Published in: Pediatric Nephrology (2003), vol. 14, iss. 5, pp. 393-399
Status: Postprint (Author's version)

Fetal renal artery flow and renal echogenicity in the chronically hypoxic state

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Abstract

The object of this study was to investigate the fetal renal arterial blood flow in normal and hyperecho-genic kidneys during the third trimester of gestation. The pregnancies screened were all chronically hypoxic. Depending on the etiology of the intrauterine chronic hypoxia, the cases were divided into two study groups. Group I comprised 120 pregnant women with pregnancy-associated hypertension and/or proteinuria. Group II consisted of 87 pregnancies with intrauterine growth retardation. Both study groups included pregnant women from the third trimester. Hyperechogenic renal medullae were detected in 15 out of 120 cases with pregnancy-associated hypertension and/or proteinuria, and in 22 fetuses of the 87 pregnancies involving intrauterine growth retardation. Fetal renal hyperechogenicity appears to be an indicator of fetal arterial circulatory depression, correlated with pathological changes in the resistance index for the fetal renal arteries. The fetal renal arterial blood flow resistance index was significantly lower in hyperechogenic cases. This may also be an in utero indication of subsequent intrauterine and neonatal complications, such as cesarean section because of fetal distress (43%), treatment in a neonatal intensive care unit (51%) or increased perinatal mortality (5.4%, as compared with 0.8-1.0% in the normal population). Detailed ultrasound and Doppler examinations of renal parenchyma and arteries appear to be useful methods in the prenatal diagnosis of reduced renal perfusion and of intrauterine hypoxia to detect possible pathological fetal conditions in utero.

Key words Fetus, Renal hyperechogenicity, Renal artery, Ultrasound, Vascular resistance

INTRODUCTION

The fetal and neonatal renal medulla is normally hypo-echogenic on ultrasonic examination and hence hyperechogenicity is a characteristic and striking sonographic feature [1-3]. Hyperechogenicity occurs in different diseases, which may have a clear diagnosis. However, in 20% of the cases of fetal renal hyperechogenicity, the pathomechanism is unclear [4]. Hyperechogenicity of both the renal cortex and the pyramids is a well-known phenomenon, but the importance of hyperechogenicity in cases with no anatomical alterations is controversial.

Flow velocity waveforms from branches of the abdominal aorta including the renal arteries potentially provide a more sensitive method to predict the adequacy of fetal oxygenation than an examination of aortic flow [5], Investigation of multiple fetal vessels improves the validity of blood flow parameters [6, 7]. Fetal renal arterial resistance index decreases moderately during the third trimester of pregnancy, possibly related to the increased blood flow of the renal circulation.

In the fetus, the high vascular resistance observed in the lower extremities during the third trimester cannot explain the reduced renal vascular resistance of advancing gestation, since this increased lower extremity vascular resistance is associated with a decreased umbilical arterial vascular resistance [8].

The aim of the present study was to establish a correlation between abnormal renal arterial blood flow and the clinical outcome in fetuses with hyperechogenic renal medullae to discern if these probes are useful in the early detection of chronically hypoxic state in the fetal life.

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MATERIAL AND METHODS

Fetal kidney ultrasound examinations were performed. Renal blood flow and echogenicity studies were carried out with two ATL ultrasound machines (Ultramark-9 and 3000), using the Combison 530 Kretz technique with a 3-5 MHz abdominal transducer, and EUB-450 ultrasound equipment with a 3.5 MHz transducer.

Umbilical artery examination

The umbilical cord was localized and the umbilical artery identified: the Doppler gate was placed in the lumen of the vessel and recordings were made on a strip-chart recorder. Signals were recorded with the fetus in a quiet state and during apnea.

Renal artery examination

An axial view of the fetus was obtained at the level of the kidneys. The Doppler gate was placed at the renal hilus, so that the maximum signal from the renal artery was obtained. The abdominal aorta gives a significantly different signal, which helps in differentiating between the two waveforms. There is no significant difference between the two sides of the renal artery [5], thus fetal renal arterial blood flow was determined on only one side.

