Fetal fluid and protein dynamics
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Hypoalbuminemia: A cause of fetal hydrops?

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Abstract

Objective
The pathophysiology of fetal hydrops is still unclear. One factor that is believed to contribute to hydrops is hypoalbuminemia. Our research question was whether hypoalbuminemia in immune hydrops is causative or a secondary effect.

Study design
Between 1987 and 2005, fetal blood samples were taken at the first fetal blood transfusion in 224 Rh-D alloimmunized pregnancies. We measured hemoglobin concentration and albumin concentration and assessed the severity of hydrops.

Results
A decrease in albumin concentration occurred only below a hemoglobin deficit of >8 SDs in 27 fetuses. In 161 nonhydropic, 44 mildly hydropic, and 19 severely hydropic fetuses, albumin concentrations were >2 SDs below the mean for gestational age in 6%, 14%, and 63%, respectively.

Conclusion
Our finding that most fetuses with immune hydrops have an albumin concentration within the normal range (71%) suggests that hypoalbuminemia is unlikely to cause the initial development of immune hydrops.
Introduction

The overall prognosis of fetal hydrops is poor, with a perinatal mortality rate between 50% and 98% [1]. In fetuses with severe alloimmune anemia, the severity of hydrops is a major determinant for the prognosis [2]. Also, in many other fetal diseases, the presence or absence of hydrops has a major influence on the chances for survival. However, the mechanisms in fetal disease that lead to hydrops remain unclear.

Several hypotheses regarding the pathophysiologic condition of fetal hydrops have been suggested [3]. Extravascular accumulation of fluid can be caused by decreased intravascular osmotic pressure, increased intravascular hydrostatic pressure, or lymphatic flow compromise.

Decreased intravascular colloid osmotic pressure can be caused by hypoalbuminemia. Leaking of albumin through endothelium may occur as a result of hypoxia-mediated damage [4]. Alternatively, decreased albumin production could be the result of fetal liver dysfunction (eg, in chronically anemic fetuses with increased extramedullary erythropoiesis or portal hypertension) [5]. Phibbs et al. [6] found, in severely anemic neonates, a relatively increased plasma volume that is associated with low albumin concentrations (Albs) and hydrops. Furthermore, elevation of umbilical venous pressure in the presence of decreased colloid osmotic pressure might be the onset of extravasation of fluid [7]. Fetal cardiac decompensation or increased intrathoracic pressures (eg, because of lung tumors or chylothorax) lead to increased central venous pressures and obstruction of lymphatic emptying, which results in the development of hydrops [8-10]. Finally, various mediators, such as atrial natriuretic factor, influence cardiovascular adaptation to anemia and hypoxia [11].

With the assumption that hypoalbuminemia is a major contributor to the development of hydrops, several investigators have tried to treat fetal hydrops using albumin infusions [12,13]. A better understanding of the cascade of events that lead to the development of hydrops may allow much needed advances in prenatal preventive or therapeutic modalities. This study was designed to evaluate the role of hypoalbuminemia in the development of fetal hydrops.
Material and methods

We searched our fetal database for all Rh-D alloimmunized pregnancies that underwent intrauterine blood transfusion between 1987 and June 2005. Fetal hemoglobin concentration (Hb) and Alb from the first fetal blood sampling in each pregnancy were recorded prospectively. We excluded fetuses with structural or chromosomal anomalies and intrauterine growth restriction or infection and pregnancies with incomplete data.

From the ultrasound report at the time of fetal blood sampling, the presence or absence of hydrops was obtained. Hydropic fetuses were classified as mild or severe, by the criteria described by van Kamp et al. [2]. Briefly, mild hydrops was defined as the presence of a distinct rim of ascites, with or without pericardial effusion; severe hydrops was defined as the presence of a more abundant amount of fluid collection, usually ascites, with skin edema.

The measured values for Hb and Alb were plotted on previously published standard reference ranges. For Hb, the reference range of Nicolaides et al. [14] was used. The nomogram that we used for fetal Alb was from Takagi et al. [15]. We calculated gestational age independent Z-values to evaluate the correlation between Hb and Alb. Linear and cubic regression were used to analyze the data. The Kruskal Wallis test was used for comparison of groups. A probability value of < .05 was considered statistically significant. The percentage of fetuses with an Alb below 2 standard deviations (SD) were calculated in each subpopulation to evaluate whether the role of hypoalbuminemia in evolving hydrops is more likely to be the primary cause or a secondary effect. These percentages were compared in a chi-square (Fisher’s exact) test. Ordinal logistic regression was performed to analyze the dependency of the decrease in Alb and the decrease in Hb for the presence of hydrops.

Results

A total of 224 fetuses could be included from which 161 fetuses were nonhydropic, 44 fetuses were mildly hydropic, and 19 fetuses were severely hydropic. Gestational age at the time of the first fetal blood sampling ranged from 17 to 38 weeks.

