Maternal ABO Phenotype as a Predictive Factor for Pregnancy Complications Related to Prematurity

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Abstract: *Objective:* The ABO blood types are associated with cancers, cardiovascular disease, and Type 2 diabetes in adult males and females. Associations of ABO blood type and adverse pregnancy outcomes have not been extensively studied. The purpose of this study was to investigate the relationship with ABO blood groups and risk of adverse pregnancy outcomes contributing to premature birth.

Study design: Data on ABO phenotypes and pregnancy outcomes were collected from the medical records of 1,462 premature infants (22-34 weeks). Adverse pregnancy outcomes that were studied in relation to maternal blood type included gestational hypertension (GHTN), preeclampsia (PREE), chorioamnionitis (CA), preterm premature rupture of membranes (PPROM), and intrauterine growth restriction (IUGR)

Results: 1,462 charts of mothers with premature infants (22-34 weeks) were studied measuring the relative risk by using standardized statistical software (SPSS).Our study group had 46 mothers with GHTN, 405 with PREE, 282 with CA, 504 with PPROM, and 94 with IUGR. A+ Caucasian mothers had a 28% increased risk of developing preeclampsia (RR= 1.28 (1.09-1.52); 95% CI= .003). B mothers are ata 46% decreased risk of developing chorioamnionitis versus all other blood groups (RR= 0.54, 95% CI= 0.36-0.81; P= .003). Conversely, O+ Caucasian mothers were 2.53 times more likely to develop chorioamnionitis compared to all other blood types (RR=2.53, 95% CI= 1.09-5.88; P= .031).

Conclusions: Maternal ABO phenotype significantly influences the incidence of preeclampsia and chorioamnionitis. Pregnancy is a unique antigen-antibody phenomenon with the fetus serving as an antigen to the mother. We postulate that blood group antigen expression at the endothelial level may influence maternal disease states.

Keywords: ABO, Prematurity, Pregnancy, Disease, Morbidity, Chorioamnionitis, Preeclampsia.

INTRODUCTION

Recent studies have shown associations between particular ABO phenotypes and pathologic events including infection, cancer, thromboembolic disease and diabetes in adult male and females [1-6]. The A and B alleles encode specific enzymes that produce both A and B antigens. The O allele encodes an inactive enzyme with neither A or B antigen synthesized. Both A and B antigens are found on the surface of red blood cells and other tissue including vascular endothelium, epidermis and glandular or other epitheliums lining visceras.

The association of ABO blood types on adverse pregnancy outcomes has been reported with varied results. Blood groups A and O were associated with an increased risk for chorioamnionitis. Blood groups A or AB were found to increase the risk of preeclampsia. Other studies found blood group AB to be protective as well as a risk factor for gestational diabetes [7-12]. The goal of this study was to evaluate ABO blood types with common adverse pregnancy events that contribute to prematurity and infant mortality worldwide. We specifically examined gestational hypertension, preeclampsia, chorioamnionitis, preterm premature rupture of membranes and intrauterine growth restriction.

METHODS

This study was approved by the university's Institutional Review Board and was conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA). We used Loyola University's perinatal database (File Maker Pro), which

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contains multiple data fields on demographic and clinical variables for mothers and neonates. We reviewed 1,462 charts of infants born at Loyola University Medical Center between January 1st 2008 to December 31st 2014, with premature gestational ages ranging from 22-34 weeks. In addition to our neonatal information (gestational age, birth weight, and race), several maternal dependent variables were reviewed in our population including gestational hypertension (GHTN), preeclampsia (PREE), chorioamnionitis (CA), preterm premature rupture of membranes (PPROM), and intrauterine growth restriction (IUGR). Independent variables reviewed included maternal age, race, and ABO phenotype.

Criteria for inclusion in our study was documented maternal ABO phenotype and all premature infants born between January 1 2008-December 31 2014, with gestational age range 22-34 weeks. Chorioamnionitis is inflammation of the chorionic and amniotic layers of the fetal membranes confirmed by pathologic review of the placenta. Gestational hypertension is the development of new hypertension in a pregnant woman after 20 weeks gestation without the presence of protein in the urine or other signs of preeclampsia. Hypertension is defined as having a blood pressure greater than 140/90 mm Hg. Preeclampsia is defined as gestational hypertension with proteinuria. Preterm premature rupture of membranes is when the amniotic sac ruptures before 37 weeks of gestation and labor has not started within one hour. Intrauterine growth restriction is defined as a fetal weight that is below the 10th percentile for gestational age as determined through ultrasound compared to expected growth parameters [13].

Differences between maternal blood groups developing selected clinical outcomes were calculated by measuring the relative risk by using standardized statistical software (SPSS).

RESULTS

In total, we found 282 mothers who had chorioamnionitis recorded in our database. (Table **1**) O+ Caucasian mothers were found to be 2.53 times more likely to develop CA compared to all other blood groups (RR= 2.53, 95% CI= 1.09-5.88; P= 0.031). (Table **2**) Conversely, B mothers (B+ and B-) are at a 46% decreased risk of developing CA versus all other blood groups (RR= 0.54, 95% CI= 0.36-0.81; P= 0.003). (Table **3**) A+ Caucasian mothers were found to have a 28% increased risk of developing preeclampsia (RR= 1.28 (1.09-1.52); 95% CI= .003). (Table **4**, Table **5**). Of the 282 babies with CA (see Table **1**) and 405 with PREE (see Table **4**), their relative risk of developing each condition was significantly different by blood group.

