Prenatal and postnatal evaluation of foetal renal hyperechogenicity in pregnancies complicated with pre-eclampsia and intrauterine growth retardation

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Publications

I  Tálosi G, Streitman K, Surányi A, Pinter S, Horvath I, Mulugeta Z:

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### 1. Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AMF</td>
<td>adenosine monophosphate</td>
</tr>
<tr>
<td>ADP</td>
<td>adenosine diphosphate</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>Ca</td>
<td>calcium</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>EPH-gestosis</td>
<td>oedema, proteinuria and hypertension during pregnancies</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>GMP</td>
<td>guanosine monophosphate</td>
</tr>
<tr>
<td>GDP</td>
<td>guanosine diphosphate</td>
</tr>
<tr>
<td>GTP</td>
<td>guanosine triphosphate</td>
</tr>
<tr>
<td>Hadlock weight estimation</td>
<td>$\log_{10}(\text{estimated foetal weight})=1.3598+0.051(\text{abdominal circumference})+0.1844(\text{femur length})-0.0037(\text{femur length})(\text{abdominal circumference})$</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>haemolysis, elevated liver enzymes, low platelets syndrome</td>
</tr>
<tr>
<td>HGFRT</td>
<td>hypoxanthine guanine phosphoribosyl transferase</td>
</tr>
<tr>
<td>HMD</td>
<td>hyaline membrane disease</td>
</tr>
<tr>
<td>H2O</td>
<td>water</td>
</tr>
<tr>
<td>IMP</td>
<td>inosine monophosphate</td>
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<tr>
<td>IRDS</td>
<td>idiopathic respiratory distress syndrome</td>
</tr>
<tr>
<td>IUGR</td>
<td>intrauterine growth retardation</td>
</tr>
<tr>
<td>i.v.</td>
<td>intravenous</td>
</tr>
<tr>
<td>K</td>
<td>potassium</td>
</tr>
<tr>
<td>kg</td>
<td>kilogram</td>
</tr>
<tr>
<td>NICU</td>
<td>neonatal intensive care unit</td>
</tr>
<tr>
<td>NST</td>
<td>non-stress test</td>
</tr>
<tr>
<td>P10</td>
<td>ten percentile</td>
</tr>
<tr>
<td>P3</td>
<td>three percentile</td>
</tr>
<tr>
<td>pCO2</td>
<td>partial carbon dioxide pressure</td>
</tr>
<tr>
<td>pH</td>
<td>negative logarithm of hydrogen ion concentration of a solution</td>
</tr>
<tr>
<td>P.I.</td>
<td>pulsatility index</td>
</tr>
<tr>
<td>pO2</td>
<td>partial oxygen pressure</td>
</tr>
<tr>
<td>R.I.</td>
<td>resistance index or Poccelot index</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SGOT/ASAT</td>
<td>serum glutamate-oxaloacetic-transaminase / aspartate aminotransferase</td>
</tr>
<tr>
<td>SGPT/ALAT</td>
<td>serum glutamate-pyruvate-transaminase / alanine aminotransferase</td>
</tr>
<tr>
<td>GGT</td>
<td>gamma-glutamyl transferase</td>
</tr>
<tr>
<td>urea-N</td>
<td>urea nitrogen</td>
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<tr>
<td>UV</td>
<td>ultraviolet</td>
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2. Summary

A longitudinal study was carried out in order to find an early indirect sign of intrauterine hypoxia by means ultrasonography. A relationship was sought between renal hyperechogenicity and the hypoxic state of foetuses. The study determined the prevalence and risk factors of foetal renal hyperechogenicity in hypoxic pregnancies.

The kidney parenchyma is very sensitive to hypoxia, and hypoxic renal failure is accompanied by hyperechogenicity of the kidneys. Real-time ultrasonography with Doppler equipment (Hitachi EUB-450, Combison 450, ATL Ultramark-9 and 3000) was used for the examination of foetal and neonatal renal hyperechogenicity. To compare groups, the chi-square test and odds ratio calculation were employed. A probability level of $p<0.05$ was considered statistically significant.

During the four-year survey on 210 pregnant women, the overall average prevalence of foetal renal hyperechogenicity in chronically hypoxic pregnancies (such as IUGR and EPH-gestosis) was 19% (40 cases). There were significant differences in the proportions of pregnancies with foetal renal hyperechogenicity. The perinatal mortality rate in pregnancies with foetal renal hyperechogenicity exhibited a significantly higher prevalence (5.4%) than that in normal patients (0.8-1.0%). This may also be an in utero indication of subsequent intrauterine and neonatal complications, such as caesarean section for foetal distress (43%), or treatment in a neonatal intensive care unit (51%).

In our opinion, the medullary hyperechogenicity of neonatal kidneys seems to be a pathological phenomenon. The statistical approach demonstrates a significant correlation between foetal renal hyperechogenicity and a pathological postnatal clinical outcome ($p<0.01$). Our data suggest that foetal renal hyperechogenicity is to be a good predictive sign of intrauterine hypoxia and the clinical outcome. However, foetal renal hyperechogenicity has a low specificity for the detection of intrauterine hypoxia, as other conditions, such as anatomical abnormalities, can present with the same ultrasonographic pattern.

Our study highlights the importance of examining the foetal renal echogenicity. The measurement of foetal renal hyperechogenicity is simple, and should therefore be performed during a routine scan. It is a sensitive sign, and subsequent measurement of the blood flow in the foetal renal arteries is essential as the changes in the flow parameters are more specific markers of intrauterine hypoxia. However, measurements on the foetal renal artery are difficult. For this reason, we propose the detection of renal echogenicity as a first-line test. If hyperechogenicity is found, the blood flow should be measured with the Doppler method in
order to detect the redistribution of the foetal circulation, as an early sign of an intrauterine hypoxic condition.

Detailed ultrasonography and Doppler examinations of the renal parenchyma and arteries of foetuses appear to be useful in the prenatal diagnosis of reduced renal perfusion and of intrauterine hypoxia and may reveal possible pathological foetal conditions in utero.

We believe that the ultrasonographic investigation of foetal kidneys and the new approach presented for studying foetal hypoxia will contribute to a better understanding of the mechanism of normal and pathological pregnancies.
3. Introduction

Modern perinatology currently poses some very important problems. One of them involves detection of the degree and duration of hypoxia, and protection against this problem. Cardiotocography and pathophysiology monitoring have helped to reduce the foetal mortality from 0.6 to 0.5 percentile. A randomized comparison of umbilical artery velocimetry and cardiotocography for the surveillance of foetuses demonstrated that the use of Doppler velocimetry makes the management of pregnancies with foetuses more cost-effective (2, 117). The number of desperate neonates is also reduced. There has been no investigation of the shock organs (e.g. the kidneys) in foetuses or neonates by ultrasonography.

![Diagram of purine nucleotide metabolism](image)

Figure 1. Schematic representation of metabolism of purine nucleotides (53)

Non-invasive monitoring is very important. Perinatal asphyxia causing organ damage is an appreciable neonatal problem (112, 123, 125). Endogenous stress is caused by pathological conditions such as intrauterine hypoxia, perinatal asphyxia, respiratory distress syndrome, congestive cardiopathy, polycytaemia, diabetic foetoopathy and pulmonary hypertension. Its study is challenging because it is difficult to measure. Because of endogenous stress, acute renal failure can develop in foetuses or and neonates. The kidney is an organ very sensitive to
ischaemic damage. Foetal and neonatal asphyxia are the main causes of a transient renal impairment or acute renal failure. The mechanism is as follows: prolonged hypoxia causes hypovolaemia, low blood pressure, and metabolic and/or respiratory acidosis (54). The renal perfusion is damaged, and the glomerular filtration and tubular functions are therefore reduced (9, 37, 68, 114, 124). The first sign is oliguria, and the intravascular volume decreases, but the level of vasopressin in the serum increase. Renal vasoconstriction develops in consequence of angiotensin-II, intrarenal adenosine, endothelin and/or catecholamine (39, 55, 64) and this mechanism causes microcirculatory problems (29).