Hbs in fetal blood that were plotted against gestational age are shown in Figure 1. All fetuses except 1 were anemic, which was defined as an Hb of >2 SD below the
mean for gestational age (Hb deficit ranged from -1.2 to -11.8 SD). In the nonhydropic group, the mean Hb deficit was 7.1 SD (range, -1.2 to -10.5 SD). Mild hydrops was observed in fetuses with a mean Hb deficit of 9.2 SD (range, -3.5 to -11.8 SD). Severe hydrops was present only in fetuses with a Hb deficit of >9.4 SD. In this group, the mean Hb deficit was 10.3 SD (range, -9.4 to -11.4 SD). Mean Hb deficit among the 3 groups was statistically significantly different (p< 0.001).

Albs in fetal blood that was plotted against gestational age are shown in Figure 2. In the nonhydropic group, the mean Alb deficit was 0.6 SD (95%CI, -0.8 to -0.5; range, +2.9 to -3.2 SD). Mildly hydropic fetuses had a mean Alb deficit of 1.1 SD (95%CI, -1.3 to -0.8; range, +0.8 to -3.0 SD). Severely hydropic fetuses had a mean Alb deficit of 2.1 SD (95%CI, -2.6 to -1.6; range, -0.1 to -4.6 SD). The mean Alb deficit among the 3 groups was statistically significantly different (p< 0.001).

Only 27 of the 244 fetuses were found to have hypoalbuminemia. Of the nonhydropic fetuses, 5.6% had an Alb outside the normal range; of the mildly hydropic fetuses, 13.6% had an Alb outside the normal range, and of the severely hydropic fetuses, 63.2% had an Alb outside the normal range. Of all hydropic fetuses combined, mild and severe together, 28.6% had an Alb <2 SD. The difference in percentage of fetuses with hypoalbuminemia between nonhydropic and mildly hydropic fetuses is not statistically significant (p= 0.097, Fisher’s exact test). The difference in percentage of hypoalbuminemia between severely hydropic fetuses and both nonhydropic and mildly hydropic fetuses is statistically significant (p< 0.001 and p< 0.001, chi-square and Fisher’s exact test).

Gestational age independent Z-values of Alb and Hb were compared (Figure 3). A cubic regression line fitted the data best for the total population. Ordinal logistic regression showed that a decrease in Alb and a decrease in Hb independently of each other are predictive of the presence and severity of hydrops (p< 0.001).
Figure 1  Hbs in nonhydropic, mildly hydropic, and severely hydropic fetuses are plotted with the normal range (* adapted from Nicolaides [14]).

Figure 2  Albs in nonhydropic, mildly hydropic, and severely hydropic fetuses are plotted with the normal range (* adapted from Takagi [15]).
Comment

In this study of a large cohort of anemic human fetuses, we found a significant negative correlation between the fetal serum Alb and the degree of fetal hydrops. However, most of the fetuses with hydrops had albumin levels within the normal range. These results suggest that hypoalbuminemia is unlikely to cause the primary onset of fetal immune hydrops. This conclusion is supported by the observation that there was little difference between nonhydropic and mildly hydropic fetuses. Only in severe hydrops was hypoalbuminemia present in more than one half of the cases. Hypoalbuminemia thus seems to occur as a secondary effect in the cascade of hydrops (eg, because of a reduced re-uptake of albumin from the interstitial compartment). Hypoalbuminemia might even be the trigger for mild hydrops to evolve into severe hydrops.

The result of our study also warrants caution in drawing conclusions about the relationship between the presence of hydrops and the Alb, because the severity of anemia seems to be a confounding factor in this relationship. Hypoalbuminemia was observed only in fetuses with an Hb deficit of >8 SDs. Severe anemia could be associated, for example, with a relatively large plasma volume, which could cause a dilution of plasma proteins. Besides a decrease in Alb, a decrease in Hb was independently predictive for the presence of hydrops. Therefore, the development

Figure 3  Z-albumin plotted against Z-hemoglobin that compares nonhydropic, mildly hydropic, and severely hydropic fetuses. The normal ranges that were used to calculate Z-values were adapted from Nicolaides [14] and Takagi [15].
of hydrops cannot be explained solely by either the severe anemia or hypoalbuminemia. Our data do not permit us to draw conclusions about the reasons that some anemic fetuses become hydropic when others remain without hydrops.

Our study confirms results from animal experiments in which fetal lambs were made anemic, with hydrops developing in some lambs and not in others. Both groups of fetal lambs were found to have the same level of plasma protein [16]. Our findings seem to be in contrast, however, to results from a study by Nicolaides et al. [17]. They compared albumin levels from 10 nonhydropic anemic fetuses and 7 hydropic anemic fetuses with normal control fetuses. They found that most hydropic fetuses (6/7) and only a few nonhydropic fetuses (2/10) had an Alb of <2 SDs. However, from a graph in their paper, it appears that, in only 3 hydropic fetuses, the albumin values clearly fell below the normal limits. The degree of anemia was the most severe in these 3 fetuses.

