IMAGING

Venous Doppler studies in low-output and high-output hydrops fetalis

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OBJECTIVE: The objective of the study was to compare fetal venous Doppler flow reflecting cardiac function in fetuses with hydrops fetalis between a group of congenital heart defect (low cardiac output) and a fetal anemia group (high cardiac output).

STUDY DESIGN: This was a prospective cross-sectional analysis. It was conducted at the Maharaj Nakorn Chiang Mai Hospital, Tertiary center, Medical School. The study included fetuses with hydrops fetalis secondary to cardiac causes (low output group) and anemia (high output group). All fetuses underwent ultrasound examination to assess ductus venosus (DV) and umbilical vein (UV) Doppler indices. The results were related to normal reference range and were also compared between the group of high-output and the low-output group.

RESULTS: Sixty-nine hydropic fetuses were available for analysis, 50 in the high-output group and 19 in the low-output group. The peak velocity index, preload index, and the pulsatility index of the DV were significantly low in the high-output group, whereas they were significantly high in the low-output group. The umbilical vein pulsations were found in 78.9% of the fetuses with low-output hydrops fetalis but only 28.0% of fetuses in the high output group ($P < .001$).

CONCLUSION: New insights gained from this study are that hydrops caused by severe anemia because of hemoglobin Bart's is not associated with high central venous pressures as is seen in hydropic fetuses with coronary heart disease. This suggests that cardiac decompensation is not the primary mechanism of hydrops in these anemic fetuses. Additionally, umbilical vein pulsations are not a sign of cardiac failure in the anemic group.

Key words: cardiac output, Doppler velocity, ductus venosus, hydrops fetalis

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Fetal hydrops represents a specific condition characterized by an increase of total body water content, defined by fluid collections in at least 2 fetal body compartments such as ascites, pleural, and/or pericardial effusion and/or the skin edema. Hydrops fetalis is not a diagnosis in itself but a symptom and the end-stage of a wide variety of disorders. In chromosomally normal fetuses, low-output (myocardial dysfunction) and high-output (anemia) hydrops fetalis account for the large portion of cases.[1] Based on the largest systematic review by Bellini et al,[1] congenital heart defect is a major cause of hydrops fetalis, accounting for 21.7%. However, in Southeast Asia hemoglobin Bart's disease is responsible for 70-85% of all cases.[2]

Pathophysiology of hydrops fetalis remains controversial. The postulated mechanisms are cardiac failure secondary to either cardiac defects (low cardiac output) or fetal anemia (high cardiac output). Additionally, other causes such as decreased colloid oncotic plasma pressure or obstruction of venous/lymphatic flow can play a role in a minority of cases.

In fetal anemia, increased cardiac output seen in these fetuses is believed to be due to a decrease in blood viscosity, which, in turn, leads to increased venous return and cardiac preload, resulting in cardiac failure and finally hydrops fetalis. However, Hecher et al[3] showed that fetal anemia in nonhydropic Rh isoimmunized fetuses is associated with a hyperdynamic circulation in both arterial and venous vessels, but even in severe anemia, there is no evidence of congestive heart failure. This is consistent with our experience in fetal anemia caused by hemoglobin Bart's disease.

We have often observed a normal cardiac function in these fetuses with frank hydrops fetalis, raising a question of cardiac failure as a primary cause of hydrops fetalis because of anemia. Therefore, this study focused on venous Doppler changes, as a surrogate marker for cardiac function assessment, in fetal hydrops secondary to low cardiac output (congenital heart disease) and high cardiac output (anemia).

There have been several studies on arterial Doppler changes in fetal anemia, but very few publications have studied on venous Doppler change, especially when hydrops fetalis has already developed. Because venous Doppler changes directly reflect cardiac decompensation, the studies may be informative for pathophysiology of hydrops fetalis. Understandings on venous Doppler changes may be helpful in

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predicting prognosis or differentiating causes or making a choice of management. Moreover, the difference between cardiac function in low-output and high-output hydrops fetalis has never been published.

The purpose of this study was to compare fetal venous Doppler indices among fetuses with hydrops fetalis between a group of congenital heart defect (low cardiac output) and a fetal anemia one (high cardiac output).

Materials and Methods

A cross-sectional prospective analytic study was conducted with the approval of the Research Ethics Committee 3, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. Singleton pregnancies with hydropic fetuses secondary to hemoglobin Bart's disease and those with cardiac causes were recruited into the study with informed written consent.

