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Hypoalbuminemia: A cause of fetal hydrops?

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KEY WORDS
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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.

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

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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 SDs (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.

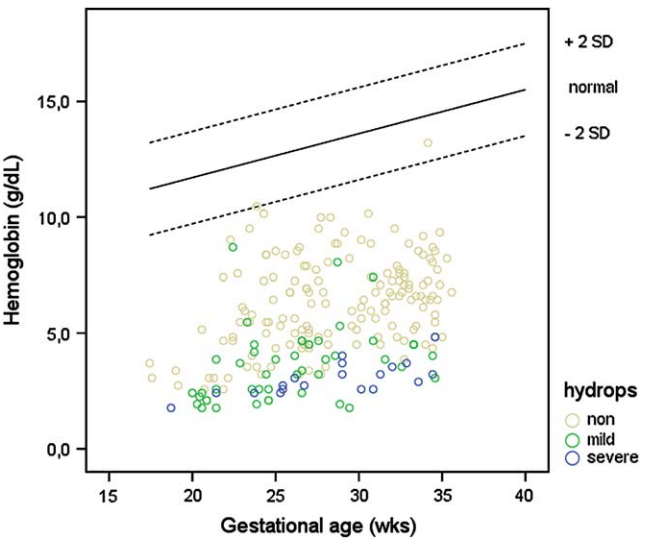

Figure 1 Hbs in nonhydropic, mildly hydropic, and severely hydropic fetuses are plotted with the normal range. (Adapted from Nicolaides[14]).

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 ($P < .001$).

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 ($P < .001$).

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