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Research Article

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The relationship between fetal ABO and Rhesus blood groups and the development of pre-eclampsia: a retrospective case control study

Abstract

Objective: The objective was to study the relationship between fetal ABO and Rhesus blood groups and the development of pre-eclampsia (PE).

Study design: This was a retrospective case control study conducted in a large public healthcare provider in Doha, Qatar. The study group consisted of 254 consecutive pregnancies with the diagnosis of PE, from the cohort of more than 18000 deliveries conducted in 2014. The control group consisted of 500 consecutive uncomplicated deliveries in the same year. Patient demographic data, maternal and fetal bloods types were collected from patient electronic medical records. Comparative analysis was done using Chi Square, Student t and Mann-Whitney tests, as applicable. The main outcome measure was the percentage of fetal ABO and Rhesus groups in the study and control groups. The secondary outcomes looked at were the distribution of maternal ABO and Rhesus groups among the groups, and the effect of maternal-fetal blood type interrelationship on the occurrence of PE.

Results: There was no significant association noted between fetal blood groups and PE. More women in the PE group were Rhesus negative (5.9% vs 2.2% OR:2.8, 95% CI: 1.3-6.2, p=0.011). In the PE group, mothers who were Rhesus negative were found more likely to have Rhesus positive fetuses (OR:13.33, 95% CI: 1.32 to 134.6, p=0.0281). There was a decrease in PE with maternal group B and fetal group O (OR:0.3, 95% CI: 0.11-0.84, p=0.021) and an increase in PE with maternal group O and the fetal group O (OR:1.73, 95% CI: 1.05-2.85, p=0.031).

Conclusion: No association has been found between fetal blood group and PE; however maternal-fetal Rhesus and ABO disparity seems to affect the incidence of PE, particularly a Rhesus negative woman with a Rhesus positive fetus. There is a need for larger prospective studies to confirm an association.

Keywords: pre-eclampsia, maternal blood group, fetal blood group

Volume 15 Issue 6 - 2024

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Received: November 28, 2024 | **Published:** December 12, 2024

Introduction

Preeclampsia (PE), a multi-system hypertensive disorder of pregnancy, has been one of the most challenging enigmas persisting in modern obstetrics. Despite being identified centuries ago and known to affect up to 8% of pregnancies worldwide, the pathogenesis, diagnosis and screening of PE all remain poorly understood and controversial.[1,2] This is problematic as it continues to be one of the leading causes of maternal and neonatal morbidity and mortality. Various risk assessment approaches include identification of well-known maternal risk factors like age, body mass index (BMI), parity, multiple pregnancy, ethnicity, low socioeconomic status, personal and family history of PE, thrombophilia, and preexisting conditions; hypertension, diabetes and chronic kidney disease, and recommended screening tests like routine blood pressure monitoring at all antenatal visits.[3] However, an ideal combination of cost effective predictive markers that can be used for routine screening is yet to be devised.

Apart from the immunological and hematological implications, the major blood group systems of ABO and Rhesus (Rh) have been studied extensively in medicine for susceptibilities to various cardiovascular diseases and malignancies. This is because these antigens are not only present on the surface of red blood cells, but also on various other tissues in the body like sensory neurons, vascular epithelium, and platelets, which could explain the involvement of these antigens in the pathology of these diseases.[4] The association between maternal ABO/Rhesus blood groups and PE has been studied before with inconclusive results. A systematic review in 2008 of 17 studies showed no clear association between maternal ABO blood group and the development of PE.[5] However, a large cohort study conducted in Sweden in 2012 showed that woman with AB group and who are Rh positive have a higher risk for PE,[6] which was similar finding to an observational study in Turkey in 2016.[7]

The relationship between fetal ABO/Rh blood groups and PE has not been studied and similarly the maternal-fetal blood group interrelationship has not been studied.

In this study, we aim to look at the association between maternal and fetal ABO and Rh blood groups and development of PE. We also aim to determine the association between maternal- fetal blood group interrelationships with the development of PE.

Patients and methods

Study design and setting

This was a retrospective case control study conducted in Women's Wellness and Research Centre, Hamad Medical Corporation (HMC), which is the principle public healthcare provider in the State of Qatar.

The hospital delivers 85% of the live births in the country and in the study period, from January 2014 till December 2014, there were more than 18,000 deliveries. The hospital health information management department (medical records) has a computerized database of all patient files with postnatal discharge diagnoses coded based on International Classification of Diseases, 10th edition, clinical modification (ICD-10-CM), which was used to select the study population. Approval was obtained from the HMC Institutional Review Board (IRB) and the Research Strategy and Assurance committee and the study was conducted in compliance with the ICH good clinical practice guidelines.