This is the first study to explore the possible role of hypoalbuminemia with a large number of severely anemic and hydropic fetuses. An obvious limitation is that our conclusions are based only on fetuses with alloimmune anemia. Other conditions that lead to hydrops may have a different pathophysiologic condition. In some of these conditions, hypoalbuminemia may play a more important role. However, many other causes of hydrops (such as viral infections, vascular tumors, hematologic conditions, and several metabolic conditions) are anemia related and thereby likely to have a pathophysiologic condition that is similar to alloimmune hemolytic disease. We speculate therefore that, in most nonimmune fetal conditions that lead to hydrops, hypoalbuminemia is unlikely to play a causative role.

In our study, we measured fetal albumin levels and assumed a close correlation with intravascular colloid osmotic pressures. Experimental protein reduction in fetal lambs was shown to decrease protein levels and colloid osmotic pressures to the same extent without causing edema [18]. Lumbers et al. [19] showed, again in fetal lambs, a close correlation between plasma protein levels and colloid osmotic pressures.

In conclusion, hypoalbuminemia was not found in most hydropic anemic fetuses. In the chain of events that leads to hydrops, other mechanisms (such as cardiac failure and lymphatic flow obstruction) are likely to be more important. In the search for better understanding that would lead eventually to effective treatment strategies for immune and nonimmune hydrops, the focus will have to be on these mechanisms.
Hypoalbuminemia and hydrops

References

Addendum: Letter to the editors
(of American Journal of Obstetrics and Gynecology)

Alfa-fetoprotein and albumin levels together are more predictive of severe fetal hydrops

To the editors
The recent paper by Pasman et al. [1] concludes that “hypoalbuminemia is unlikely to cause the initial development of immune hydrops”, yet in severe hydrops, hypoalbuminemia was present in more than half the cases. Alfa-fetoprotein, a fetal liver product, may be involved in (extramedullary) fetal hematopoiesis and in the development of severe allo-immune hydrops [2]. Alfa-fetoprotein levels vary by compartment (fetal, placental, maternal), gestational age, and physiologic variables [3], so that both low and high maternal serum values have been described as clinically important fetal markers [4]. We suggest that concomitant assessment of albumin and alfa-fetoprotein may be predictive of severe fetal hydrops (rather than the absolute value of fetal albumin or alfa-fetoprotein alone) because together they are reflective of the sequence of events in red blood cell allo-immunized pregnancies and fetuses. We believe that findings of overt fetal hypoalbuminemia together with elevated fetal alfa-fetoprotein may differentiate the fetus with severe hydrops from the fetus whose course will be milder.

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References
Reply

We appreciate the interest of Dr Elstein in our work. We apparently succeeded in one of our main goals, which was to stimulate discussion and development of new hypotheses. Dr Elstein speculates on the possible relation of alpha-fetoprotein (AFP) to albumin with the severity of fetal hydrops. She suggests that albumin and AFP together are reflective of the sequence of events in red blood cell allo-immunized pregnancies. First, one of the important factors, oncotic pressure, is unlikely to be influenced significantly by AFP changes, since the concentration of AFP in fetal serum is about 10 times lower than albumin concentration, with similar molecular size. Only when a large difference in negative charges would be present, which is unlikely to be the case in these similar proteins, would a more important contribution of AFP be understandable.

Second, AFP may be a regulating factor in hematopoiesis. Bartha et al. showed that AFP in maternal serum correlates with fetal MCA Doppler measurements and hemoglobin concentrations [1]. However, in a previous study by the same group, a decrease of maternal serum AFP in severely anemic and often hydropic fetuses was found [2]. Strikingly, this is very similar to our observation that fetal serum albumin concentration was decreased only in severely anemic fetuses that were often, but not always, hydropic. It is compelling to hypothesize that the decrease in albumin and AFP in severe anemia has a common etiology. Zhang et al. showed that hepatoblast cells express both albumin and AFP and seem to facilitate hematopoiesis in the human fetal liver [3]. Increased venous pressure and excessive erythropoiesis are thought to affect fetal liver function, which could result in decreased AFP and albumin production. In turn, these changes could aggrevate anemia and fluid shifts.

It would be of interest to assess associations between maternal serum AFP, fetal albumin concentrations, and severity of fetal anemia and hydrops. Because we studied human fetuses during treatment, we were only able to obtain fetal blood samples at one moment in time. To provide more insight in the roles of AFP and albumin in the development of hydrops, frequent serial blood sampling without giving any treatment would be needed. Such an invasive study is obviously not justifiable in human pregnancies.

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References