In severe hypoxia, numerous mediators play roles in controlling the haemodynamic and tubular functions, such as renal adenosine, the renin-angiotensin system, atrial natriuretic peptide, the prostaglandin system, purine nucleotides (Fig. 1.), free radicals, nitric oxide, etc. (23, 28, 49, 51, 64, 67, 76, 101, 106, 118)

Uric acid precipitation has been detected in the renal medulla and in the distal tubules. Polarised light microscopy has revealed uric acid accumulation in the inferior tubules, i.e. urate-caused nephropathy.

Neonates always have hyperuricaemia in a severe hypoxic condition (7, 28, 38, 111), with a very good correlation to the seriousness of the disease (1). There is a possibility of renal failure, if the uric acid level is more than 400 μmol/l in neonates with respiratory distress (7). If neonates are treated for respiratory distress with allopurinol and peritoneal dialysis, the survival increases significantly (7). First of all, vasomotor nephropathy develops in renal failure caused by hypoxic shock. In this stage, there is no organic damage, but vasoconstriction and antidiuretic effects are important. When the hypoxic condition is more serious, it is urate-caused nephropathy in acute shock, in which there is uric acid precipitation. Later, due to the good renal function, the precipitation will disappear, but the renal tubules will be damaged. On normalisation of the serum uric acid level, the renal pyramids are restricted during some days (28, 63, 85).

Urate-caused nephropathy in acute shock can be detected by ultrasonography. In the pyramids, there are transitory hyperechogenic areas. If urate-caused nephropathy in acute shock is long-lasting and the renal blood circulation does not normalize, the severe hypoxia causes necrosis in the sensitive tubules. The impaired tubular perfusion causes necrosis in the tubular epithelium. For this reason, liquid passes from the tubular lumen to the interstitial space. The potentialities of regeneration fall, because of damage to the tubular basal membrane. The serious hypoxia damages the proximal and distal tubules (7, 65). This condition is renal necrosis, which is a permanent disease.
In 1968, Voight and Farber documented (119) the fact, that the cellular ATP levels fell by 85-90% within 5-10 minutes of complete occlusion of the renal artery. With the application of in vivo nuclear magnetic resonance spectroscopy, it has been possible to delineate further alterations in the adenine nucleotide metabolism that occur as a consequence of renal hypoperfusion or ischaemia (4). Three phases of this are demonstrated in Fig. 2.

Figure 2. Schematic representation of alterations in cellular ATP that occur during and after renal ischaemia as determined by in vivo nuclear magnetic resonance spectroscopy (101).

During phase I, ATP is rapidly depleted to a steady-state level that depends on the degree of reduction in renal blood flow. Immediately upon reflow, phase II, the cellular ATP returns toward pre-ischaemic values and the level of recovery is related to the residual adenine nucleotide pool during ischaemia (phase I). During phase III, the cellular ATP continues to recover, but at a slower rate, which is dependent on complex mechanisms of ATP synthesis.

The cellular energy metabolism is closely linked to a large number of factors that contribute to renal cell injury (71, 84, 122). A depletion of the cellular ATP can be expected to result in alterations in intracellular calcium, the production of reactive oxygen molecules, and the activation of phospholipases and proteases, with degradation of the plasma membrane (23, 24, 25, 67, 76, 103, 122).

Boda et al. (7) studied the pathophysiology of acute shock urate nephropathy. The purine metabolism of the animals was made similar to that of humans by blocking uricase activity with oxonic acid. In this way, endogenous hyperuricaemia could be induced in a shock state. The medullary precipitation of uric acid could be observed in the kidneys at autopsy by microscopic and polarized light optical examinations (65).
Neonates with severe hyaline membrane disease display various degrees of hyperuricaemia, which very sensitively reflects the severity of the disease (7). It is probable that, in the first phase of a hypoxaemic metabolic disturbance, vasomotor nephropathy develops (28) and, if the hypoxemia worsens, the reversible neonatal metabolic insufficiency enters the second phase and shock uric acid nephropathy can be observed. Certain phases of metabolic insufficiency can be favourably influenced by different drugs such as dopamine and allopurinol (7). Effective therapy can be expected only if the moderate and more severe functional and morphological changes in the hypoxaemic kidney are known in detail. The animal model of urate precipitation in the kidney allowed ultrasonography examination of the phenomenon.

An intrauterine hypoxic condition is present in pre-eclampsia. The mechanism and pathophysiology of this serious disease is not well defined (122, 127). We have accepted a possible mechanism, see Fig.4.
Figure 4. Model of the pathogenesis of pre-eclampsia based on endothelial cell and injury as the key factor (121).

The altered lipid metabolism in pre-eclampsia is also reflected in changes in the lipid membrane composition of the platelets and red cells. Uncontrolled lipid peroxidation, caused by interaction of oxygen-free radicals with unsaturated fatty acids, may contribute to endothelial cell damage and dysfunction (108). There is evidence that increased placental cyclo-oxygenase activity and thromboxane production and activation of the neutrophils stimulate formation of oxygen radicals in pre- eclamptic women. The antioxidant activity appeared to be reduced in sera from pre-eclamptic subjects. A low antioxidant activity has been shown to induce the release of the macrophage-derived cytokines, which stimulate further release of oxidising free radicals (122). Estroff et al. examined foetal and neonatal hyperechogenicity (20). The foetal and neonatal renal medulla is hyperechogenic in its normal state, so hyperechogenicity is a characteristic and striking feature on ultrasonography examination (47, 99, 107). Neonatal renal hyperechogenicity is a characteristic feature in chronic or acute perinatal hypoxia (12, 99). The cause of foetal renal hyperechogenicity in hypoxic cases is presumed to be the accumulation of ATP depletion products.
Hyperechogenicity can be found in other diseases as well. Hyperechogenic kidneys have been reported to be due to urinary tract obstruction, polycystic and glomerulocystic kidney disease, obstructive nephrological disease and nephrocalcinosis (18, 45, 72, 98).

In about 20 per cent of cases of foetal renal hyperechogenicity, the mechanism and diagnosis are unclear (21). The possibility of a connection between intrauterine growth retardation and hyperechogenicity has not been examined so far. Hyperechogenic kidney is diagnosed when the foetal kidney displays an echogenicity higher than that of the liver or the spleen (20). Hyperechogenicity of the renal cortex and especially the renal pyramids is a well-known phenomenon, but the importance of hyperechogenicity in cases with no anatomical alterations is controversial. Chiara et al. examined a large population of neonates with hyperechogenic pyramids, but no anatomical abnormality was ever found among survivors of foetal asphyxia (12).

Flow velocity waveforms from branches of the abdominal aorta including the renal arteries potentially provide a more sensitive method for the prediction of foetal oxygenation than an examination of aortic flow (121). Investigation of multiple foetal vessels improves the validity of blood flow parameters (21, 44). Among foetuses with absent or reversed end-diastolic flow in the umbilical artery, there was an association between abnormal end-diastolic umbilical cord venous pulsation and perinatal (34). The foetal renal arterial resistance index decreases moderately during the third trimester of pregnancy, possibly in relation to the increased renal blood flow.

