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Original Article

Quantitative evaluation of renal arteries using three-dimensional power Doppler ultrasonography and serum cystatin C for diagnosing fetal hydronephrosis

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Abstract: This study evaluated the predictive value of quantitative analysis of renal arteries using three-dimensional power Doppler ultrasonography (3D-PDU) and serum cystatin C (CysC) in diagnosing fetal hydronephrosis (HN). A total of 208 fetuses with HN (a case group) and 210 healthy fetuses (a control group) were selected for this study. 3D-PDU was used to measure vascularization index (VI), flow index (FI), and vascularization flow index (VFI) of renal arteries in newborns. Enzyme-linked immunosorbent assay (ELISA) was used to evaluate serum CysC level in umbilical cord blood. A receiver operating characteristic (ROC) curve was applied to evaluate the diagnostic power of renal artery index and serum CysC for fetal HN. Logistic regression analysis was performed to identify risk factors for fetal HN. Compared with the control group, VI and VFI obviously decreased and serum CysC level significantly increased in the case group. The VI and VFI were positively correlated with gestational age, but negatively correlated with the disease degree of fetal HN. However, serum CysC level was positively associated with the disease degree of fetal HN. VI and VFI were negatively correlated with the disease degree of fetal HN. ROC curves indicated that the 3D-PDU showed a highest value in diagnosing fetal HN, when the optimal cut-off value of VI = 6.275 (sensitivity = 84.3, specificity = 69.7) and serum CysC = 1.745 (sensitivity = 92.8, specificity = 76.2). Logistic regression analysis indicated that fetal HN was associated with VI, VFI, and serum CysC level. These findings elucidated that fetal renal VI, VFI and serum CysC could be useful diagnostic tools for fetal HN.

Keywords: Cystatin C, fetal hydronephrosis, quantitative analysis, renal artery, three-dimensional power Doppler, vascularization flow index, vascularization index

Introduction

Fetal hydronephrosis, also called mildrenal pyelectasis, is one of the most common abnormal findings detected on prenatal mid-trimester ultrasound, with an estimated prevalence of approximately 1-4.5% [1, 2]. Fetal HN could-develop during the pregnancy into more severe and even deleterious conditions, but if the promptly diagnosis and treatment were taken, generally it would not cause any long-term problems [3]. A total of 35% of newborns healthy upon ultrasound examination; however, all of them were diagnosed HN in prenatal examination [4].

Urinary tract obstruction, commonly at the ureteropelvic junction and vesicoureteral reflux may be the possible explanations for fetal HN [5]. HN could be one of urogenic abnormalities, which needs promptly diagnosis and treatment to protect renal function [6]. The current treatment modalities for fetal HN based on the results of major clinical trials were evaluated in a report including serial ultrasound examinations throughout gestation that may include serial ultrasound and magnetic resonance imaging (MRI) [7]. In addition, patients may undergo postnatal examinations that may include a variable combination of serial renal ultrasound, voiding cystourethrogram (VCUG), diuretic renogram, intravenous pyelogram, and MRI urogram [8]. In recent years, 3D power Doppler ultrasonography (3D-PDU) has been promising in evaluating morphological studies and quantifying total blood flows in the placental vascular network for detecting fetal malformations [9, 10]. 3D quantification of blood flow using power

Table 1. The baseline characteristics of the case and control groups

Parameters	Case group (n = 208)	Control group (n = 210)	*P* value
Mean age (years)	28 ± 4	28 ± 4	0.398
Gestational age (weeks)	29 ± 5	29 ± 5	0.378
BMI	19.51 ± 2.04	19.23 ± 2.02	0.159
History of drinking (%)	32 (15.38%)	28 (13.33%)	0.550
Gender			0.376
Male	126	136	
Female	82	74	
Gestational week			0.834
20-23	30 (14.42%)	26 (12.38%)	
24-27	55 (26.44%)	56 (26.67%)	
28-31	66 (31.73%)	63 (30.00%)	
32-35	33 (15.87%)	42 (20.00%)	
36-40	24 (11.54%)	23 (10.95%)	

Note: BMI, Body Mass Index, BMI = weight (kg)/height^2 (m^2).