Flow measurements were interpreted with respect to the normal ranges for the umbilical and renal arteries. The normal range was defined by regression lines and confidence values: the mean (a regression line in the middle) ± standard deviation (SD; two lines below and above the mean line). The normal field was taken from literature data on the umbilical artery [9] and the renal artery [5, 10, 11]. We employed the international standard.

Measurements were made during the absence of fetal breathing movements, since fetal breathing movements are known to exert marked effects on blood flow. The most uniform frozen waveform was used for calculation of the resistance index, defined as the difference between the peak systolic and end-diastolic frequency shifts divided by the peak systolic frequency shift [12]. The mean and the SD of the resistance index were calculated for both fetal vessels, a normal distribution being assumed [13].

The study group consisted of 207 pregnancies complicated by chronic hypoxia in the third trimester. Pregnancies were investigated between 24 and 39 weeks of gestation. The gestational age was calculated according to Naegele's rule and a first trimester ultrasound examination. The clinical outcome of the neonates was investigated until 14 days after birth.

Depending on the etiology of intrauterine chronic hypoxia, the pregnancies were divided into two study groups. Group I comprised those cases with pregnancy-associated hypertension and/or proteinuria (120 cases). This group was further subdivided into a positive group (15 cases) and a control group, those cases in which fetal renal hyperechogenicity was detected without any fetal anatomical abnormalities (105 cases).

Pregnancy-associated hypertension and/or proteinuria was defined according to the guidelines of the Committee of the American Obstetricians and Gynecologists [14], which recommend that a total protein concentration of 300 mg or more per liter in a 24-h urine collection should be regarded as abnormal; hypertension in pregnancy was defined as two consecutive measurements of diastolic blood pressure of 90 mmHg or more 4 h or more apart. The finding of edema and weight gain in pregnancy as a sign of preeclampsia is a matter of dispute, and although edema and excess weight gain may be valuable signs in particular clinical circumstances, they are unsuitable signs for classification purposes [14].

Group II comprised pregnancies involving intrauterine growth retardation (87 cases). Intrauterine growth retardation was established by the Hadlock weight estimation, based on biparietal diameter, abdominal circumference and femur length. The 22 positive cases were compared with the remaining intrauterine growth-retarded neonates (65 cases).

Hyperechoic pyramids were detected by comparison with the renal cortex, liver or spleen since normal medullary pyramids are hypoechogenic in the fetus and in newborns. The sonographic finding of hyperechogenicity is, thus, noteworthy [15].

The abnormal waveforms of the renal arteries that were detected were decreased systolic flow, diastolic zero flow, reverse flow, postsystolic ischemia or higher flow parameters than those of the normal field [3].

The umbilical artery and renal artery blood flow resistance indices were analyzed statistically to compare the cases with and without fetal renal hyperechogenicity. The results were analyzed by the Chi-square test. The method was analyzed via the odds ratio.

RESULTS

For this study, 217 fetuses in 207 pregnancies were examined for hyperechogenicity of the renal medulla: these included 120 pregnancies (120 babies) with pregnancy-associated hypertension and/or proteinuria (group I), and 87 pregnancies (97 babies) with intrauterine growth retardation (group II).

In group I (58%), the 120 pregnancies with pregnancy-associated hypertension and/or proteinuria included 15 cases with fetal renal hyperechogenicity. Table 1 shows the data and clinical outcome of these 15 babies (6 girls and 9 boys). The mean (± SD) duration of gestation at birth was 35.7 ± 3.3 weeks and the mean (± SD) birth weight was 2438 ± 741 g. The Apgar scores were 7.5 ± 2.5 at the 1st min and 8.9 ± 1.3 at the 5th min. In the postnatal period, ultrasonography revealed renal hypoplasia in 1 case (6.6%) and transitory renal hyperechogenicity in 6 cases (40%), but there were no other renal lesions in the hyperechogenic group. In the control group (babies without medullary hyperechogenicity, whose mothers had pregnancy-associated hypertension and/or proteinuria), 3 polycystic kidneys were identified in the fetuses in the intrauterine period. The mode of delivery was cesarean section in 7 cases in the hyperechogenic group (46%), and in 6 cases in the control group (6%). Babies with hyperechoic medullae were transferred to the neonatal intensive care unit in 6 cases (40%). In the postnatal period, respiratory distress developed in 3 cases (13.6%) and necrotizing enterocolitis in 1 case (4.5%) in the positive group, while there were no instances in the control group. Babies with hyperechoic medullae have six times the risk (analyzed by the odds ratio) of a pathological clinical outcome compared to babies with a normal echoic kidney in pregnancy-associated hypertension and/or proteinuria: the odds ratio was 6.22 (95% confidence limits: 2.84, 13.62).