In the foetus, 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 (52). We investigated the echogenicity of the foetal kidneys during the last period of intrauterine life in normal and pathological pregnancies, focusing on pregnancies complicated by chronic foetal hypoxia (pregnancy-induced hypertension and pre-eclampsia) and IUGR.
4. Alms of the Investigation

The aims of our study were:

1. To reproduce experimental urate nephropathy and to detect pyramidal by renal ultrasonographyc examinations. Tourniquet shock stimulates endogenous shock. Urate nephropathy was produced by an exogenous uric acid intake.

2. Morphological and ultrasonographic experiences were collected from the experimental model to investigate the pathophysiology and ultrasonographic morphology in kidneys of hypoxic neonates.

3. To perform the foetal ultrasonographic examinations to clarify the perinatal ultrasonographic changes, the pathophysiological condition of the foetuses and the clinical outcome of the neonates in complicated pregnancies.

3.1. EPH-gestosis

We investigated the echogenicity of the foetal kidneys during the third trimester in normal and pathological pregnancies, focusing on pregnancies complicated by chronic foetal hypoxia (pregnancy-induced hypertension and pre-eclampsia). Pregnancy-induced hypertension does not always involve intrauterine hypoxia, but in our cases this was the case.

These foetal examinations were designed to screen for medullary hyperechogenicity, and to examine whether there is a connection between the hyperechogenicity of the foetal kidney and the presence of an intrauterine hypoxic state.

3.2. IUGR

In our study, we wished to demonstrate how the echogenicity of the kidneys during the last period of intrauterine life in normal and intrauterine retarded pregnancies correlates with the early postnatal outcome, in the first 5 days. Newborns were examined prospectively in the first 5 days after birth.

During our foetal examinations, the medullary hyperechogenicity was screened, as a possible indicator of a foetal pathological state. We examined whether there is a connection between the hyperechogenicity of foetal kidneys and growth retardation.
3.3. Renal artery investigation
The aim of the present study was to establish a correlation between an abnormal renal arterial blood flow and the clinical outcome in foetuses with hyperechogenic renal medullae, in order to discern if these probes are useful in the early detection of a chronically hypoxic state in foetal life.
5. Materials and methods

5.1. Experimental model

Adult rabbits (New Zealand white rabbits) weighing 2.9±0.3 (mean±SD) kg were used in our experiments.

Group I (n=7)
The rabbits received urate solution (0.8 g/kg) by the i.v. route once. One per cent uric acid solution with the use of 2.75% triethanolamine.

Group II (n=5)
The rabbits received 1% urate solution (.0.4 g/kg) by the i.v. route, four times, in every second hour.

Control group

Each animal served as its own control. In both group I and group II at the starting-point beginning (0 hours), before the administration of urate ultrasonographic photos were taken and blood samples were prepared to control the later changes.

Tourniquet shock was applied continuously for 0-4 hours. Examinations were made after 0, 4 and 8 hours happened. We collected blood samples, which were analysed by routine laboratory tests (e.g. hypoxanthine, uric acid, creatinine and urea-N). High-pressure liquid chromatography was performed to determinate the hypoxanthine level (42).

The other parameters were determined by using routine laboratory techniques.
At the same time, ultrasound detection was utilized to observe the renal medullary echogenic changes (ATL Ultramark 4 Plus real-time equipment with a 7.5 MHz transducer).
The results were evaluated biometrically by means of Student’s t-test, and are reported together with the SD.

5.2. Human investigations

5.2.1. Neonatal observations

Our examinations were performed in the Neonatal Intensive Care Unit, Department of Paediatrics, Albert Szent-Györgyi Medical Center, University of Szeged. Four newborns were examined after perinatal asphyxia. Three of them were born in full term and one of them was immature. All cases suffered from very serious hypoxia, which means an Apgar score of less than 4 at 1 minute, a pH less than 7.2 in the umbilical artery and paO₂ less than 50 mm Hg. The were examined first during day of 1. The examinations were continued untill day 14.
Blood tests were performed to detect hypoxanthine, uric acid, creatinine and urea-N. High-pressure liquid chromatography was performed to determine the hypoxanthine level. The other parameters were determined using routine laboratory techniques. The kidneys of the neonates were examined by means of Hitachi EUB-450 real-time ultrasound equipment fitted with a 5 MHz transducer.

The urinary output was measured and the urine calcium, creatinine, uric acid and creatinine rates were calculated (56, 118). The statistical analyses were performed by Student’s t-test.

5.2.2. Perinatal investigations
5.2.2.1. EPH-gestosis

120 pregnancies were investigated between week 28 and 36 of gestation. All these women suffered from toxaemia, as defined by the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO); EPH-gestosis is oedema, proteinuria and hypertension. The term is taken to include the condition with either or both hypertension and proteinuria in pregnancy. The significance of oedema and weight gain in pregnancy is a matter of dispute and, though oedema and an excess weight gain may be valuable signs in particular clinical circumstances, they are unsuitable signs for classification purposes (16). The age of gestation was calculated according to the Naegeli rule and the first-trimester ultrasonographic examination. In the positive group (15 cases), foetal renal hyperechogenicity was diagnosed, but there were no other foetal anatomical abnormalities. The control group comprised the other 105 cases from the 120 pathological pregnancies.

The maternal liver and kidneys and the foetal brain, heart, bowel, liver and renal parenchyma were screened by ultrasonography. The blood flows of the foetal renal artery and the umbilical artery were measured by Doppler. Examinations were performed with Hitachi EUB-450 ultrasound equipment fitted with a 3.5 MHz transducer. Hyperechogenic kidney was diagnosed when the foetal renal medulla or cortex displayed an echogenicity similar to that of the surrounding bone, but higher than that of the liver or spleen. The pathological waveforms of the renal arteries were diastolic zero flow, reverse flow, postsystolic incisura or higher flow parameters than those of the normal field (99).

Between week 28 and 36 of gestation, at the same time as the ultrasonographic examinations, blood was taken from the mothers for determination of electrolytes (Na, K, Ca and Cl) and for kidney (creatinine, urea-N, uric acid, triglyceride and cholesterol) and liver (SGOT, SGPT, GGT and bilirubin) function tests. Blood was also collected after the delivery,
from the pulsating umbilical artery and from the cubital vein of the mothers, for the same reasons. Blood was collected from the non-pulsating umbilical artery within the first 15 minutes of life, for determination of the acid-base parameters (pH, bicarbonate, pCO₂, pO₂ and O₂ saturation) as a usual investigation. Blood samples were examined by standard laboratory techniques.

The liver and kidneys of the neonates were screened with Hitachi EUB-450 ultrasound equipment fitted with a 3.5 MHz transducer within the first 5 days after birth. The results were analysed by the chi-square test with the Yates correction.

5.2.2.2. IUGR

382 pregnant women were included in our study (April to October, 1997). Both normal and pathological cases were investigated.

There were 90 cases of growth retardation among the investigated pregnancies. Intrauterine growth retardation was established by Hadlock weight estimation, based on biparietal diameter, abdominal circumference and femur length (40). The 25 hyperechoic cases were compared with the remaining intrauterine growth-retarded neonates (65 cases).

After delivery, the progress of abnormal newborns was followed for 14 days.