The study group of 254 consecutive pregnancies with a postnatal discharge diagnosis of preeclampsia (PE), was selected using ICD-10 codes for PE, including unspecified, moderate to severe PE, HELLP syndrome, and eclampsia (codes O140, O141, O142, O149, O151 and O152), from the cohort of more than 18000 deliveries conducted during the study period. The control group constituted 500 consecutive uncomplicated singleton deliveries (codes O80 and Z37), not coded for any other diagnoses.

The individual patient electronic medical records (EMR) was accessed using unique patient health card (HC) numbers and demographic data including age, body mass index (BMI), parity, nationality was recorded from the antenatal summaries of each pregnancy. The delivery records were accessed to record the gender of the baby and birth weight. The maternal ABO and Rhesus groups were recorded from the blood bank reports of blood grouping performed at the booking visit. Similarly, the neonatal blood group was obtained from the baby's file using the mother-baby link feature of the EMR, this blood group being determined from cord blood samples. The maternal and neonatal blood groups were classified as A, B, AB or O, and Rhesus positive or negative.

Data collection spreadsheets were completed, and the access was restricted to the study investigators. Patient identifiable data were not saved in the spreadsheet. There was no direct patient or public involvement in this study as this was a retrospective data review. A core outcome set (COS) has not been used as the development of COS for hypertensive disease in pregnancies is currently on going.

The data analysis was done using SPSS version 25 for Windows (IBM, SPSS Statistics, Chicago IL, USA). Descriptive statistics including frequencies, percentages, mean and standard deviation was used to describe the demographic variables. Comparisons between the PE and the control group were done using Chi Square, Student t-test and Mann-Whitney test as applicable. Univariate analysis was done for each variable to determine crude odds ratio with 95% confidence intervals. Logistic regression models were applied to account for confounding factors of age, BMI, parity and nationality when significant difference was found in the univariate analysis, to determine the adjusted odds ratio. A p value of < 0.05 was set to denote statistical significance.

Results

The comparison of the demographic variables of the 254 women in the PE group and the 500 women in the control group is as shown in Table 1. More than half of the women in either group were aged between 26 and 35 years, with older women found significantly more in the PE group (23% vs 7%, OR: 3.9, 95% CI: 2.5-6.1, p=0.0001). Significantly more women in the PE group were nulliparous (38.6% vs 25.8%, OR: 1.8, 95% CI: 1.3-2.5, p=0.0003) and with a BMI of 30 and above (60.2% vs 35.8%, OR: 2.7, 95% CI: 1.9-3.7, p=0.0001) when compared to the control group. There was a significant difference noted in the distribution of the women according to their country of origin, with more African and Phillippino mothers in the PE group.

There was no significant difference noted in the distribution of fetal ABO and Rhesus groups among the PE and control groups. Most women in both groups had O blood group, followed by A, B, and finally AB group. However, there was no difference noted in the distribution of maternal ABO blood groups, except for O group found to be more in the PE group (50.4% vs 42.8%, p=0.047). Most women in both groups were Rhesus positive (more than 90%). However, here a significant difference between the groups was noted, with more women in the PE group being Rhesus negative (5.9% vs 2.2% OR: 2.8, 95% CI: 1.3-6.2, p=0.011). This difference remained significant after adjusting for confounding factors such as age, BMI, parity and nationality with adjusted OR=2.7, 95% CI: 1.1-6.8, p=0.03.

Cross tabulations of maternal ABO with neonatal ABO and maternal Rhesus with neonatal Rhesus groups were done to look for any further associations, as shown in Table 2. Although the numbers are small, in the PE group, mothers who were Rhesus negative were found more likely to give birth to Rhesus positive neonates when compared to the control group (OR:13.33, 95% CI: 1.32 to 134.6, p=0.0281). Alternately, where the mother is Rhesus positive, no difference was noted in the distribution of neonatal Rhesus groups among the PE and control groups.