The prenatal diagnosis of hydrops fetalis was defined by demonstration of fluid accumulations in at least 2 fetal body compartments such as serous cavities of the fetus (abdominal ascites, pleural, and/or pericardial effusion) and/or the skin edema. When hydrops fetalis was diagnosed, detailed ultrasound was performed and causes of hydrops fetalis were identified. Hydrops fetalis due to causes other than hemoglobin Bart's and congenital heart defects was excluded from analysis.

The diagnosis of hemoglobin Bart's disease was based on fetal cord blood analysis, whereas the diagnosis of congenital heart diseases was based on detailed fetal echocardiography by an experienced examiner. Ultrasound examinations were performed using real-time machines either Aloka alpha-10 (Tokyo, Japan) or Voluson E8 (GE Healthcare, Indianapolis, IN). The maximal ultrasound intensity was set at 100 mV/cm^2 spatial peak temporal average and the high-frequency filter set at 125 Hz to remove signals from slow moving tissues. On ultrasound examination, venous Doppler waveforms were recorded from the ductus venosus and the umbilical vein at a free-floating loop of the cord. The size of the sample volume was adapted to the vessel diameter to cover it entirely.

All recordings used for measurements were obtained in the absence of fetal breathing movements, and the angle between the ultrasound beam and the direction of blood flow was less than 30°, and velocity measurements were taken after correction for the angle of insonation. The best 3 consecutive waveforms were automatically analyzed by the built-in software.

The venous Doppler indices examined included the peak forward velocity during systole (S), representing forward flow secondary to dilatation of right atrium during ventricular systole, peak forward velocity during diastole (D), reflecting ventricle filling during diastole, and lowest forward velocity or peak reversed velocity during atrial contraction (a) as well as the time average maximum velocity (Tamx) were determined. The peak velocity in veins (PVIV; S-a/D), preload index (PLI; S-a/S), and the pulsatility index for veins (PIV; S-a/Tamx) were automatically calculated during the measurement.

Umbilical venous blood velocity was recorded. Pulsating blood velocity in the umbilical vein was defined as a decrease in velocity by more than 15% of the maximal velocity. When more than 1 ultrasound examinations were performed, only the last one was included to the analysis. The results were related to normal reference range data of venous Doppler for the ductus venosus.[4] The data were also compared between the group of high-output hydrops fetalis and the low-output group.

Statistical analysis was performed with SPSS version 17 for Windows (SPSS, Inc, Chicago, IL). Student *t* test or Mann-Whitney *U* test were used for the comparison of continuous variables. The Kruskal-Wallis nonparametric test was used to evaluate trends in z-score or mean difference. Comparison of proportion was performed with χ^2 or Fisher's exact test where appropriate. $P < .05$ was considered statistically significant.

TABLE 1
Distribution of the causes of hydrops fetalis

Causes	n
High-output hydrops fetalis	50
Hemoglobin Bart's disease	50
Low-output hydrops fetalis	19
Ebstein's anomaly	5
Hypoplasia left heart	4
Atrial flutter/supraventricular tachycardia	3
Heterotaxy	3
Small heart syndrome	3
Tricuspid atresia	1

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Results

Sixty-nine singleton pregnancies with fetal hydrops were successfully recorded for venous Doppler waveforms and available for analysis. Of these, 50 fetuses had hydropic changes due to hemoglobin Bart's disease, classified as the high-output hydrops fetalis and 19 were hydrops fetalis secondary to congenital heart defect, classified as the low-output hydrops fetalis. The causes of hydrops fetalis are summarized and presented in Table 1. The mean gestational age was 26.3 ± 5.2 weeks (range, 17–36 weeks), 27.7 ± 5.2 weeks, and 25.7 ± 3.7 weeks for all fetuses, the high-output group, and the low-output group, respectively.

Venous Doppler studies show that most fetuses in both groups had significantly difference in ductus venosus indices, in terms of PLI, PVIV, and PIV. When compared with the normal values of the reference ranges reported by Baschat,[4] the mean differences from normal mean of the Doppler indices in the high-output group were significantly lower (Student *t* test; $P < .001$), whereas the mean differences of the Doppler indices in the low-output group were significantly higher than those in normal mean for each gestational week (Student *t* test; $P < .001$) (Table 2). The scattergram of PLI, PVIV, and PIV of the ductus venosus is presented in Figure 1.