The examinations during pregnancy were carried out with ATL Ultramark-9 and 3000 equipment fitted with a 3-5 MHz transabdominal transducer and during neonatal life with ATL-3000 equipment fitted with 7.5 MHz linear and sectorial transducer.

Hyperechoic pyramids were detected by comparison with the renal cortex, liver or spleen since normal medullary pyramids are hypoechoic in the foetus and in newborns (43). The results were analysed by means of the chi-square test. The method was analysed via the odds ratio.

5.2.2.3. Renal artery investigations

Foetal kidney ultrasonography examinations were performed. Renal blood flow and echogenicity studies were carried out with two ATL ultrasound machines (Ultramark-9 and 3000), 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 examinations: 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 foetus in a quiet state and during apnoea.
Renal artery examinations: An axial view of the foetus was obtained at the level of the kidneys. The Doppler gate was placed at the renal hilus, the maximum signal then being obtained from the renal artery. The abdominal aorta gives a significantly different signal, which helps in differentiating between the two waveforms. There is not a significant difference between the two sides of the renal artery (121), therefore foetal 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 involves the use of regression lines and confidence values: the mean (a regression line in the middle) and ±SD (two lines below and above the mean line). The normal field was defined from literature data on the umbilical artery (79) and the renal artery (117, 121).

We employed the international standard. Measurements were made during the absence of foetal breathing movements, since foetal breathing movements are known to exert marked effects on blood flow. The most uniform frozen waveforms were 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 (83). The mean and the standard deviation of the resistance indices were calculated for both foetal vessels, a normal distribution being assumed (114). The gestational age was calculated according to Naegele rule and a first trimester ultrasound examination.

The study group consisted of 207 pregnancies complicated by chronic hypoxia in the third trimester. Pregnancies were investigated between weeks 24 and 39 gestation. The clinical outcome of the neonates was investigated until 14 days after birth.

Depending on the aetiology of the intrauterine chronic hypoxia, the pregnancies were divided into two study groups.

Group I comprised cases with pregnancy-associated hypertension and/or proteinuria (120 cases). This group was further subdivided into a positive group (15 cases with foetal renal hyperechogenicity) and a control group (105 cases without foetal renal hyperechogenicity). In those cases in which foetal renal hyperechogenicity was detected, no foetal anatomical abnormalities were observed.

Pregnancy-associated hypertension and/or proteinuria was defined by The Committee of the American Obstetricians and Gynecologists (16), which recommended that a total protein concentration of 300 mg or more per litre in a 24-hour urine collection should be regarded as abnormal, and hypertension in pregnancy was defined as two consecutive measurements of a diastolic blood pressure of 90 mm Hg or more 4 hours or more apart. The finding of oedema
and weight gain in pregnancy as signs of pre-eclampsia is a matter of dispute, and though oedema and excess weight gain may be signs in particular clinical circumstances, they are unsuitable signs for classification purposes (16).

Group II comprised of intrauterine growth-retarded pregnancies (87 cases). Intrauterine growth retardation was established by Hadlock weight estimation, based on abdominal circumference and femur length (40).

The 22 cases with foetal renal hyperechogenicity were compared with the remaining intrauterine growth-retarded neonates (65 cases without foetal renal hyperechogenicity). Hyperechoic pyramids were detected by comparison with the renal cortex, liver or spleen since normal medullary pyramids are hypoechoic in the foetus and in newborns. The ultrasonographic finding of hyperechogenicity is therefore, noteworthy (43). The abnormal waveforms of the renal arteries that were detected were a decreased systolic flow, zero diastolic flow, reverse flow, post-systolic incisura or higher flow parameters than those of the normal field (99). The umbilical artery and renal artery blood flow resistance indices were analysed statistically to compare the cases with and without foetal renal hyperechogenicity. The results were analysed by the chi-square test. The method was analysed via the odds ratio.
6. Results

6.1. Results with experimental model

At 0 time, ultrasonographic examination revealed no pathological changes in 12 rabbits (Fig. 5).

Fig. 5. Control ultrasonography examination in rabbits. No pathological change was detected in any case.

Table I lists the purine metabolite and kidney blood chemistry data. In group I, the combination of tourniquet shock and a single dose of uric acid i.v. increased the levels of hypoxanthine, uric acid, blood creatinine and urea-N considerably after 4 hours, those of hypoxanthine and uric acid rising significantly.

Group I exhibited a rather severe hypervolaemic circulation insufficiency. Nephrosonographic examination revealed no uric acid precipitation. In group II, which received a combination of tourniquet shock and uric acid in four i.v. doses every 2 hours, all of the animals survived. 4 hours and 8 hours later, the hypoxanthine levels were significantly elevated relative to the 0-hour value.

The uric acid level was increased at both time points, but significantly only at 8 hours. Although the blood creatinine levels were increased at both times relative to that at 0 hours, the elevations were not statistically significant. The urea-N levels did not exhibit a change at either time.

The ultrasonographic results on group II (Table II) at 4 hours revealed enlarged kidneys with mildly increased echogenicity in the pyramids near the papillae (Fig. 6)
Table I.
Purine metabolites and blood chemistry in acute shock uric acid nephropathy in rabbits in group I (N=7)

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Hypoxanthine (µmol/l)</th>
<th>Uric acid (µmol/l)</th>
<th>Creatinine (µmol/l)</th>
<th>Urea nitrogen (mmol/l)</th>
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<th>Pathohistology</th>
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<td>0</td>
<td>3.8±2.7</td>
<td>12.8±3.4</td>
<td>121±19</td>
<td>8.5±1.5</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>4</td>
<td>15.7±10.2</td>
<td>89±10</td>
<td>243±20</td>
<td>11.4±2.9</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

Table II.
Purine metabolites and blood chemistry in acute shock uric acid nephropathy in rabbits in group II (N=5)

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Hypoxanthine (µmol/l)</th>
<th>Uric acid (µmol/l)</th>
<th>Creatinine (µmol/l)</th>
<th>Urea nitrogen (mmol/l)</th>
<th>Kidney sonography</th>
<th>Pathohistology</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.5±2.5</td>
<td>13.9±3.9</td>
<td>117.0±5.0</td>
<td>8.3±1.0</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>4</td>
<td>15.7±6.7</td>
<td>21.4±8.4</td>
<td>124.0±3.0</td>
<td>7.5±1.8</td>
<td>positive</td>
<td>negative</td>
</tr>
<tr>
<td>8</td>
<td>34.9±9.9</td>
<td>36.2±9.2</td>
<td>204.0±9.0</td>
<td>6.9±1.5</td>
<td>positive</td>
<td>positive</td>
</tr>
</tbody>
</table>

Group I. received 0.8 g/kg urate solution i.v. at the beginning of the experiment
Group II. received 0.4 g/kg urate solution i.v. four times every second hour
Negative: Uric acid precipitation was not detectable in the kidney
Positive: Uric acid precipitation was detectable in the kidney
Fig. 6 In group II renal hyperplasia and pyramidal hyperechogenicity were detected at 4 hours.

At 8 hours, the kidneys were not further enlarged and the increased echogenicity of the pyramids and cortex was unambiguous (Fig. 7).

Fig. 7. In group II a renal enlargement was not detected, but the cortex and pyramid hyperechogenicity was unambiguous.
After 24 hours the increased echogenicity of the pyramids was unchanged (Fig. 8).

Fig. 8. After 1 day, pyramidal hyperechogenicity was still detected.

At 8 hours, the kidney pathocytology of 4 animals from group II was examined by polarized light microscopy. Uric acid precipitation was detected in the tubules (Fig. 9).