Doppler with virtual organ computer-aided program (VOCAL) provides 3 vascular indexes: VI, FI and VFI [11]. Morel *et al.* observed a linear correlation between placental cotyledonal vascular indexes and real blood flow in animal models [12]. Furthermore, these three indexes have also been studied in some fetal organs, such as lung and kidney, to predict postnatal prognosis in fetuses displaying diaphragmatic hernia and intrauterine growth restriction [11]. Cystatin C (CysC) is a small and an endogenous protein produced at a constant rate, it freely filtered through the glomerular membrane [13]. A study has shown that serum CysC level was correlated with glomerular filtration rate (GFR) [14]. As an important indicator of renal function, GFR is essential for the detection, evaluation and management of chronic kidney disease [15].

Since there is relatively little research on the vascular evaluation of fetal kidneys with HN using 3D-PDU combined with serum CysC. In this study, we aimed to evaluate the predictive value of quantitative analysis of renal arteries using 3D-PDU and serum CysC in fetal HN.

Subjects and methods

Ethics statement

This study was approved by the Ethics Committee and Institutional Review Board of the Maternal and Child Health Hospital of Hunan Province and all pregnant women have signed the informed consents.

Study subjects

A total of 208 fetuses with HN (126 males, 82 females) were selected as a case group and 210 healthy fetuses (136 males, 74 females) were randomly recruited as a control group, pregnant women of both two groups had underwent prenatally examination and fetuses were born in the Maternal and Child Health Hospital of Hunan Province between January 2014 and December 2015. The pregnant women in two groups were aged between 22 and 40 years old with 20-40 weeks of gestation. All fetuses were examined by renal ultrasonography, and the abdominal transverse section was taken. The spinal column was chosen as the center of the examination and anteroposterior diameter (APD) was measured to ensure whether fetus has HN. The inclusion criteria of fetal HN [16] were APD ≥ 8 mm (20-30 weeks' gestation) and APD ≥ 10 mm (> 30 weeks' gestation). Based on the Grignon Classification, fetal HN diagnosed with ultrasound was classified into five degrees: I (n = 58), II (n = 49), III (n = 41), IV (n = 36) and V (n = 24) [17]. All study subjects were singleton pregnancies and ultrasound examination during pregnancy showed no fetal abnormalities. All the pregnant women had nopregnancy-related conditions, history of low-birthweight infants or macrosomia and fetal growth restriction.

Quantitative analysis of renal arteries by 3D-PDU

The Doppler ultrasonography of pregnant women was performed with Volusion 730 color Doppler imaging machine (General Electric Co, Schenectady, New York, USA). RAB4 probe with a frequency of 4-8 MHz was selected according to the instructions. Pregnant women were placed in supineposition without bladder filling status. The width and depth of the probe were adjusted according to the size of the fetal kidney to display the fetal kidney volume maximum section as the initial section, the 3D power Doppler volume imaging of fetal kidney and renal artery were collected and it's data was measured, 3D power Doppler histograms was used to calculate vascular indexes at the

