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REVIEW PAPER

Blood group relevance for the newborn – the ABO system and neonatal diseases

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ABSTRACT

Blood group antigens, present on blood cells, can influence the susceptibility to or severity of various diseases. There are many studies describing such relationships in adults. However, in the case of newborns, there are only a few publications concerning the influence of blood type on diseases in the neonatal period.
The present literature review deals with the influence of the ABO blood group system on the incidence and course of necrotizing enterocolitis and sepsis in the neonatal period. The review also concerns the effects of bleeding disorders and other changes in peripheral blood counts.
Data presented on the relationship between blood group and the risk of developing or affecting the severity of the disease may be useful in neonatal practice, especially in the case of very small premature babies. There is a potentially faster, more accurate diagnosis, that will allow effective treatment of neonates.

KEY WORDS:

congenital heart defects, necrotizing enterocolitis, ABO blood group system, newborn diseases, coagulation disorders.

INTRODUCTION

Many relationships between the ABO group system and various diseases have been described in the adult population. Group O was associated with a higher incidence of tuberculosis, plague, cholera and mumps. An increased risk of chickenpox and *Pseudomonas aeruginosa* infections was found among those with blood type A. Blood type B has a correlation with more frequent infections with *Streptococcus pneumoniae*, *Escherichia coli*, *Salmonella* and *Neisseria gonorrhoeae* [1]. A higher risk of coronary artery disease has been described in people with blood type A, and a lower risk of the disease in people with blood type O [2]. Moreover, blood type AB has been linked to a higher incidence of ischemic stroke [3].

ABO blood grouping by antigens reduces the risk of complications in blood transfusions and transplants. The polymorphisms of the antigens present on erythrocytes and platelets vary from person to person and result in the formation of specific antibodies in the case of exposure. Exposure can occur, for example, during pregnancy [4]. The antigens of different blood types can cause different reactions in the body in response to disease-causing agents. Among newborns, these relationships are not yet as thoroughly understood as they are among adults, but the topic is attracting increasing scientific interest.

DNA genotyping by checking the level of maternal antibodies directed against erythrocyte or platelet antigens enables more efficient diagnosis of hemolytic disease of the fetus and newborn (HDFN), and fetal and neonatal alloimmune thrombocytopenia (FNAIT) [4]. Determination of free DNA from maternal plasma is also used to diagnose HDFN [5].

Tests determining the blood type of the fetus in utero could be useful in preventing and more rapidly diagnosing diseases of the neonatal period. However, there are

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only few publications proving the links between blood groups in newborns and diseases of the adaptive period. The largest group of studies describe HDFN and incompatibility in the Rh or ABO blood group system between mother and child.

If the mother produces antibodies against the ABO or Rh system of the fetus, HDFN is recognized [6, 7]. Hemolytic disease of the fetus and newborn, otherwise known as *erythroblastosis fetalis*, due to the successful prevention of Rh incompatibility, is now most commonly found in the ABO system. In Poland, the 2015 recommendations for the use of anti-RhD immunoglobulin are in effect. Intra-pregnancy prophylaxis is administration of 300 μg at 28–30 weeks of gestation to any Rh-negative woman in whom anti-RhD antibodies have not been detected. Women who have free-circulating fetal DNA analysis in plasma and are shown to be Rh negative may be exempt from this procedure. Unfortunately, we currently do not have any comparable screening procedure to predict and prevent HDFN in the ABO group. The disease is more frequent in children with blood type A or B whose mothers have blood type O. Antibody titers to ABO group antigens may be elevated due to previous immunization during pregnancy or other unknown causes. High antibody titers may result in a more severe course of HDFN. A child from a first pregnancy may already be exposed to antibodies, but most often this is not threatening to the child. However, even in such a case, bilirubin levels should be monitored to quickly implement phototherapy and avoid exchange transfusions. Moreover, there is a greater risk of a severe course of HDFN in a subsequent pregnancy [6–9].