Fig. 9. In the kidney of rabbits, tubular uric acid precipitation was visualized by polarized light microscopy.
6.2. Results of human investigations

6.2.1. Neonatal investigations

We examined four neonates after perinatal asphyxia. This was a preliminary study, so we analysed the cases individually.

Case 1

A male infant born at 40 weeks of gestation weighing 4000 g. Apgar scores at 1, 5 and 10 minutes: 2, 6 and 8 respectively. Meconium aspiration syndrome was presented. After successful resuscitation, nasal continuous airway pressure was started, using 60% oxygen. The arterial pO₂ was 48 mm Hg, while pH at the age of 12 hours was 7.18. Ultrasonographic examination of the kidneys was performed on day 1 of life. Hyperechogenicity of the apices was detected in the medullary pyramids of the right kidney. This was no longer visible after the day 3 of life (Table III, IV).

Case 2

A female infant born at 38 weeks of gestation weighing 2950 g. Apgar scores at 1, 5 and 10 minutes: 4, 7 and 9. At 17 hours, the baby unexpectedly collapsed with sudden infant death syndrome. Resuscitation was partially successful. She was having repeated convulsions. She was intubated and ventilator treatment was started. The hypoxic state lasted tree hours. On day 2, the reflectivity of the renal cortices was increased (Fig. 10), which was be confirmed to be present in the pyramids of both kidneys. By day 3, the hyperechogenicity of the cortices and of the medulla could no longer be decreased. This patient died at the age of 10 days.

![Fig. 10. Renal hyperechogenicity in the weighing 2950 g (case 2).](image-url)
Table III
Purine metabolites and renal hyperechogenicity in neonatal hypoxic acute shock

<table>
<thead>
<tr>
<th>Case number</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Gestation age (weeks)</th>
<th>Delivery weight (g)</th>
<th>Apgar score (1st, 5th)</th>
<th>paO2 (mmHg)</th>
<th>Serum pH</th>
<th>Uric acid (mmol/l)</th>
<th>Hypoxanthine (mmol/l)</th>
<th>Pathological renal ultrasound</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>MAS</td>
<td>m</td>
<td>40</td>
<td>4100</td>
<td>2.6,8</td>
<td>48</td>
<td>7.18</td>
<td>3.37</td>
<td>8.4</td>
<td>1st day of life</td>
</tr>
<tr>
<td>2</td>
<td>SIDS</td>
<td>f</td>
<td>36</td>
<td>2950</td>
<td>4.7,9</td>
<td>39</td>
<td>7.12</td>
<td>5.70</td>
<td>8.4</td>
<td>2nd day of life</td>
</tr>
<tr>
<td>3</td>
<td>foetal distress</td>
<td>f</td>
<td>36</td>
<td>3850</td>
<td>0.1,1</td>
<td>50</td>
<td>7.17</td>
<td>6.45</td>
<td>6.4</td>
<td>4th day of life</td>
</tr>
<tr>
<td>4</td>
<td>IRDS</td>
<td>f</td>
<td>27</td>
<td>720</td>
<td>1.1,3</td>
<td>44</td>
<td>7.2</td>
<td>6.88</td>
<td>20.1</td>
<td>1st day of life</td>
</tr>
</tbody>
</table>

MAS: meconium aspiration syndrome
SIDS: sudden infant death syndrome
IRDS: Infant respiratory distress syndrome

Table IV
Blood and urine values in neonatal hypoxic state on 1st day of life

<table>
<thead>
<tr>
<th>Case number</th>
<th>Urea-N (mmol/l)</th>
<th>Creatinine (umol/l)</th>
<th>UA/Creatinine (mg/mg)</th>
<th>Ca (mmol/l)</th>
<th>CA/Creatinine (mg/mg)</th>
<th>Quantity of urine (ml/kg/h)</th>
<th>Osmolality of urine (mosm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.9</td>
<td>142.5</td>
<td>2.7</td>
<td>1.68</td>
<td>0.11</td>
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<td>2</td>
<td>7</td>
<td>110</td>
<td>2.9</td>
<td>2.2</td>
<td>0.06</td>
<td>1.4</td>
<td>392</td>
</tr>
<tr>
<td>3</td>
<td>11.4</td>
<td>154</td>
<td>6.2</td>
<td>1.82</td>
<td>0.4</td>
<td>0.2</td>
<td>286</td>
</tr>
<tr>
<td>4</td>
<td>19.5</td>
<td>137</td>
<td>2.1</td>
<td>1.06</td>
<td>0.22</td>
<td>0.6</td>
<td>175</td>
</tr>
</tbody>
</table>
Case 3
Female infant born at 36 weeks of gestation weighing 3680 g. The clinical diagnoses were foetal distress and diabetic foetopathy. Comprehensive resuscitation was required because asphyxia was severe, Apgar scores at 1, 5 and 10 minutes: were 0, 1 and 1. After intubation, ventilation was commenced. Her oxygen requirement was 55%. At the age of 4 days, marked echogenicity was found in the medulla of both kidneys. By day 14, the renal medullary hyperechogenicity had disappeared.

Case 4
Female infant born at 27 weeks of gestation weighing 720 g. Apgar scores at 1, 5 and 10 minutes: 1, 1 and 3. She was intubated and transported to our department immediately because of prematurity and infant respiratory distress syndrome. At 1 day of age, an increased echogenicity of the kidney was found. The neonate died of intraventricular haemorrhage on day 4 of life.

6.2.2. Perinatal investigations
6.2.2.1. EPH-gestosis

15 of 120 pathological pregnancies involved foetal renal hyperechogenicity without any other foetal anatomical abnormalities. In the control group, 21 of the 105 cases displayed some pathological foetal and neonatal state, but without foetal renal hyperechogenicity. The pregnant in the hyperechogenic group suffered from toxaemia after week 28 of gestation. Serious hypertension was detected in 9 mothers. The pregnant women had normal electrolyte levels. The kidney function was abnormal in 3 mothers. In 2 cases there were pathological urea-N levels and in 3 cases pathological creatinine levels. Two women had pathological urea-N and creatinine levels, and one had abnormal uric acid, urea-N and creatinine levels. Pathological uric acid levels were observed in 4 cases. All of the investigated maternal cases exhibited increased liver enzyme levels (Table V).