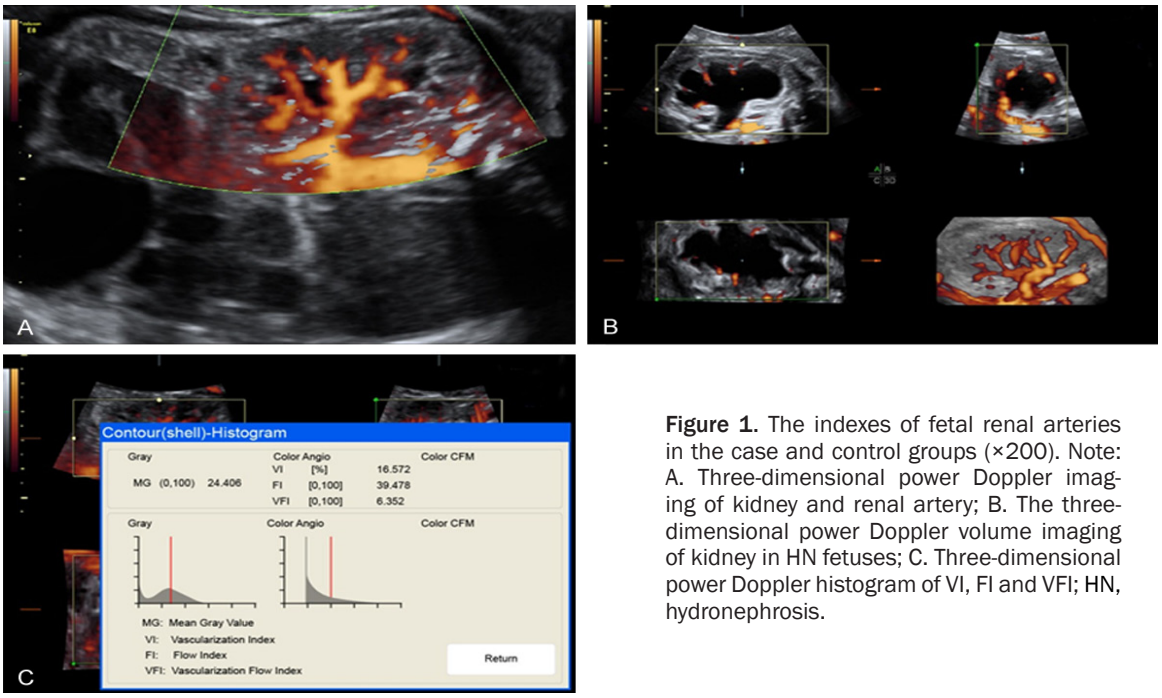

Figure 1. The indexes of fetal renal arteries in the case and control groups (×200). Note: A. Three-dimensional power Doppler imaging of kidney and renal artery; B. The three-dimensional power Doppler volume imaging of kidney in HN fetuses; C. Three-dimensional power Doppler histogram of VI, FI and VFI; HN, hydronephrosis.

same time, including VI, FI, and VFI (VFI = VI×FI/100). Each vascular index was performed in triplicate to obtain the average value.

Detection of serum CysC

Fetal blood samples (2 ml) from all the fetuses were collected by umbilical vein puncture under ultrasound guidance and placed at room temperature for 2 h. The blood was centrifuged at 3000 rpm and the serum was obtained. Serum CysC level was determined by double antibodies sandwich enzyme-linked immunosorbent assay (ELISA). The ELISA kit was purchased from Zhongshan Gloden Bridge Biotechnology Technology Co., Ltd., Beijing, China. CysC protein obtained from human CysC monoclonal antibody, which was pre-coated with ELISA plate. Biotin-labeled anti-human CysC antibodies were added after washing, and then sandwich immune complex was formed. Horseradish peroxidase (HRP)-labeled biotin that avidin specifically bound to secondary antibody was added, and then the substrate for HRP was used for color-developing and the absorbance at 450 nm was measured. Serum concentration of CysC in samples was calculated from the standard curve.

Statistical analysis

Data were analyzed using the Social Sciences (SPSS) version 21.0 (SPSS Inc., Chicago, IL, USA). Measurement data were displayed as means ± standard deviations and differences among multiple groups were analyzed by *t* test. Enumeration data were expressed as ratios or percentages, and differences among groups were compared by using the chi-square test. The Spearman or Pearson correlation coefficient test was used to evaluate the correlation between the vascular indices, serum CysC, gestational week and the disease degree of fetal HN. Logistic regression analysis was used to investigate the association of baseline characteristics of the pregnant women, renal artery indexes and serum CysC with the disease degree of fetal HN. Receiver operating characteristic (ROC) curves were applied to determine the diagnostic value of renal artery indexes and serum CysC level in the diagnosis offetal HN. $P < 0.05$ was considered statistical significance.