Table 1 Demographics in each group with crude Odds Ratio

Variable		PE (N=254)		Control (N=500)		P value	Odd Ratio (95%CI) [Control as reference]
		n	%N	n	%N		
Age groups (yrs)	≤25	54	21.3	180	36	0.0001	0.5(0.3-0.7)
	26-35	141	55.5	284	56.8	NS	
	≥36	59	23.2	36	7.2	0.0001	3.9(2.5-6.1)
Parity	0	98	38.6	129	25.8	0.0003	1.8(1.3-2.5)
	1-3	121	47.6	287	57.4	0.01	
	≥4	35	13.8	84	16.8	NS	
BMI (kg/m2)	≥30	153	60.2	179	35.8	0.0001	2.7(1.9-3.7)
	<30	101	39.8	321	64.2		
Nationality	Qatari	76	29.9	120	24	NS	
	Arab	57	22.4	219	43.8	0.0001	0.23(0.2-0.3)
	Non-Arab	53	20.8	98	19.6	NS	
	Africans	23	9.1	25	5	0.033	1.9(1.1-3.4)
	Philipino	45	17.7	38	7.6	0.0001	2.8(1.7-4.4)

Citation: Minisha F, Deniz M, Abreo M, et al. The relationship between fetal ABO and Rhesus blood groups and the development of pre-eclampsia: a retrospective case control study. *Obstet Gynecol Int J.* 2024;15(6):301–305. DOI: 10.15406/ogij.2024.15.00775

Table 1 Continued...

Variable		PE (N=254)		Control (N=500)		P value	Odd Ratio (95%CI) [Control as reference]
		n	%N	n	%N		
Mother ABO group	A	61	24	150	30	NS	
	B	50	19.7	110	22	NS	
	AB	15	5.9	26	5.2	NS	
	O	128	50.4	214	42.8	0.047	
Mother Rhesus group	Negative	15	5.9	11	2.2	0.011	2.8(1.3-6.2)*
	Positive	239	94.1	489	97.8		
Baby Rhesus group	Positive	222	87.4	456	91.2	NS	
	Negative	21	8.2	42	8.4		
Baby ABO group	A	63	24.8	140	28	NS	
	B	52	20.4	114	22.8	NS	
	AB	13	5.1	31	6.2	NS	
	O	115	45.2	213	42.6	NS	

Significant p value <0.05, NS: not significant

*Corrected Odds Ratio (corrected for age, BMI, parity, and nationality): 2.7(1.1-6.8), p=0.03

Table 2 Cross tabulation between mother Rh and ABO blood group with fetal blood group

Variable	PET	Control	Total	OR (95%CI) [Reference Control]	P value
Mother Rh negative					
Baby Rh positive	8	1	9	13.33 (1.32 to 134.6)	0.0281
Baby Rh negative	6	10	16		
Total	14	11	25		
Mother Rh positive					
Baby Rh positive	214	455	669	1.003(0.53 to 1.89)	0.99
Baby Rh negative	15	32	47		
Total	229	487	716		
Mother A group					
Baby A group	33	78	111	1.087 (Vs Non A)	0.782
Baby B group	3	13	16	0.564 (Vs Non B)	0.386
Baby AB group	6	13	19	1.19 (Vs Non AB)	0.734
Baby O group	17	46	63	0.915 (Vs Non O)	0.7928
Total	59	150	209		
Mother B group					
Baby A group	7	10	17	1.75 (Vs Non A)	0.288
Baby B group	30	57	87	1.64 (Vs Non B)	0.16
Baby AB group	5	12	17	0.97 (Vs Non AB)	0.96
Baby O group	5	31	36	0.3 (Vs Non O)	0.021
Total	47	110	157		
Mother AB group					
Baby A group	4	9	13	0.75 (Vs Non A)	0.69
Baby B group	8	11	19	1.81 (Vs Non B)	0.37
Baby AB group	2	6	8	0.55 (Vs Non AB)	0.51
Total	14	26	40		
Mother O group					
Baby A group	19	43	62	0.72 (Vs Non A)	0.27
Baby B group	11	33	44	0.53 (Vs Non B)	0.087
Baby O group	93	136	229	1.73 (Vs Non O)	0.031
Total	123	212	335		

Significance p<0.05

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There was a significant decrease in PE when the mother was group B and the fetus group O (OR: 0.3, 95% CI: 0.11-0.84, p=0.021) and a significant increase in PE when the mother was group O and the fetus group O (OR: 1.73, 95% CI: 1.05-2.85, p=0.031).

Discussion

This is the first study to investigate the possible association between fetal ABO and Rhesus group with development of PE. In this cohort of women, there was no significant link between fetal blood groups and PE. The effect of maternal - fetal blood group interrelationships on PE was also studied by cross-tabulating the maternal and fetal blood groups. The mothers with Rhesus negative blood group giving birth to Rhesus positive babies were 13 times more likely to be in PE group, however with a large confidence interval. Since the numbers were small, the adjusted odds ratios was not calculated, and this paves the way for further large prospective studies.