In group II (42%), 87 pregnancies with intrauterine growth retardation involved 22 cases with fetal renal hyperechogenicity. Table 2 contains data on these 22 babies (16 girls and 6 boys). The mean duration of gestation at birth was 37.6 ± 2.4 weeks and the mean birth weight was 2683±727 g. The Apgar scores were 7.2±1.8 at the 1st min and 8.5 ± 1.4 at the 5th min. In this group there were no anatomical abnormalities in the kidneys. In the control group there were 2 renal malformations (2.6%): 1 multicystic kidney, and 1 hydronephrosis. Pathological fluid was observed in only 1 case (4.5%) among the babies with hyperechoic medullae, as compared with 1 case with polyhydramnios (0.9%) and 8 with oligohydramnionos (7.6%) in the control group. Five babies had a perinatal infection (23%) (unconfirmed in 1 case). Two babies had an intrauterine parvovirus infection and in 1 case there was a suspicion of this, but the origin was unclear (9%). Overall, the infection rate was 32%. In the control group, infection was observed in 4 babies (5.2%). Two of them were twins, whose mother was HIV positive; the others 2 involved cytomegalovirus infections.

Cesarean sections were performed in 9 infants in the hyperechogenic group (40.9%), and in 13 of the control group (17%). Babies with hyperechoic medullae were transferred to the neonatal intensive care unit in 13 cases (59%).

There were very serious complications in 2 cases (9%). One baby died in utero. One newborn died on the 2nd day of life with bradycardia, apnea, metabolic acidosis, cataract and intraventricular hemorrhage.

In the control group there were serious complications in 3 pregnancies (3.9%). One was a twin pregnancy, where the baby died because of a heart malformation, the result of a rubella infection. The twin sibling exhibited only retarded growth, but the clinical outcome was good. The other stillbirth in the control group was due to left ventricular hypoplasia. A third baby with a heart malformation was born alive.

In case 12 (Table 2), meconial amniotical fluid was-noted and the newborn was resuscitated. Intrauterine parvovirus infection and fetal hydrops had been recognized before the birth.

In the control group of intrauterine growth-retarded pregnancies, the following pathological cases were found: hydrocephalus (1 case), microcephalia (1 case), agenesia of the corpus callosum (1 case), facial malformation (1 case), spina bifida (1 case), oesophageal atresia (1 case), gastroschisis (1 case) and single umbilical artery (1 case) (comprising 10.4% of the control group).

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Table 1 *Characterization of neonates with hyperechogenic medullae in pregnancy-associated hypertension and/or proteinuria (NICU neonatal intensive care unit)*

Case no.	Sex	Delivery weight (g)	Delivery age (weeks)	Apgar score (1st min)	Postnatal clinical outcome (5th min)	Transfer to NICU	
1	M	1600	35	4	7	Cesarean section, uricosuria, azotemia, anuria, postnatal renal hyperechogenicity	+
2	M	3600	32	7	9	Cesarean section, without any problem	-
3	M	2200	36	7	9	Without any problem	-
4	M	1460	31	2	4	Cesarean section, postnatal renal hyperechogenicity, renal hypoplasia on right side, necrotizing enterocolitis	+
5	F	2980	39	10	10	Without any problem	-
6	M	2750	39	10	10	Postnatal renal hyperechogenicity	-
7	F	3740	38	9	10	Without any problem	-
8	F	1500	31	5	7	Cesarean section, respiratory distress syndrome	+
9	M	3010	38	9	10	Without any problem	-
10	M	2940	38	10	10	Without any problem	-
11	M	3170	40	10	10	Cesarean section, postnatal renal hyperechogenicity	-
12	F	2870	38	10	10	Without any problem	-
13	F	1130	28	7	9	Cesarean section, prematurity labor, respiratory distress syndrome, postnatal renal hyperechogenicity	+
14	F	2180	40	10	10	Prematurity labor, cesarean section, prematurity labor, respiratory distress	+
15	M	1440	32	2	8	Syndrome, postnatal renal hyperechogenicity	+
Mean		2438.00	35.67	7.47	8.87		
SD		740.8	3.33	2.44	1.26		