NECROTIZING ENTEROCOLITIS

Thomson *et al.* examined how ABO group system antigens and isoagglutinins affect the development of necrotizing enterocolitis (NEC). The analysis included 276 neonates who were treated for NEC, stage IIa or higher. No statistically significant differences were described between the gender of babies who died of NEC and babies who survived. However, neonates who died of NEC had significantly lower birth weight and lower gestational age. Forty-three percent of children with blood type AB died from NEC. Among other blood groups, the mortality rate was between 18 and 23%. Statistical analysis proved that newborns with AB blood group had significantly lower chances of survival, in comparison to other blood groups ($p = 0.003$). The highest risk of death due to NEC was in children with blood group AB, whose mothers had blood group A or AB ($p = 0.044$). The authors stated that infants with blood type AB have much higher risk of an immune response, such as to blood transfusions, that leads to the development of NEC. For this reason, these babies may have a significantly worse prognosis if they develop NEC. The resolution to this problem may be transfusion, if necessary, the same blood type as the infant has, rather than giving the common type O Rh-negative [10].

Dos Santos Martins *et al.* included 237 infants with a gestational age of < 37 diagnosed with NEC. They divided the degrees of severity of NEC based on the Bell's stage, need for surgery, and mortality. Bell's stage III was significantly more common in infants with AB blood type, after correlating with gestational age ($p = 0.003$). When surgery was required, after correlating with gestational age, the risk was significantly higher among neonates with AB blood type ($p = 0.001$). Blood type AB was also significantly associated with higher mortality from NEC than other blood types ($p = 0.001$). The researchers stressed that physicians should be aware of the poorer outcomes of NEC in the AB blood group of newborns, and that more research on this issue is needed [11].

In 2021, Martynov *et al.* conducted a study on 10,257 very low birth weight infants (birth weight < 1500 g), among whom 441 had a diagnosis of NEC or focal intestinal perforation (FIP). The results showed a significantly higher incidence of surgical NEC/FIP in preterm infants with AB blood group compared to non-AB groups ($p = 0.02$). For this reason, the authors believe that AB blood group may be considered a new risk factor for the development of NEC/FIP in very low birth weight infants, but due to the relatively small number of AB babies with NEC/FIP in the study ($n = 39$; 5.9%), the study should be repeated on other populations [12].

Also in 2021, Eaton published a commentary summarizing the findings of Thomson *et al.*, Dos Santos Martins *et al.* and Martynov *et al.* [8–12], in which he accused the studies by Thomson *et al.* and Martins *et al.* of failing to answer the question whether the risk of developing NEC in premature babies with low birth weight is higher in infants with blood type AB. A study by Martynov *et al.* proved a correlation between AB blood type and very low birth weight in infants. None of these studies conclusively prove an increased risk of NEC in AB blood type. However, given the theory that group A and B antigens may influence the development of NEC, either through endothelial interaction with the coagulation pathway or mucin glycoprotein interactions with microbiota, further research into the blood group dependence of NEC incidence is required and may contribute to understanding the pathomechanism of NEC [13].

It is important to remember that in the case of NEC, the pathophysiology of the disease process is complex and is not yet fully understood. The results of the above studies can contribute to faster diagnosis and prevention of NEC only in the case of correlation with other already known risk factors for this disease.

SEPSIS

In the first study reported by McMahon *et al.* in 2017, researchers compared the incidence of sepsis among in-

fants with blood type AB compared to those with other blood types. There was a significantly higher risk of sepsis in infants with blood type AB ($p < 0.0002$) than non-AB ($p = 0.9418$) [14]. In 2019, McMahon *et al.* reported an increased risk of sepsis by up to 58% in infants with blood type AB ($p = 0.0006$). The researchers proposed the hypothesis that hemolysis due to polymorphisms in the ABO group system may increase iron levels in the blood, which contributes to bacterial proliferation and sepsis [15].

Boral *et al.* in 2013, on the other hand, found a significantly increased risk of sepsis with *Enterobacter cloacae* etiology in infants with blood type O, compared to those with non-O blood type [16].

Kuo *et al.* in 2011 studied 23 children and newborns with *Pseudomonas aeruginosa* bacteremia. Statistical analysis showed that sepsis with *Pseudomonas aeruginosa* etiology was significantly more common in children with blood type B ($p < 0.001$) [17].