There are various studies that aim to identify women at moderate to high risk for PE by classifying various past and present risk factors, so that measures such as close monitoring and administration of anti-platelet agents can be initiated at an early stage in pregnancy. This study shows that various factors like advanced maternal age, high BMI, and nulliparity are more in the PE groups, findings that are similar to the findings of a systematic review and meta-analysis including 92 cohort studies and 25 million pregnancies over 15 years.[8] It is also noted that there is an increased number of women from Africa and Philippines in the PE group. This variation in PE according to maternal country of origin has been previously demonstrated in studies from the UK and Canada, showing similar increased incidence in women coming from Sub-Saharan Africa and the Philippines.[9,10]

The association between maternal ABO blood groups and PE has been studied over the years, with varying results. In 2008, a review, of 17 studies examining the association between ABO groups and PE was conducted. This showed no consistent link between maternal AB blood type and PE, as reported previously. On comparing group O with all non-O groups, a similar result was obtained; hence the conclusion was that there is no clear link between maternal ABO blood types and PE.[5] A review and meta-analysis of 2 original studies in 2013, however, showed a possible link between maternal AB group and PE.[11] In 2016, a meta-analysis of 9 case-control and cohort studies, showed an association between non -O blood group and the development of PE. This was particularly higher for women with AB blood group, with OR=1.94; 95% CI= 1.2-3.3.[12]

This inconsistency is reflected in our study as well. We had a significant increase in maternal O blood group in PE group compared to the control group, which contrasts with the results of the reviews and analyses published previously. The distribution of all the other ABO groups was similar in both groups.

In comparison, there are fewer studies looking into the association between Rhesus and PE. A large cohort study of almost 650,000 pregnant women of Sweden performed in 2012, showed maternal group AB had the highest risk for PE (OR=1.10, 95% CI 1.04–1.16) and Rhesus positive mothers with an increased risk for PE (OR=1.07, 95% CI 1.03–1.10).[6] A retrospective analysis in Brazil analyzed maternal Rhesus group as a risk factor for PE and found no significant difference between the PE and control group.[13] A study from Turkey performed in 2016 showed an increased risk of developing essential hypertension after preeclampsia in patients who were Rhesus positive.[7]

This study finds that maternal Rhesus negative group increases the odds of developing PE by 2.8, which remained significant after adjusting for confounding factors such as age, parity, BMI and nationality. Furthermore this risk was added to it if the fetus was Rhesus positive. The small number of Rhesus negative women in each group makes it necessary to confirm these findings with larger prospective studies.

This study was conducted in a tertiary care hospital caring for the needs of women in Qatar, handling 85% of the total nationwide deliveries. Maternal and fetal blood group analyses are routine tests offered to every pregnant woman and neonate. To the best of our knowledge, it's the first study to look into the association between fetal blood groups and PE, and the effect of maternal-fetal blood group interrelationships. Various studies demonstrate the effect of ABO blood group system on blood circulation and in turn placental circulation, the abnormality of which is thought to be the cause for PE. In this study the aim was to investigate if maternal-fetal ABO and Rhesus disparity can influence the incidence of PE. However, being a retrospective study, there are some limitations including the numbers in each group and unavailability of various confounding factors such as a history of PE, concurrent medical illnesses, presence of antiphospholipid syndrome etc. that have shown to be predictive for PE. There is a requirement for larger prospective studies that can consider most of the potential confounding factors and confirm the results of our study.

Conclusion

Maternal blood group antigens have been implicated in adverse outcomes in pregnancy, including thromboembolism, fetal growth restriction and preeclampsia without any conclusive results. This study shows an increase in the incidence of PE with maternal O blood group and Rhesus negative. No association has been found between fetal blood groups and PE; however maternal-fetal Rhesus and ABO disparity seems to affect the incidence of PE, particularly a Rhesus negative woman with a Rhesus positive fetus. There is a need for larger prospective studies to prove this association.

Acknowledgments

The authors thank the Medical Research Centre, Hamad Medical Corporation, for the help with data extraction.

Contribution to authorship

MD, MA, NK and SL co-designed the study and applied for ethical exemption. FM, MD and SL collected the data, assisted with the data analysis, data interpretation and preparation of the manuscript. FM, MD, SL, NK and MA reviewed and approved the final manuscript.

Details of ethics approval

The study was approved by the institutional review board and the research strategy and assurance committee. As data used for analysis were anonymized, exemption from formal ethical approval was granted from the Medical Research Centre, Hamad Medical Corporation, Doha, Qatar, and was conducted in compliance with the ICH good clinical practice guidelines.

Funding

No funding was received for performing this study.

Conflicts of interest

The authors have no conflict of interests to declare. The completed disclosure of interests form is available to view online as supporting information.

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