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Table 2 Characterization of neonates with hyperechogenic medullae in intrauterine growth retardation *(HELLP* hemolysis, elevated liver enzymes, low platelets)

Case no.	Sex	Delivery weight (g)	Delivery age (weeks)	Apgar score (1st min)	Postnatal clinical outcome (5th min)	Transfer to NICU	
1	F	2170	40	9	10	Without any problem	+
2	F	3035	40	8	9	Perinatal infection, fetal tachycardia	+
3	F	3030	39	8	9	Without any problem	-
4	F	3600	40	9	10	Perinatal infection	+
5	M	3320	39	9	10	Perinatal infection	+
6	M	3100	38	8	9	Cesarean section	-
7	M	2030	35.5	9	10	Toxicoman mother, cesarean section	+
8	F	2020	38	8	9	Fetal infection?	+
9	M	950	31	1	6	Bradycardia, apnea, metabolic acidosis, cataract, intraventricular hemorrhage, death on 2nd day	+
10	F	3260	41	5	7	Without any problem	-
11	F	1580	33	7	9	HELLP syndrome, cesarean section	+
12	F	2260	33	4	8	Intrauterine parvovirus infection, hydrops fetalis, meconial amniotic fluid, Cesarean section, reanimation	+
13	F	3455	39.5	7	8	Cesarean section	+
14	F	3800	40	8	9	Without any problem	+
15	F	2860	37	9	9	Cesarean section	-
16	M	2910	38	9	10	Without any problem	-
17	F	3720	39	8	8	Perinatal infection	+
18	F	2460	36	8	9	Without any problem	-
19	F	2260	38	7	9	Oligohydramnios, perinatal infection?	+
20	F	3600	39	9	9	Cesarean section	-
21	F	3190	41	9	10	Without any problem	-
22	M	420	31	0	0	Stillborn	No transfer
Mean		2683.18	37.55	7.23	8.50		
SD		727.15	2.43	1.78	1.27		

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There was pathological amniotic fluid in 1 baby with hyperechogenic medullae (4.6%), versus 9 cases (11.8%) in the control group. Babies with hyperechoic medullae had 1.5 times the risk by the odds ratio of an abnormal postnatal outcome compared with babies with normal echoic kidneys in intrauterine growth retardation: the odds ratio was 1.5 (95% confidence limits: 1.00, 2.26).

Doppler flow studies of umbilical arterial blood flow velocity did not reveal any significant differences in any case. This applies to groups I and II without fetal renal hyperechogenicity [χ^2=2.049 (P<0.05) in pregnancy-associated hypertension and/or proteinuria cases and χ^2=0.075 (P<0.05) in intrauterine growth-retarded cases] (Figs. 1, 2).

Doppler ultrasonography of the renal artery revealed a significant disparity between babies with hyperechoic medullae in pregnancy-associated hypertension and/or proteinuria (Fig. 3) or intrauterine growth retardation (Fig. 4). As compared with the normal picture (Fig. 5), the renal arterial blood flow velocities displayed pathological waveforms, including decreased systolic flow (Fig. 6) or postsystolic incisura (Fig. 7).

The chi-square test was applied for statistical analyses [χ^2=3.71 (P<0.05) in pregnancy-associated hypertension and/or proteinuria cases, and χ^2=3.76 (P<0.05) in intrauterine growth retarded cases]. In cases without fetal renal hyperechogenicity, there was a reduced resistance index, but differences were not significant.