The study by Cakir *et al.* involved 2,548 newborns born < 32 weeks of gestational age and birth weight < 1,500 g. Newborns with blood type AB had a significantly higher risk of developing early onset neonatal sepsis compared to other blood types ($p < 0.001$) and also a higher risk of death ($p = 0.001$). The researchers believe that this result may be related to the presence of maternal isoagglutinins. Furthermore, a significantly higher incidence of meningitis was noted in the group of newborns with blood type B, compared to blood types A ($p = 0.026$), O ($p = 0.004$) and AB ($p = 0.046$). In contrast, neonates with blood type O had a significantly lower risk of developing late onset neonatal sepsis compared to other blood types ($p = 0.003$). However, the study only considered prenatal newborns with very low birth weight, so it should be repeated on a larger population of children [18]. The described results give hope for reducing the incidence of sepsis in neonatal wards through proper prophylaxis and hygiene of newborns with high-risk blood groups. However, as in the case of NEC, it is important to remember that the etiology of sepsis can be varied, and there may be more contributing factors. Further research on the topic is needed to improve rapid recognition and prevention of sepsis in newborns.

CONGENITAL HEART DEFECTS

In 2008, Odegard *et al.* conducted a study to examine the distribution of ABO blood groups among 1985 patients with congenital heart defects (CHD). The study included patients diagnosed with left heart obstructive lesions, tetralogy of Fallot (TOF), abnormal arrangement, septal defects, right heart lesions) and discordant ventriculo-arterial connections. The authors were unable to find any significant differences in the distribution of blood groups among CHD patients compared to the general population of the United States of America. Nevertheless, the researchers do not rule out that in studies on a wider population and depending on the distribution of ethnic groups, the results may be different [19].

In a study conducted in 2016, Zu *et al.* examined the relationship between the blood type of the newborn and the incidence of CHD such as ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), TOF, pulmonary atresia (PA), double outlet right ventricle (DORV), transposition of the great arteries (TGA) and coarctation of aorta (COA). The study demonstrated a lower risk of isolated congenital heart disease in infants with blood group A compared to blood group O. The results were confirmed for every isolated heart defect studied: VSD ($p < 0.001$), ASD ($p < 0.001$), PDA ($p < 0.001$), TOF ($p = 0.009$), PA ($p = 0.036$), DORV ($p = 0.003$), TGA ($p = 0.001$) and COA ($p = 0.001$). No significant correlations in incidence were seen in B and AB groups, but an increased risk of TOF was found among newborns with blood type B or AB. It was hypothesized that the relationship between blood type and CHD may be due to the proximity of the location of the genes encoding the ABO group system and the Notch1 and EHMT1 genes, which play an important role in cardiovascular development. The study proved that blood type A may be a protective factor in CHD, but further studies are needed to confirm the results of Zu *et al.* [20].

Cakir *et al.* also found a significantly higher incidence of PDA in premature infants with blood group A than with non-A blood groups [21].

However, in 2019 McMahon *et al.* found no statistically significant difference in the incidence of PDA in infants with AB and non-AB blood groups ($p = 0.14$).

The results of researchers describing the relationship between heart defects and blood type in newborns are inconclusive. Further studies, on larger and more diverse populations, are definitely needed to determine whether such relationships exist.

COAGULATION DISORDERS AND OTHER CHANGES IN BLOOD COUNT

Several studies have attempted to prove the dependence of FNAIT on incompatibility between mother and newborn. Arneth in a review noted that NAIT is more common in babies whose mothers have blood type A than in those whose mothers have blood type O. It was also noted that the risk of development and pathogenesis of NAIT depends on ABO antigens – some individuals, with blood type A or B, may have platelets that may have antigens incompatible with those of the mother, and these individuals have higher levels of A1 and B antigens on platelets. These results led to the assumption that newborns with type II high-expresser traits may have a higher risk of developing NAIT. However, the author highlights the need for further research on this issue [22].