Results

The baseline characteristicsof the case and control groups

The case group consisted of 208 fetal HN patients (126 males, 82 females) with a mean gestational age of 29 ± 5 weeks. A total of 210 healthy fetuses (136 males, 74 females) with a mean gestational age of 29 ± 5 weeks were included in the control group. The baseline characteristics of these group subjects are shown in detail in **Table 1**, which revealed no significant difference in terms of mean age,

Table 2. The VI value of the case and control groups in different gestational weeks

Gestational week	Control group (n = 210)	Case group (n = 208)				
		I	II	III	IV	V
20-23	5.66 ± 0.93	3.94 ± 0.71[e]	3.70 ± 0.67[f]	3.38 ± 0.65[g]	2.88 ± 0.51[h]	2.32 ± 0.49[j]
24-27	7.06 ± 0.96[a]	5.02 ± 0.73[a,e]	4.77 ± 0.66[a,f]	4.35 ± 0.63[a,g]	3.96 ± 0.50[a,h]	3.06 ± 0.47[a,i]
28-31	8.56 ± 0.94[b]	6.17 ± 0.70[b,e]	6.00 ± 0.68[b,f]	5.52 ± 0.61[b,g]	4.78 ± 0.54[b,h]	4.32 ± 0.52[b,i]
32-35	10.81 ± 0.95[c]	7.81 ± 0.68[c,e]	7.63 ± 0.64[c,f]	7.17 ± 0.59[c,g]	6.78 ± 0.52[c,h]	5.96 ± 0.48[c,i]
36-40	12.79 ± 0.97[d]	9.33 ± 0.74[d,e]	9.14 ± 0.65[d,f]	8.76 ± 0.62[d,g]	8.52 ± 0.53[d,h]	8.24 ± 0.51[d,i]

Note: a, $P < 0.05$, compared with gestational age of 20-23 weeks; b, $P < 0.05$, compared with gestational age of 24-27 weeks; c, $P < 0.05$, compared with gestational age of 28-31 weeks; d, $P < 0.05$, compared with gestational age of 32-35 weeks; e, $P < 0.05$, compared with the control group in the same gestational week; f, $P < 0.05$, compared with grade I in the same gestational week; g, $P < 0.05$, compared with grade II in the same gestational week; h, $P < 0.05$, compared with grade III in the same gestational week; i, $P < 0.05$, compared with grade IV in the same gestational week; VI, vascularization index.

Table 3. The FI value of the case and control groups in different gestational weeks

Gestational age (weeks)	Control group (n = 210)	Case group (n = 208)				
		I	II	III	IV	V
20-23	25.24 ± 8.23	26.76 ± 8.18	26.24 ± 8.19	30.63 ± 8.23	28.92 ± 8.19	29.25 ± 8.17
24-27	26.67 ± 8.21	29.91 ± 8.23	29.32 ± 8.24	28.53 ± 8.18	27.03 ± 8.17	28.47 ± 8.16
28-31	28.67 ± 8.22	29.90 ± 8.19	32.34 ± 8.22	31.54 ± 8.26	29.05 ± 8.20	29.56 ± 8.19
32-35	26.67 ± 8.24	28.90 ± 8.24	29.31 ± 8.21	28.45 ± 8.20	28.89 ± 8.24	28.92 ± 8.21
36-40	30.67 ± 8.20	29.50 ± 8.15	28.89 ± 8.20	28.10 ± 8.21	27.78 ± 8.21	29.37 ± 8.23

Note: FI, the flow index.

Table 4. The VFI value of the case and control groups in different gestational weeks

Gestational age (weeks)	Control group (n = 210)	Case group (n = 208)				
		I	II	III	IV	V
20-23	1.10 ± 0.43	0.70 ± 0.29[e]	0.60 ± 0.27[f]	0.53 ± 0.26[g]	0.43 ± 0.24[h]	0.34 ± 0.23[j]
24-27	1.63 ± 0.44[a]	1.00 ± 0.32[a,e]	0.92 ± 0.29[a,f]	0.80 ± 0.25[a,g]	0.68 ± 0.26[a,h]	0.51 ± 0.24[a,i]
28-31	2.26 ± 0.41[b]	1.41 ± 0.30[b,e]	1.34 ± 0.30[b,f]	1.19 ± 0.27[b,g]	0.92 ± 0.26[b,h]	0.83 ± 0.23[b,i]
32-35	3.22 ± 0.39[c]	2.03 ± 0.31[c,e]	1.91 ± 0.31[c,f]	1.75 ± 0.28[c,g]	1.61 ± 0.25[c,h]	1.48 ± 0.24[c,i]
36-40	4.38 ± 0.42[d]	2.77 ± 0.28[d,e]	2.58 ± 0.28[d,f]	2.44 ± 0.27[d,g]	2.27 ± 0.27[d,h]	2.09 ± 0.22[d,i]