Fig. 1 *Resistance index of umbilical arteries (fetuses with hyperechoic medullae in pregnancy-associated hypertension and/or proteinuria) (n=15) (RI resistance index)*

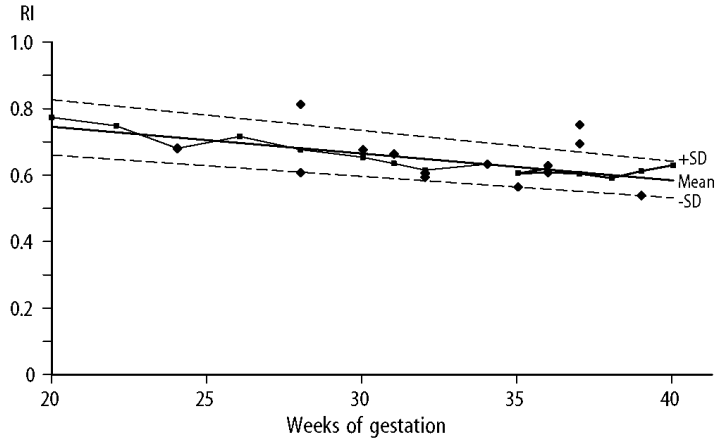

Fig. 2 *Resistance index of umbilical arteries (fetuses with hyperechoic medullae with intrauterine growth retardation) (n=22)*

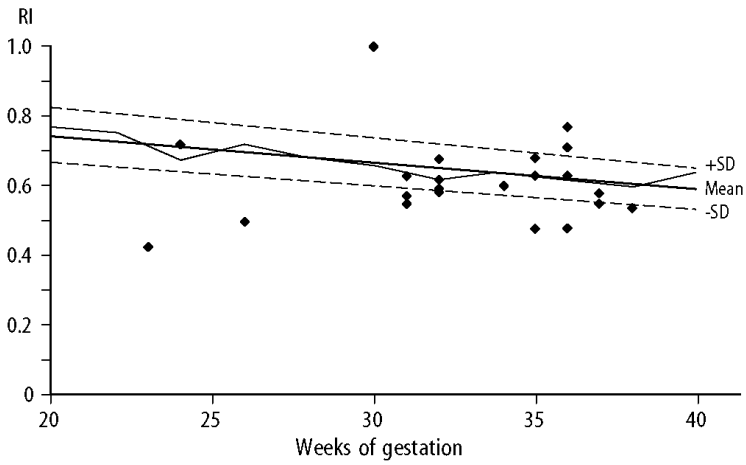

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Fig. 3 *Resistance index of renal arteries (fetuses with hyperechoic medullae in pregnancy-associated hypertension and/or proteinuria) (n=15)*

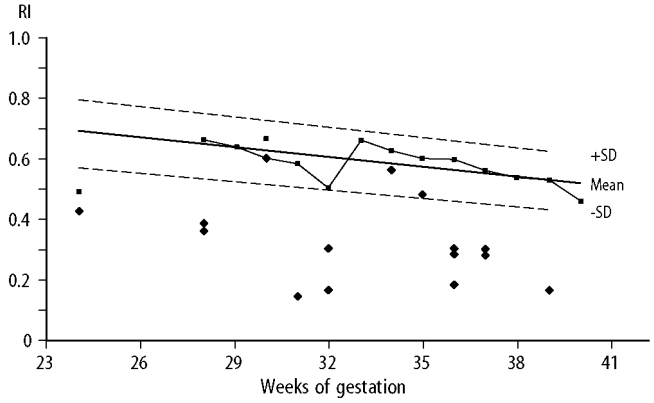


Fig. 4 *Resistance index of renal arteries (fetuses with hyperechoic medullae with intrauterine growth retardation) (n=22)*

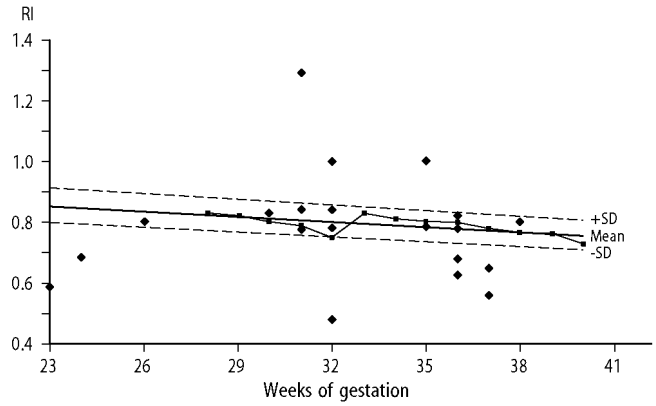


Fig. 5 *Normal blood flow-velocity waveforms in the fetal renal artery at 28th week of gestation. The Doppler gate is positioned over the main renal artery*

