sharma Y.P. Significance of blood cellular lxr-_ gene aberration in coronary

heart disease subjects, *Res J Recent Sci*, **1(1),** 69-72 **(2012)**

[7] M. Campos, W. Sun, F. Yu et al., "Genetic determinants of plasma vonWillebrand factor antigen levels: a target gene SNP and haplotype analysis of ARIC cohort," *Blood*, vol. 117, no. 19, pp. 5224–5230, 2011

[8] Sun C,Chen Y,Zhang W,Yu S. Association between von Willebrand factor gene polymorphism and preeclampsia: Journal of Perinatal Medicine. Volume 37, Issue 1, Pages 36–42.(2008)

[9] Namesure B,Wu S Y,Hennis A,Leske M C. Hypertension, type 2 diabetes, and blood groups in a population of African ancestry: Ethnicity & Disease, Volume 16, Autumn 16(4). pg 822-829. (2006.)

[10] Jenkins PV, O'Donnell JS. ABO blood group de termines plasma von Willebrand factor levels: a biological function after all? Tranfusion 2006; 46: 1836–1844

[11] Qi L, Cornelis MC, Kraft P, Jensen M, van Dam RM, Sun Q et al. Genetic variants in ABO blood group region, plasma soluble E-selectin levels and risk of type 2 diabetes. Hum Mol Genet 2010; 19: 1856–1862.

[12] Pare´ G, Chasman DI, Kellogg M, Zee RY, Rifai N, Badola S et al. Novel association of ABO histo-blood group antigen with soluble ICAM-1: results of a genome-wide association study of 6578 women. PLoS Genet 2008; 4: e1000118

[13] Kesteloot H, Van Houte O. An epidemiologic survey of arterial blood pressure in a large male population group. Am J Epidemiol. 1974; 99:14–29.

[14] Kark JD, Friedlander Y. ABO and Rh bloodgroups and blood pressure in Jerusalem 17 year olds. Hum Biol. 1984;56:759–769**.**

[15] Williams Obstetrics.23rd Edition;Section VII:Chapter 34-15

[16] Nadar SK, Al Yemeni E, Blann AD, Lip GY. Thrombomodulin, von Willebrand factorand E-selectin as plasma markers of endothelial damage/dysfunction and activation in pregnancy induced hypertension. Thromb Res 2004; 113: 123–128

[17] Parra-Cordero M, Bosco C, Gonza´lez J, Gutie´rrez R, Barja P, Rodrigo R. Immunohistochemical expression of von Willebrand factor in the preeclamptic placenta. J Mol Histol 2011; 42: 459–465.

[18] Vitoratos N, Economou E, Iavazzo C, Panoulis K, Creatsas G. Maternal serum levels of TNF-alpha and IL-6 long after delivery in preeclamptic and normotensive pregnant women. Mediators Inflamm 2010; 2010: 908649.

[19] Szarka A, Rigo´ Jr J, La´za´r L, Beko G, Molvarec A. Circulating cytokines, chemokines and adhesion molecules in normal pregnancy and preeclampsia determined by multiplex suspension assay. BMC Immunol 2010; 11: 59.

[20] May D. Letter: maternal blood group A and pre-eclampsia. Br Med J 1973; 4: 738.

[21] Hiltunen LM, Laivuori H, Rautanen A, Kaaja R, Kere J, Krusius T et al. Blood group AB and factor V Leiden as risk factors for pre-eclampsia: a population-based nested casecontrol study. Thromb Res 2009; 124: 167–173

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