Note: a, $P < 0.05$, compared with gestational age of 20-23 weeks; b, $P < 0.05$, compared with gestational age of 24-27 weeks; c, $P < 0.05$, compared with gestational age of 28-31 weeks; d, $P < 0.05$, compared with gestational age of 32-35 weeks; e, $P < 0.05$, compared with the control group in the same gestational week; f, $P < 0.05$, compared with grade I in the same gestational week; g, $P < 0.05$, compared with grade II in the same gestational week; h, $P < 0.05$, compared with grade III in the same gestational week; i, $P < 0.05$, compared with grade IV in the same gestational week; VFI, the vascularization flow index.

mean gestational age, body mass indexes (BMI), fetal gender and gestational week between the case and control groups (all $P > 0.05$).

The indexes of fetal renal arteries (VI, FI and VFI) in the case and control groups in different gestational week

The 3D-PDU imaging was performed to get the 3D power Doppler volume imaging of kidney and renal artery, and then the data of 3D power Doppler volume imaging was measured. Fetal vascular indexes (VI, FI and VFI) were obtained by 3D power Doppler histogram, as shown in **Figure 1**.

As shown in **Tables 2**-**4**, VI and VFI were significantly decreased in the case group compared with the control group (all $P < 0.05$). In the case group, VI and VFI showed a negative correlation with the disease degree of fetal HN in the same gestational week (all $P < 0.05$), but FI showed no significant difference (all $P > 0.05$). Both VI and VFI significantly increased with the advancement of gestational age (all $P < 0.05$) while FI

Table 5. The serum CysC levels of the case and control groups in different gestational week

Gestational age (weeks)	Control group (n = 210)	Case group (n = 208)				
		I	II	III	IV	V
20-23	1.56 ± 0.28	1.79 ± 0.16[a]	2.01 ± 0.12[b]	2.16 ± 0.13[c]	2.31 ± 0.12[d]	2.47 ± 0.11[e]
24-27	1.54 ± 0.30	1.86 ± 0.15[a]	1.96 ± 0.14[b]	2.17 ± 0.15[c]	2.30 ± 0.10[d]	2.48 ± 0.12[e]
28-31	1.57 ± 0.26	1.84 ± 0.14[a]	2.02 ± 0.13[b]	2.15 ± 0.12[c]	2.28 ± 0.13[d]	2.46 ± 0.11[e]
32-35	1.55 ± 0.28	1.77 ± 0.15[a]	2.00 ± 0.12[b]	2.18 ± 0.13[c]	2.33 ± 0.15[d]	2.52 ± 0.14[e]
36-40	1.58 ± 0.25	1.82 ± 0.16[a]	1.98 ± 0.15[b]	2.14 ± 0.14[c]	2.29 ± 0.14[d]	2.49 ± 0.13[e]

Note: a, $P < 0.05$, compared with the control group in the same gestational week; b, $P < 0.05$, compared with grade I in the same gestational week; c, $P < 0.05$, compared with grade II in the same gestational week; d, $P < 0.05$, compared with grade III in the same gestational week; e, $P < 0.05$, compared with grade IV in the same gestational week; CysC, cystatin C.