Table VI lists the umbilical artery serum parameters at delivery. 15 newborns suffered from hyperuricaemia, especially cases 1 and 4. In 4 cases there were elevated creatinine levels and in 7 cases high urea-N levels. In the control group, there were no kidney function abnormalities. Similarly, no abnormalities were found in the blood samples taken for determination of the acid-base parameters within the first 15 minutes in the two groups of newborns. In the postnatal period, ultrasonography revealed pathological renal morphology (renal hypoplasia) in 1 case and transitory renal hyperechogenicity in 6 cases, but there were no
<table>
<thead>
<tr>
<th>Case number</th>
<th>Diagnosis</th>
<th>Gestation age (weeks)</th>
<th>RR (mmHg)</th>
<th>Proteinuria</th>
<th>Uric acid (mmol/l)</th>
<th>CN (mmol/l)</th>
<th>Creatinin (umol/l)</th>
<th>SGOT (mmol/l)</th>
<th>SGPT (mmol/l)</th>
<th>GGT (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EPH gestosis I.4 Oligohydramnion, I. u distress</td>
<td>35</td>
<td>170/120</td>
<td>3+</td>
<td>381</td>
<td>5.8</td>
<td>64</td>
<td>54</td>
<td>76</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>EPH gestosis I.3 Diabetes mellitus</td>
<td>32</td>
<td>140/85</td>
<td>1+</td>
<td>390</td>
<td>3.9</td>
<td>75</td>
<td>35</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>EPH gestosis I.3 IUGR Oligohydramnion</td>
<td>36</td>
<td>140/90</td>
<td>1+</td>
<td>268</td>
<td>3.6</td>
<td>70</td>
<td>18</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>EPH gestosis I.5 I. u. distress Oligohydramnion</td>
<td>31</td>
<td>170/100</td>
<td>1+</td>
<td>414</td>
<td>9.1</td>
<td>162</td>
<td>43</td>
<td>52</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>EPH gestosis I.3</td>
<td>32</td>
<td>130/90</td>
<td>1+</td>
<td>192</td>
<td>2.6</td>
<td>79</td>
<td>22</td>
<td>17</td>
<td>30</td>
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<tr>
<td>6</td>
<td>EPH gestosis I.3</td>
<td>24</td>
<td>100/60</td>
<td>-</td>
<td>273</td>
<td>3</td>
<td>48</td>
<td>31</td>
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<td>5</td>
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<tr>
<td>7</td>
<td>EPH gestosis I.3 gestation diabetes mellitus</td>
<td>34</td>
<td>130/90</td>
<td>1+</td>
<td>266</td>
<td>1.4</td>
<td>57</td>
<td>14</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>EPH gestosis I.3 hyperthyroidism</td>
<td>30</td>
<td>140/80</td>
<td>-</td>
<td>161</td>
<td>5.2</td>
<td>52</td>
<td>19</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>9</td>
<td>EPH gestosis I.3</td>
<td>36</td>
<td>120/80</td>
<td>1+</td>
<td>365</td>
<td>8.9</td>
<td>127</td>
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<td>160/110</td>
<td>3+</td>
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</tr>
<tr>
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<td>-</td>
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<td>71</td>
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<td>17</td>
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<tr>
<td>12</td>
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<td>36</td>
<td>130/90</td>
<td>-</td>
<td>391</td>
<td>4.2</td>
<td>102</td>
<td>34</td>
<td>30</td>
<td>27</td>
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<tr>
<td>13</td>
<td>EPH gestosis I.4 pre-eclampsia</td>
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<td>190/120</td>
<td>3+</td>
<td>280</td>
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<td>49</td>
<td>47</td>
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<td>41</td>
</tr>
<tr>
<td>14</td>
<td>EPH gestosis I.2 IUGR Oligohydramnion</td>
<td>38</td>
<td>145/90</td>
<td>-</td>
<td>190</td>
<td>2.8</td>
<td>53</td>
<td>14</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>EPH gestosis I.7 oligohydramnion</td>
<td>28</td>
<td>150/90</td>
<td>3+</td>
<td>145</td>
<td>5.9</td>
<td>116</td>
<td>43</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>Case number</td>
<td>Delivery age (weeks)</td>
<td>Delivery weight (g)</td>
<td>Apgar score (1'-5'10')</td>
<td>Acid-base parameters pH-st.bicarb-CO2-O2</td>
<td>Uric acid (umol/l)</td>
<td>CN (mmol/l)</td>
<td>Creatinine (umol/l)</td>
<td>Notes</td>
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<td></td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------</td>
<td>---------------------</td>
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</tr>
<tr>
<td>1</td>
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<td>1600</td>
<td>4,7,9</td>
<td>7.32-24.2-44.3-60.1</td>
<td>419</td>
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<td>148</td>
<td>sectio c., IUGR, uricosuria, azotemia, anuria, postnatal renal hyperechogenicity</td>
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</tr>
<tr>
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<td>7,9,9</td>
<td>7.34-21.3-43.6-64.4</td>
<td>242</td>
<td>2.8</td>
<td>56</td>
<td>sectio c., WAC</td>
<td></td>
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</tr>
<tr>
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<td>2200</td>
<td>7,3,10</td>
<td>7.26-19.3-45.2-67.3</td>
<td>259</td>
<td>3.4</td>
<td>75</td>
<td>PVN, IUGR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>1450</td>
<td>2,4,7</td>
<td>7.24-21.7-39.2-47,1</td>
<td>399</td>
<td>8.2</td>
<td>153</td>
<td>sectio c., PRH, renal hypoplasia on right side, NEC</td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>39</td>
<td>2980</td>
<td>10,10,10</td>
<td>7.36-21.0-42.2-71.3</td>
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<td>PVN, WAC</td>
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<tr>
<td>6</td>
<td>39</td>
<td>2750</td>
<td>10,10,10</td>
<td>7.37-17.2-30.6-43.9</td>
<td>259</td>
<td>3.4</td>
<td>66</td>
<td>PVN, IUGR, PRH on left side</td>
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<tr>
<td>7</td>
<td>38</td>
<td>3740</td>
<td>9,10,10</td>
<td>7.30-22.3-46.1-33.0</td>
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<td>3.2</td>
<td>79</td>
<td>PVN, WAC</td>
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<td>7.33-24.1-46.9-63.8</td>
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<td>4.1</td>
<td>101</td>
<td>sectio c., IRDS</td>
<td></td>
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</tr>
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<td>9</td>
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<td>3010</td>
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<td>7.20-22.1-48.8-30.0</td>
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<td>38</td>
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<td>10,10,10</td>
<td>7.39-18.4-31.3-79.3</td>
<td>401</td>
<td>5.2</td>
<td>123</td>
<td>PVN, WAC</td>
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</tr>
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<td>40</td>
<td>3170</td>
<td>10,10,10</td>
<td>7.31-20.3-41.5-38.3</td>
<td>376</td>
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<td>sectio c., IUGR, PRH</td>
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<td>2870</td>
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<td>7.14-13.4-40.1-35.3</td>
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<td>4.2</td>
<td>97</td>
<td>PVN, WAC</td>
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<tr>
<td>13</td>
<td>26</td>
<td>1130</td>
<td>7,9,10</td>
<td>7.36-25.0-45.7-27.1</td>
<td>240</td>
<td>2.7</td>
<td>56</td>
<td>sectio c., part.preemat., IRDS, PRH</td>
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<td></td>
</tr>
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<td>40</td>
<td>2180</td>
<td>10,10,10</td>
<td>7.43-23.2-35.7-66.4</td>
<td>234</td>
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<td>57</td>
<td>PVN, IUGR, part.preemat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>32</td>
<td>1440</td>
<td>2,8,9</td>
<td>7.21-21.6-56.0-57.0</td>
<td>365</td>
<td>3.6</td>
<td>69</td>
<td>sectio c., IUGR, part.preemat., IRDS, PRH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PRH: postnatal renal hyperechogenicity  
PVN: per via naturales  
IUGR: intrauterine growth retardation  
IRDS: idiopathic respiratory distress syndrome  
sectsio c.: cesarean section  
part.preemat.: partus praematurus  
NEC: necrotic enterocolitis  
WAC: without any complication
renal lesions in the other cases in the hyperechogenic group. In the control group 3 polycystic kidneys were identified in the intrauterine condition. In the hyperechogenic group there were 6 cases of IUGR (40%), whereas in the control group there were only 3 cases (3%). The mode of delivery was caesarean section in 7 cases in the hyperechogenic group (46%), and in 6 cases in the control group (6%).