Table 1: Chorioamnionitis by ABO Phenotype in Our Population

Blood Group	Overall
A-	18 (6%)
A+	92 (33%)
B-	2 (0.007%)
B+	20 (7%)
AB-	0 (0%)
AB+	6 (2%)
O-	16 (6%)
O+	128 (45%)
Total	282

Table 2: O+ Phenotype and Increased Risk of Chorioamnionitis

	+Chorioamnionitis	-Chorioamnionitis
O+ Caucasian	10	27
All Others	8	67
RR	2.53	1.09-5.88
P	0.031	

Table 3: Protective Effect of B Phenotype

	+ Chorioamnionitis	-Chorioamnionitis
B+/ B-	22	176
All Others	260	1004
RR	0.54	0.36-0.81
P	0.003	

Table 4: Preeclampsia by ABO Phenotype in Our Population

Blood Group	Overall
A-	12 (3%)
A+	158 (39%)
B-	4 (0.009%)
B+	44 (11%)
AB-	8 (0.02%)
AB+	14 (0.03%)
O-	16 (0.04%)
O+	149 (37%)
Total	405

Table 5: A+ Phenotype and Increased Risk of Preeclampsia

	+Preeclampsia	-Preeclampsia
A+	158	327
All Others	247	727
RR	1.28	1.09-1.52
P	0.003	

DISCUSSION

The four major blood groups in humans are based on the presence of A and B antigens on the surface red blood cells. Both A and B antigens are found not only on the surface of red blood cells, but also on many other tissues, epithelial and endothelial linings. The approximate ABO distribution in the United States is O type (44%), A type (42%), B type (10%), and AB type (4%) [14]. Despite their common prevalence as "histo-blood" antigens, an important corollary to recognize about these carbohydrate antigens is that there still is no known physiologic function for them. Absent this knowledge, their relationship as risk factors to disease states makes understanding mechanisms of associated diseases more difficult to appreciate.

It is known that anti-A and anti-B antibodies (isohemagglutanins) are primarily of the IgM isotype, whereas the O antibodies are chiefly of IgG isotype. IgM isohemagglutinins are endogenously synthesized in the first years of life due to "natural" sensitization from exposure to environmental substances, such as food, bacteria (such as *Enterobacteriaceae*), or viruses [15]. The relative lack of IgM antibodies in individuals with the O blood group could predispose mothers to an increased risk of chorioamnionitis. It can further be hypothesized that O blood type mothers inherently lacking these antibodies and being in an physiologically immune-modulated pregnancy state, may be less predisposed to mount an antibody and/or complement-mediated defense along the choriodecidual space and amniotic membranes. A study by Aly, *et al*. found blood types A and O are associated with increased risk for chorioamnionitis [16]. Our study produced similar results in that Caucasian O+ mothers were 2.53 times more likely to develop CA compared to all other blood groups.

A+ Caucasian mothers were at increased risk of PREE compared to other phenotypes. Mothers with B phenotype, overall, were more protected from complications of the dependent variables in our study. Our hypothesis that blood group antigen expression on the endothelial surface may influence maternal disease states is strongly represented in our CA and PREE findings. It has been shown in previous studies that maternal ABO phenotype may play a role in unfavorable pregnancy outcomes. Phaloprakarn *et al.* and Alpoim *et al.* concluded that maternal ABO phenotypes AB and A were associated with increased risk of preeclampsia [17-18]. In our study population our findings were similar to Phaloprakarn, *et al*. and Alpoim, *et al.*: Mothers with the A phenotype were at an increased risk of preeclampsia.

A previous study by Thomson, *et al*., demonstrated an increased risk of AB phenotype in relation to active or passive humoral factors (isoagglutinin hypotheses) showing that neonatal blood type is associated with the mortality in necrotizing enterocolitis (NEC). They found that neonates with AB blood group were indeed at significantly higher risk of mortality from NEC compared to neonates with other blood groups (HR 2.87; 95% CI 1.40 to 6.589; P= 0.003) [19]. The authors concluded that a humoral immune reaction between blood group antigens on the neonatal gastrointestinal mucosa and passively transferred isoagglutinins may have a role in the development of NEC. A further study by Manuat *et al*., established the morphologic relationship of A and B antigens and isoagglutinins as expressed on intestinal endothelium using immunohistochemical staining. They found that blood group antigens, A more than B or AB together, may increase the risk of a neonate to develop NEC in the presence of passively or actively transferred isoagglutinins [20].

Limitations in our study include retrospective study, a cohort from a single academic institution, surveying only relative risks and established expanded maternal "risk markers" (simple associations) to be distinguished from risk factors (cause-effect relationships). Strengths of our study included sample size, heterogeneity of our population, as well as consistent ABO phenotype breakdown as to be statistically expected in the Unites States. We had statistically significant and strong correlations between maternal ABO phenotype and our additional dependent variables.

We are encouraged to continue to seek further associations to support the role of maternal ABO phenotype and adverse outcomes as they apply to the neonate. We have found maternal ABO phenotypes to significantly affect the rates of CA and PREE. Further randomized prospective studies are needed to ascertain if maternal ABO phenotype significantly

influences the incidence and severity of maternal intra-partum disease states. By identifying at-risk mothers based on blood type, potential early interventions could optimize maternal and neonatal outcomes.

There are no disclaimers or conflicts of interest.

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