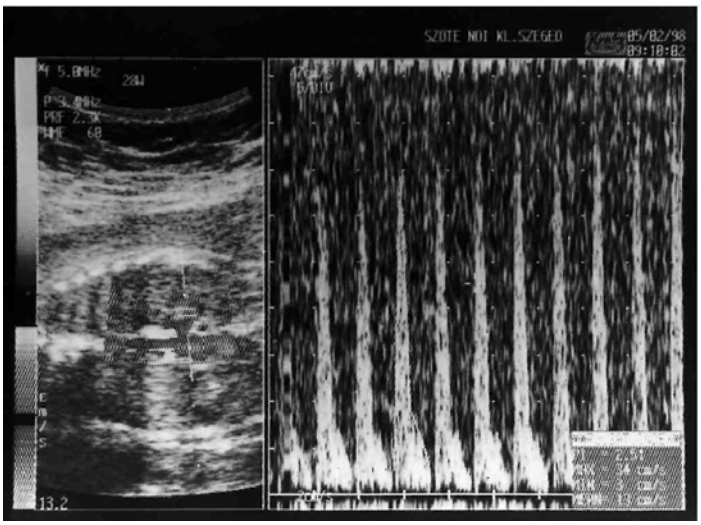


Fig. 6 *Decreased blood flow-velocity waveforms in the renal artery at 32nd week of gestation. The Doppler gate is positioned over the main renal artery*

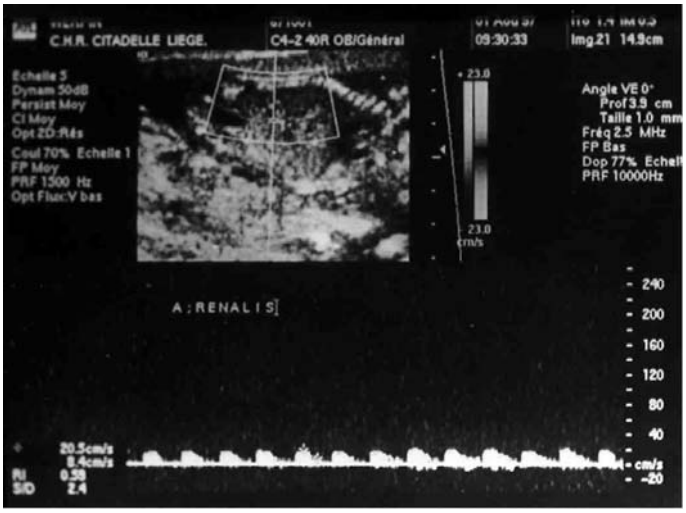
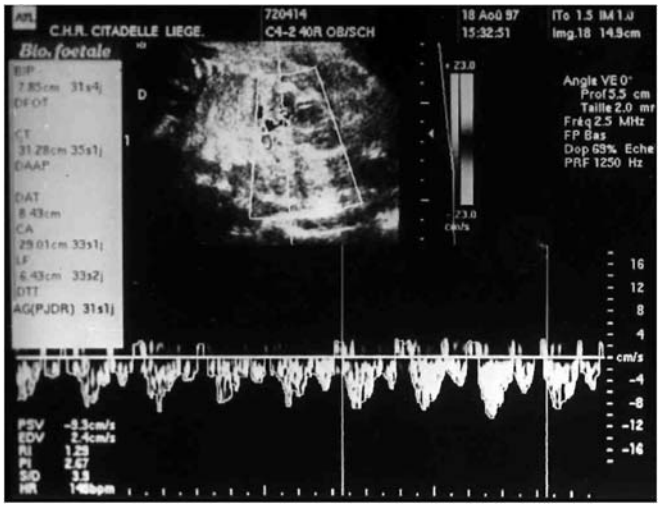