The results were evaluated statistically by the chi-square test with the Yates correction ($\chi^2$ test 9.16, p<0.01), sensitivity: 93%, specificity: 30%, positive predictive value: 60%, negative predictive value: 80%, validation: 77%.

6.2.2.2. IUGR

In our study, we examined the foetal hyperechogenic cases in the normal and pathological pregnancies. When foetal renal hyperechogenicity was demonstrated, we followed the cases after the delivery in the maternity or NICU (Fig. 11).

Fig. 11. Longitudinal view of a normal-sized hyperechogenic fetal kidney (31st week of gestation). The kidney gives pattern D (78).

There was no problem in 292 cases, while 90 newborns were transferred to the NICU. 55 newborns suffered from IUGR. 15 cases had IUGR, but so minimal that transfer to NICU was not necessary. The number of foetuses diagnosed as involving IUGR was less than the number at birth (25%). The explanation for this discrepancy may lie in the severity of cases of IUGR. All of the IUGR diagnosed prenatally were below P3 at birth. The others were located between P3 and P10 or above P10 (Fig. 12,13).
Figure 12. Intrauterine non diagnosed IUGR cases (N=68)

Figure 13. Intrauterine diagnosed IUGR cases (N=22)

Figure 14. Longitudinal view of a normal echoic fetal kidney (34th week of gestation).

The connection between intrauterine foetal renal hyperechogenicity and transfer to the NICU was analysed in all cases. The sensitivity was 23%, the specificity was 7%, the positive predictive value was 84% and the negative predictive value in our cases was 5.8%.
We also examined the relationship between the intrauterine foetal hyperechogenicity and the NICU transfer, especially in IUGR cases. This revealed a sensitivity of 11.5%, a specificity of 53%, a positive predictive value of 100% and a negative predictive value of 9.5%.

25 cases of foetal renal hyperechogenicity were identified out of 382 cases, a prevalence of 6.6% (Table VII, VIII, IX). In 8 cases the pregnancies were normal, without any pathological signs (Fig. 14). The remainder were pathological: 9 pregnant women suffered from hypertension, 2 cases out of pathological pregnancies involved both pathological conditions (hypertension and HELLP syndrome), one case had intrauterine parvovirus infection and 5 cases were IUGR with unclear aetiology. In 1 case out of 382 pregnancies, the diagnosis was multicystic kidney in intrauterine life. Earliest we detected renal hyperechogenicity was week 18 of gestation. We started serial examinations, but later a different aetiology was identified, and we therefore eliminated this from the cases of foetal renal hyperechogenicity without anatomical alteration.

Two of the 25 cases of foetal renal hyperechogenicity were stillborn.

A stillbirth of a retarded foetus accurred in week 31 of gestation (delivery weight: 420 g).
A postnatal death on day 2 of life was observed after a caesarean section. The intervention was indicated by pre-eclampsia, bilateral notch of the uterine artery, and pathological NST. The newborn was premature, hypotrophic, bradycardic and suffered from apnoea, metabolic acidosis, cataract and intraventricular haemorrhage (delivery weight: 950 g in week 31 of gestation).

6.2.2.3. Renal artery investigations

217 foetuses in 207 pregnancies were examined for hyperechogenicity of the renal medulla: 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 foetal renal hyperechogenicity. Table VI 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 (mean±SD) at 1 minute and 8.9±1.3 (mean±SD) at 5 minutes. 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,
<table>
<thead>
<tr>
<th>Case</th>
<th>Mother</th>
<th>Pregnancy</th>
<th>Sex</th>
<th>Weight (g)</th>
<th>Gestational age (weeks)</th>
<th>Appgar score ('1' '5')</th>
<th>Renal hyperechogenicity detected (weeks)</th>
<th>Notes</th>
<th>NICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A.M.</td>
<td>IUGR</td>
<td>f</td>
<td>2170</td>
<td>40</td>
<td>9/10</td>
<td>35</td>
<td>without any problem</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>B.N.A.</td>
<td>hypertension</td>
<td>f</td>
<td>3035</td>
<td>40</td>
<td>8/9</td>
<td>35</td>
<td>perinatal infection, tachycardia</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>B.S.</td>
<td>hypertension</td>
<td>f</td>
<td>3030</td>
<td>39</td>
<td>8/9</td>
<td>37</td>
<td>without any problem</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>B.J.</td>
<td>normal</td>
<td>f</td>
<td>3500</td>
<td>40</td>
<td>9/10</td>
<td>37</td>
<td>perinatal infection</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>B.F.</td>
<td>normal</td>
<td>m</td>
<td>3320</td>
<td>39</td>
<td>9/10</td>
<td>26</td>
<td>perinatal infection</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>B.M.J.</td>
<td>hypertension</td>
<td>m</td>
<td>3100</td>
<td>38</td>
<td>8/9</td>
<td>34</td>
<td>caesarean section</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>B.C.H.</td>
<td>IUGR, toxocoman</td>
<td>m</td>
<td>2030</td>
<td>35.5</td>
<td>9/10</td>
<td>34</td>
<td>caesarean section</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>B.A.</td>
<td>renal malformation</td>
<td>m</td>
<td>3260</td>
<td>38</td>
<td>7/8</td>
<td>18</td>
<td>multicystical kidney</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>B.C.H.</td>
<td>IUGR</td>
<td>f</td>
<td>2020</td>
<td>38</td>
<td>8/9</td>
<td>36</td>
<td>foetal infection?</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>C.C.</td>
<td>IUGR, hypertension</td>
<td>m</td>
<td>950</td>
<td>31</td>
<td>1/6</td>
<td>30</td>
<td>bradycardia, apnoea, met.acid., cataract, intraventr. haemorrhagia, death on 2nd day</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>C.R.</td>
<td>hypertension</td>
<td>f</td>
<td>3260</td>
<td>41</td>
<td>5/7</td>
<td>37</td>
<td>without any problem</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>F.B.</td>
<td>hypertension</td>
<td>f</td>
<td>1690</td>
<td>37</td>
<td>8/9</td>
<td>34</td>
<td>gemini &quot;A&quot;</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>F.B.</td>
<td>hypertension</td>
<td>f</td>
<td>1870</td>
<td>37</td>
<td>4/8</td>
<td>34</td>
<td>gemini &quot;B&quot;</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>G.C.</td>
<td>IUGR, HELLP-sy</td>
<td>f</td>
<td>1580</td>
<td>33</td>
<td>7/9</td>
<td>32</td>
<td>caesarean section</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>K.P.</td>
<td>IUGR, I.u.p. parvovirus inf., hydrops fetalis</td>
<td>f</td>
<td>2260</td>
<td>33</td>
<td>4/8</td>
<td>31</td>
<td>caesarean section, reanimation, meconial amnial fluid</td>
<td>+</td>
</tr>
<tr>
<td>16</td>
<td>L.F.</td>
<td>hypertension</td>
<td>f</td>
<td>3455</td>
<td>39.5</td>
<td>7/9</td>
<td>24</td>
<td>caesarean section</td>
<td>+</td>
</tr>
<tr>
<td>17</td>
<td>L.J.</td>
<td>normal</td>
<td>f</td>
<td>3800</td>
<td>40</td>
<td>8/9</td>
<td>36</td>
<td>without any problem</td>
<td>+</td>
</tr>
<tr>
<td>18</td>
<td>P.M.</td>
<td>normal</td>
<td>f</td>
<td>2860</td>
<td>37</td>
<td>9/9</td>
<td>35</td>
<td>caesarean section</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>P.J.</td>
<td>normal</td>
<td>m</td>
<td>2910</td>
<td>38</td>
<td>9/10</td>
<td>36</td>
<td>without any problem</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>P.N.</td>
<td>normal</td>
<td>f</td>
<td>3720</td>
<td>39</td>
<td>8/8</td>
<td>32</td>
<td>perinatal infection</td>
<td>+</td>
</tr>
<tr>
<td>21</td>
<td>R.F.R.</td>
<td>hypertension</td>
<td>f</td>
<td>2460</td>
<td>36</td>
<td>8/9</td>
<td>33</td>
<td>without any problem</td>
<td>-</td>
</tr>
<tr>
<td>22</td>
<td>S.G.FR.</td>
<td>IUGR, hypertension, oligohydramnion</td>
<td>f</td>
<td>2260</td>
<td>38</td>
<td>7/9</td>
<td>37</td>
<td>perinatal infection?</td>
<td>+</td>
</tr>
<tr>
<td>23</td>
<td>S.C.</td>
<td>normal</td>
<td>f</td>
<td>3600</td>
<td>39</td>
<td>9/9</td>
<td>35</td>
<td>caesarean section</td>
<td>-</td>
</tr>
<tr>
<td>24</td>
<td>T.C.</td>
<td>hypertension</td>
<td>f</td>
<td>3190</td>
<td>41</td>
<td>9/10</td>
<td>32</td>
<td>without any problem</td>
<td>-</td>
</tr>
<tr>
<td>25</td>
<td>W.K.</td>
<td>IUGR</td>
<td>m</td>
<td>420</td>
<td>31</td>
<td>0/0</td>
<td>27</td>
<td>stillborn</td>
<td>no transfer</td>
</tr>
</tbody>
</table>
Table VIII
Comparison of two groups of prenatally diagnosed IUGR cases:
with or without renal medullae hyperechogenicity