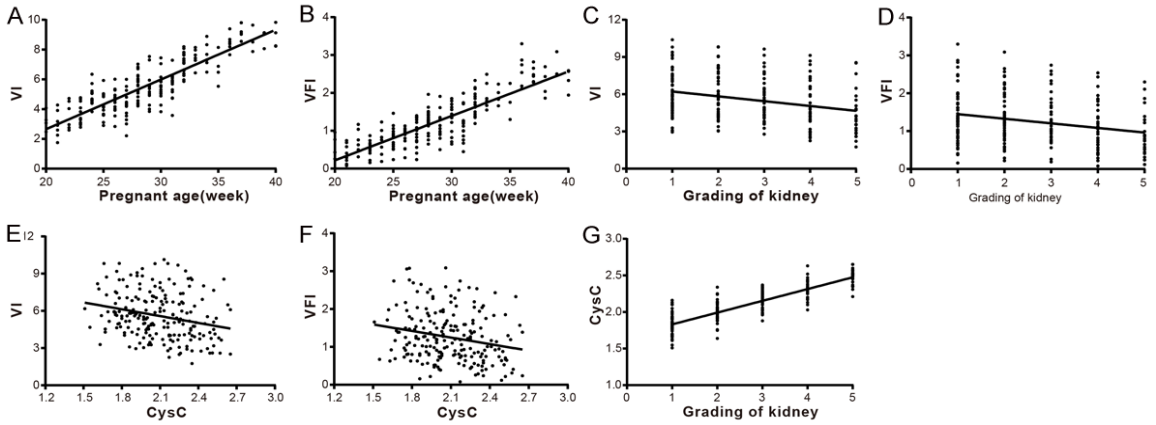

Figure 2. The correlations of the renal artery indexes, serum CysC, gestational week and the disease degree of fetal HN of patients in the case group. Note: A. VI was positively associated with gestational week; B. VFI was positively associated with gestational week; C. VI was negatively associated with the severity of fetal HN; D. VFI was negatively associated with the severity of fetal HN; E. VI was negatively associated with serum CysC; F. VFI was negatively associated with serum CysC; G. Serum CysC was positively associated with the severity of fetal HN; HN, hydronephrosis; CysC, cystatin C; VI, vascularization index; FI, the flow index; VFI, the vascularization flow index.

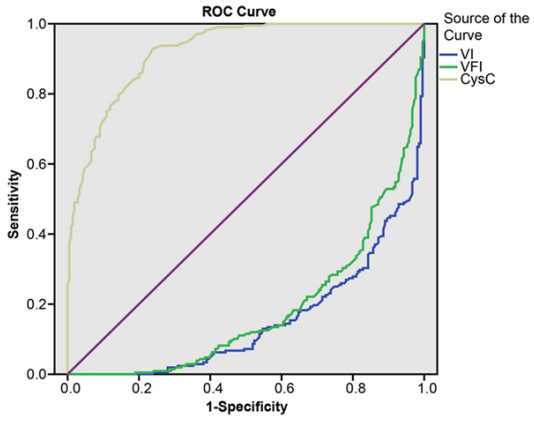

Figure 3. ROC analysis of renal artery indexes (VI, VFI) and serum CysC levels in predicting fetal HN. Note: ROC, receiver operating characteristic; HN, hydronephrosis; CysC, cystatin C; VI, vascularization index; VFI, the vascularization flow index.

had nosignificant difference between the case and control groups ($P > 0.05$).

The serum CysC levels of the case and control groups in different gestational week

Blood samples were extracted from the umbilical cord to detect serum CysC level and the results (**Table 5**) indicated that there was no significant difference of the serum CysC level-between 20-40 weeks of gestation in the control group ($P > 0.05$). Serum CysC level significantly increased in the case group compared with the control group. Serum CysC level was not significantly associated with gestational week in the case group ($P > 0.05$), while it was positively associated with the disease degree of fetal HN in the same gestational week.

The correlations of the renal artery indexes, serum CysC, gestational week and the disease degree of fetal HN of patients in the case group

The correlations of the renal artery indexes, serum CysC, gestational week and the disease

Table 6. ROC analysis of renal arteries indexes (VI, VFI) and serum CysC levels in predicting fetal HN

Parameters	AUC	Optimal cut-off value	Sensitivity (%)	Specificity (%)
VI	0.849	6.275	84.3	69.7
VFI	0.816	1.480	78.1	69.7
CysC	0.922	1.745	92.8	76.2

Note: ROC, receiver operating characteristic; AUC, area under the receiver operating characteristics curve; HN, hydronephrosis; CysC, cystatin C; VI, vascularization index; VFI, the vascularization flow index.