In a study by Lee *et al.* conducted on 11,098 cord blood samples donated to the Seoul Metropolitan Public

Cord Blood Bank, it was noted that newborns with blood type O, despite having a lower birth weight, had higher values of total nucleated cells (TNCs). Also, the number of CD34+ cells was significantly higher in newborns with blood group O than in those with groups A ($p = 0.005$), B ($p = 0.010$) and AB ($p < 0.001$). The study also detected a correlation of the number of CD4+ cells with cord blood volume, gestational age and birth weight. The results regarding the relationship between blood groups and TNCs and CD34+ cells may have implications for clinical outcomes of transplantation, but further research on this issue is needed [23].

In 2017, McMahon *et al*. collected a group of 94 newborns who had type AB. Among the newborns, the researchers found a higher prevalence of neutropenia at birth, compared to babies with other blood types ($p < 0.0001$ vs. $p = 0.0804$) [14]. In their next study, from 2019, McMahon *et al*. also described an increased risk of neutropenia at birth in infants with AB blood type – from the data collected, they concluded that the risk was increased by as much as 89% ($p < 0.0001$) [15].

In the adult population, it has been detected that those with blood type O have 25% lower levels of von Willebrand factor (vWF) and factor VIII (FVIII) compared to non-O groups [24]. In a 2019 study by Lai *et al*. describing the ABO blood group system and procoagulant factors in newborns, a statistically significant difference was noted in the increase in vWF and FVIII levels at 3 weeks of life in neonates with non-O blood groups compared to those with O groups. It was noted that from the day of birth, the levels of vWF and FVIII are lower in neonates with group O, but a significant difference appears only at 3 weeks of life [25] (Table 1).

TABLE 1. Diseases and correlation with blood type

Disease	Correlation with blood type	Source
NEC		
Increased risk in blood type AB		[10–12]
Increased mortality in blood type AB		[10]
Poorer outcomes in blood group AB		[11]
Sepsis	Higher risk in blood type AB	[14]
Sepsis with *Enterobacter cloacae* etiology	Increased risk with blood type O	[16]
Sepsis with *Pseudomonas aeruginosa* etiology	Increased risk with blood type B	[17]
Early onset neonatal sepsis		
Increased risk in blood type AB		[18]
Increased mortality in blood type AB		[18]
Late onset neonatal sepsis	Lower risk with blood type O	[18]
Meningitidis	Increased risk with blood type B	[18]
PDA	Increased risk with blood type A	[18]
TOF	Increased risk with blood types B and AB	[20]
Isolated congenital heart disease	Lower risk with blood type A	[20]
TNCs	Higher values in blood type O	[22]
Neutropenia at birth	Increased risk with blood type AB	[15]
vWF and FVIII	Lower values in blood type O	[25]

NEC – necrotizing enterocolitis, PDA – patent ductus arteriosus, TNCs – total nucleated cells, TOF – tetralogy of Fallot, vWF – von Willebrand factor

CONCLUSIONS

The limited number of studies on the relationship between neonatal blood groups and infant diseases does not make it possible to unequivocally confirm or exclude the existence of such an association. Undoubtedly, further research is needed to answer the question of whether blood group influences the occurrence and course of various diseases of the neonatal period.

We can note, however, that already in several issues groups of researchers are unanimous – more often we can observe NEC in newborns with blood group AB, which was confirmed by studies performed by Thomson *et al.*[10], Martins *et al.*[11] and Martynov *et al.* [12]. Another proven correlation seems to be higher risk of neutropenia at birth and sepsis with AB blood neonates [15, 16].

However, the main limitation of this article is that each of the diseases described in the article has multiple risk factors. Associating a particular blood type with an increased incidence of NEC or sepsis is not synonymous with designating that blood type as the cause of the disease.

It should also be recognized that ethnographic affiliation, latitude, as well as the course of pregnancy, the type of birth and the course of the neonatal period itself may play an important role in these correlations.

Blood group determination is a relatively non-invasive test, available even during fetal life. Its use in the prevention and faster diagnosis of diseases in the neonatal period could significantly reduce hospital costs associated with the treatment of certain diseases – earlier diagnosis reduces the time of treatment and hospitalization. Currently, due to the insufficiency of scientific evidence, blood type should not be the decisive factor determining medical interventions. Therefore, further studies in large and well-described populations are needed.

DISCLOSURE

The authors declare no conflict of interest.

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