Fig. 7 *Flow-velocity waveforms with postsystolic incisura in the renal artery at 31st week of gestation. The Doppler gate is positioned over the main renal artery*



DISCUSSION

Visualization of small fetal vessels such as the renal artery was described by Campbell et al. in 1988 [16]. The renal blood flow is estimated as 2-3% of the cardiac output under physiological conditions because of the very high pulsatility index (i.e., a very high resistance) in the human fetal renal artery. During hypoxemia, the renal blood flow fell by 25-50% as compared to the baseline values, but the exact mechanism of this reduction has not been elucidated [17]. This would imply that, instead of a local vasoconstriction of the renal vasculature, the fetal renal blood flow may be maintained by a combination of mechanisms including an increase in arterial pressure and the intrarenal action of various metabolites, which ultimately induce a similar hemodynamic change [18]. A direct relationship has been reported between hypoxia and the renal artery pulsatility index (e.g., resistance) [19].

Perinatal renal hyperechogenicity may have different causes, but in a considerable proportion of cases (about 20%), there was no anatomical alteration [4]. Intrauterine and/or neonatal renal hyperechogenicity has been interpreted as a sign of intrauterine hypoxia [20, 21].

We investigated intrauterine hypoxia using indirect ultrasonographic signs: renal hyperechogenicity, and decreased flow parameters in the umbilical artery and the renal artery [5, 17, 20]. The screened pregnancies were those with chronic hypoxia, caused by pregnancy-associated hypertension and/or proteinuria and intrauterine growth retardation. We selected these causes because they are well defined and the diagnosis is possible in the prenatal period. There is similarity between these two populations in terms of the causes of the intrauterine chronic hypoxia. We examined these two types of pathological pregnancies to determine other chance differences and investigate the importance of renal hyperechogenicity in hypoxia. In this study, we investigated these parameters in parallel with the clinical outcome.

The blood flow parameters measured in 15 fetal cases with pregnancy-associated hypertension and/or proteinuria and in 22 cases with intrauterine growth retardation suggest that a pathological renal circulation is connected with the chronic hypoxic state. We found no significant deviation in the umbilical artery, despite the fact that renal artery flow parameters were significantly different.

There is good correlation between the progressive increase in renal vascular resistance and the decreased organ perfusion [22]. By Doppler methods, both fetal and uterine blood flow can be measured, thereby permitting an assessment and detection of dysfunction affecting the uteroplacental circulation. In fetuses in a chronically hypoxic state, these were significantly below the lower limits of the normal range ($P<0.05$).

The statistical results suggest a good relation between the diagnostic method and the clinical outcome. We used the chi-square test for statistical analyses of vessel flow abnormalities because we expected the blood flow data to lie in a standardized range, not a fixed one. The odds ratio was used to analyze the association between prenatal pathological renal echogenicity and postnatal clinical outcome. A 6 times higher risk of a pathological outcome was demonstrated by the odds ratio method when kidneys were hyperechoic in pregnancy-associated hypertension and/or proteinuria. In intrauterine growth retardation, the risk was 1.5 times higher than normal. This intrauterine growth retardation group is a very heterogeneous population. The cause of the retardation is not necessarily intrauterine hypoxia, but there is a very strong suspicion of it. This explains why the risk of a pathological outcome is lower than in pregnancy-associated hypertension and/or proteinuria.

We extended the ultrasonographic study over the intrauterine period and observed consequences of acute/chronicle intrauterine hypoxia such as retarded growth (birth weight below P_{10}) and Cesarean section as the mode of delivery. There were higher rates of cesarean section (12 times), perinatal infection (8 times), transfer to the neonatal intensive care unit (11 times), perinatal mortality (4.5 times) and necrotizing enterocolitis (3 times) among babies with hyperechoic medullae than in the control group, where there was a suspected chronic hypoxic state with a normal echoic fetal kidney. Of course, these conditions arise with much lower rates in the normal population.