Table 7. Logistic regression analysis for risk factors of baseline characteristics, renal vascular indexes and CysC levels of fetal HN

Variable	Regression coefficient	*P* value	OR (95% CI)
Gestational age (weeks)	1.19	< 0.001	3.297 (2.2-5.43)
VI	-2.35	< 0.001	0.10 (0.04-0.21)
VFI	-2.59	< 0.001	0.08 (0.02-0.30)
CysC	0.54	< 0.001	1.72 (1.33-2.23)

Note: OR, odds ratio; CI, confidence interval; HN, hydronephrosis; CysC, cystatin C; VI, vascularization index; FI, the flow index; VFI, the vascularization flow index; BMI, Body Mass Index.

degree of fetal HN of patients in the case group was analyzed, the result (**Figure 2**) showed VI and VFI were positively associated with gestational week (r = 0.860/0.841, all $P < 0.001$). VI and VFI were negatively correlated with the disease degree of fetal HN (r = -0.285/-0.251, all $P < 0.001$). VI and VFI were negatively associated with serum CysC (r = -0.250/-0.221, all $P < 0.001$). There was positive correlation between serum CysC and the disease degree of fetal HN (r = 0.860, $P < 0.001$). No association was existed between gestational week and serum CysC or the disease degree of fetal HN ($P > 0.05$).

ROC analysis of renal artery indexes (VI, VFI) and serum CysC levels in predicting fetal HN

The ROC curves (**Figure 3**) were drawn with three test variables (VI, VFI and serum CysC), and a state variable of whether fetus had HN. The result indicated that the area under the ROC curve (AUC) of VI, VFI and serum CysC were 0.849, 0.816 and 0.922 respectively, which had moderate value in diagnosing fetal HN. The 3D-PDU showed a highest value in diagnosing fetal HN, when the optimal cut-off value of VI = 6.275 (sensitivity = 84.3, specificity = 69.7) and serum CysC = 1.745 (sensitivity = 92.8, specificity = 76.2). Based on the Youden Indexes [18], the optimal cut-off value, sensitivity and specificity of each parameter for analyzing the therapeutic effects of the patients were shown in **Table 6**.

Logistic regression analysis for the risk factors of baseline characteristics, renal artery indexes and serum CysC levels of fetal HN

Non-conditional logistic regression analysis was conducted using fetal HN as independent variable, and influential factors such as gestational age, renal vascular index (VI and VFI) and fetal serum CysC as dependent variables (**Table 7**). The results indicated that VI, VFI and serum CysC were associated with fetal HN (all $P < 0.05$); with VI and VFI decreased and serum CysC level increased, suggesting an increase of risk of fetal HN.

Discussion

The goal of this study was to verify renal arteries by 3D-PDU combined with serum CysC in fetal HN. Our study indicated that fetal renal VI, VFI and serum CysC could be useful diagnostic tools for fetal HN.

In our study, VI and VFI obviously decreased and serum CysC level significantly increased in HN fetuses. It was observed that VI and VFI were significantly lower in fetuses with HN and then subsequently developed renal failure compared with fetuses with HN and normal renal function [12]. It has been demonstrated that serum CysC was a possible alternative marker of renal function, especially in the detection of glomerular filtration rate (GFR) [19]. As an important indicator, GFR is used to evaluate kidney function [20]. A study showed that CysC has served as an alternate and maybe much more reliable filtration marker in estimating GFR [21].

One of the main findings in our study was that both VI and VFI significantly increased with the advancement of gestational week. The renal arteryization and the renal blood flow increased with the advancement of gestational week [22]. When being evaluated in small parts of the placenta, placental vascular indices may correlate

with gestational age [23]. Additionally, our result elucidated that gestational week was not associated with serum CysC or the disease degree of fetal HN. It has been reported that serum CysC was not associated with gestational week [24]. Serum CysC levels would not change with gestational week, and fetal gender, birth weight or bilirubin level had no significant effect on CysC levels [25]. Also, there was no significant difference in the predictive value of fetal HN in gestational week [26].

There are some limitations in our study. First, the limited sample size in our study may predispose the association of serum CysC and fetal HN, but not consider the correlation between other risk factors and fetal HN. Second, the study did not consider other results that could correlate with fetal HN. The limitations can be overcome by more specific studies with larger samples, and more advanced technologies.

In conclusion, this study indicated that VI and VFI were negatively correlated with the disease degree of fetal HN, and serum CysC level was positively associated with the disease degree of fetal HN. And the combination of VI and VFI and serum CysC level had higher diagnostic accuracy for fetal HN. We expect this study will be helpful for physicians in the diagnosis of fetal HN.

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Disclosure of conflict of interest

None.

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