The redistribution of the fetal circulation results in abnormal renal flow. The redistribution of the blood flow is due to fetal hypoxemia. During this process, the fetal kidneys are among those organs that are sometimes compromised, leading to transient renal insufficiency, usually a benign disease [23]. In theory, fetal hypoxia triggers a discordant vasomotor reaction in the common carotid artery and descending thoracic aorta. In the descending thoracic aorta, a reduction in the mean blood velocity and an increase in the pulsatility index of flow velocity develop, while in the common carotid artery the mean blood velocity rises in parallel with a decrease in the pulsatility index in the flow velocity waveform [5]. The increased resistance index of the descending thoracic aorta could be a component of the centralization of the fetal circulation due to chronic hypoxia. The fetal renal blood flow may similarly be affected as a result of an elevated intravascular resistance, leading to a decline in renal perfusion [10].

In those neonates where there had been renal hyper-echogenicity due to fetal hypoxia, this modified echogenicity of the renal medulla is usually preserved during the short postnatal oliguric period [1, 24]. These ultrasound signs disappear quickly after the first postnatal urinary evacuation. In our investigations the hyperechoic features were found to be lost by day 2 in 51% and by the end of the 2nd week in 73% of the cases. In 27%, the intrauterine renal hyperechogenicity demonstrated no ultrasonographic features. This presumed protein blockage disappeared with the start of urinary production after birth, and this was connected with the relatively rapid decrease in hyperechogenicity in the postnatal period.

In the postnatal period it is possible to identify the different etiologies of fetal renal hyperechogenicity (nephro-calcinosis, Bartter syndrome, renal tubular acidosis, etc.) [25]. The etiology is sometimes already clear during the fetal period (e.g., polycystic kidney) [26]. In contrast, renal hyperechogenicity due to fetal hypoxia develops in the last period of pregnancy, in our cases between the 25th and 39th weeks of gestation. Our results show that

the fetal circulation can compensate for the hypoxic state for a rather long time. In transient hyperechogenic cases, the cause is transient renal insufficiency. The increased echogenicity may represent a tubular blockage caused by Tamm-Horsfall protein precipitation [3, 23, 27]. There is a body of evidence supporting the idea that the transient renal insufficiency is correlated with Tamm-Horsfall proteinuria in the postnatal period [23].

Renal hyperechogenicity as a complication of fetal hypoxia is benign if transitory. Fetal renal failure of hypoxic origin does not automatically lead to tubular necrosis. The etiology and clinical features of acute necrosis and acute blockage of the tubules are the same. Transitory renal failure and necrosis can, therefore, be differentiated only by the degree and the course of the disease [28, 29]. In our cases the echogenicity of the medullae could be explained by the same mechanism, which started in the final trimester of intrauterine life.

Change in the renal artery flow resistance is seen much sooner using the Doppler data than change in umbilical arterial flow. The study shows that the renal artery flow resistance already deviates significantly from the normal range, while that for the umbilical artery is in the normal field. The renal medullary hyperechogenicity and the decrease in renal artery flow appear to be good predictive signs of serious intrauterine hypoxia.

The measurement fetal renal hyperechogenicity is a simple examination, and should, therefore, be performed during a routine scan. It is a sensitive sign, and measurement of the fetal renal artery blood flow is essential because the changes in the flow parameters are more characteristic. However, measurements on the fetal renal artery are difficult. For this reason, we suggest initial detection of renal echogenicity. Then, if hyperechogenicity is found, the blood flow can be measured with the Dopp-ler method to detect the redistribution of the fetal circulation, as an early sign of an intrauterine hypoxic state. It is important, therefore, to direct women with such pregnancies to a perinatal intensive care center to detect the possible pathological fetal state.

It is hoped that new conception for the study of fetal hypoxia - such as fetal kidney ultrasonographic investigation - will enhance our understanding of the complex issue of normal and abnormal development of pathological pregnancies.

Our study shows that the combined use of echogenicity of the fetal renal parenchyma and Doppler flow study of the fetal renal artery can detect pathological changes in the renal artery. It may provide a better prediction of outcome in chronically hypoxic pregnancies. Thus, besides the routine scan, renal ultrasonography may be important in the diagnosis of fetal hypoxia at an early state.

Whether there is a quantitative relation between the magnitude of the hypoxia and the amplitude of the renal flow reduction reflected by hyperechogenicity of the fetal renal medulla remains to be elucidated.

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