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IUGR with renal medullae hyperechogenicity (25 cases)</td>
<td>IUGR without renal medullae hyperechogenicity (65 cases)</td>
</tr>
<tr>
<td>gestational age at delivery(weeks)</td>
<td>37.5±2.2</td>
<td>33.6±2.7</td>
</tr>
<tr>
<td>birthweight (g)</td>
<td>2634±741</td>
<td>1945±681</td>
</tr>
<tr>
<td>delivery by cesareane section</td>
<td>9 (36%)</td>
<td>13 (20%)</td>
</tr>
<tr>
<td>fetal dystress</td>
<td>9 (36%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>renal malformation</td>
<td>no</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>pathological amniotic fluid</td>
<td>1 (4%)</td>
<td>9 (14%)</td>
</tr>
<tr>
<td>perinatal infection</td>
<td>6 (24%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>meconium stained amniotic fluid</td>
<td>1 (4%)</td>
<td>no</td>
</tr>
<tr>
<td>brain malformations</td>
<td>no</td>
<td>3 (4.6%)</td>
</tr>
<tr>
<td>facial malformation</td>
<td>no</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>spina bifida</td>
<td>no</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>gastrointestinal tract malformations</td>
<td>no</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>single umbilical artery</td>
<td>no</td>
<td>1 (1.5%)</td>
</tr>
</tbody>
</table>

Table IX
Differences in the outcome of two groups of prenatally diagnosed
IUGR cases: with or without renal medullae hyperechogenicity

<table>
<thead>
<tr>
<th></th>
<th>IUGR with renal medullae hyperechogenicity (25 cases)</th>
<th>IUGR without renal medullae hyperechogenicity (65 cases)</th>
<th>rate (hyperechoic to normoechoic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>neonatal mortality</td>
<td>2 (8%)</td>
<td>3 (4.6%)</td>
<td>1.7</td>
</tr>
<tr>
<td>neonatal morbidity</td>
<td>17 (68%)</td>
<td>30 (42%)</td>
<td>1.6</td>
</tr>
<tr>
<td>NICU stay</td>
<td>16 (64%)</td>
<td>38 (55%)</td>
<td>1.2</td>
</tr>
</tbody>
</table>
whose mothers had pregnancy-associated hypertension and/or proteinuria), 3 polycystic kidneys were identified in the mothers in the intrauterine period. The mode of delivery was caesarean 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 NICU 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 had 6 times the risk (analysed by the odds ratio) of a pathological clinical outcome as compared to babies with a normal echoic kidney in pregnancy-associated hypertension and/or proteinuria: the odds ratio was 6.22 (2.84;13.62) on 95% confidence bounds.

In group II (42%), 87 pregnancies with intrauterine growth retardation involved 22 cases with foetal renal hyperechogenicity. Table VII contains data on these 22 babies (16 girls and 6 boys). The mean (±SD) duration of gestation at birth was 37.5±2.2 weeks and the mean (±SD) birth weight was 2634±741 g. The Appar scores were 7.2±1.8 (mean±SD) at 1 minute and 8.5±1.4 (mean±SD) at 5 minute. In this group, there were no anatomical abnormalities in the kidneys (Table VIII). In the control group, there were 2 renal malformations (2.6%): 1 multicystic kidney, and 1 hydrenephrosis. 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 cases with oligohydramnion (7.6%) in the control group. The babies had a perinatal infection in 5 cases (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 other two involved cytomegalovirus infections.

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

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

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 15 (Table VII), meconium staining was noted and the newborn was resuscitated. Intrauterine parvovirus infection and foetal hydrops had been recognized before the birth.

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

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 as compared with babies with normal-echoic kidneys in intrauterine growth retardation: the odds ratio was 1.5 (1.00;2.26) on 95% confidence bounds.

Doppler flow studies of the umbilical arterial blood flow velocity did not reveal any significant differences in any case. This applied to groups I and II without foetal renal hyperechogenicity [$\chi^2=2.049$ (p<0.05) in pregnancy-associated hypertension and/or proteinuria cases, and $\chi^2=0.075$ (p<0.05) in intrauterine growth-retarded cases] (Figs. 15 and 16).

![Figure 15](image)

**Figure 15.** Resistance index of umbilical artery in cases with foetal renal hyperechogenicity in EPH-gestosis (N=15)
Doppler ultrasonography of the renal artery revealed a significant disparity between babies with hyperechoic medullae in pregnancy-associated hypertension and/or proteinuria (Fig. 17) or intrauterine growth retardation (Fig. 18). As compared with the normal picture (Fig. 19), the renal arterial blood flow velocities displayed pathological waveforms, including decreased systolic flow (Fig. 20) or postsystolic incisura (Fig. 22).
Doppler ultrasonography of the renal artery revealed a significant disparity between babies with hyperechoic medullae in pregnancy-associated hypertension and/or proteinuria (Fig. 17) or intrauterine growth retardation (Fig. 18). As compared with the normal picture (Fig. 19), the renal arterial blood flow velocities displayed pathological waveforms, including decreased systolic flow (Fig. 20) or postsystolic incisura (Fig. 22).
Figure 18. Resistance index of renal artery in cases with foetal renal hyperechogenicity in IUGR (N=22)

Figure 19. Normal blood flow-velocity waveforms in the foetal renal artery at 28th week of gestation. The Doppler gate is positioned over the main renal artery.

Figure 20. Decreased blood flow-velocity waveforms in the renal artery at 32nd week of gestation. The Doppler gate is positioned over the main renal artery.
Figure 21. 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.

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

7.1. Discussion of experimental model and neonatal investigation

In animal experiments uric acid nephropathy due to acute shock could be induced, and ultrasonography examination revealed hyperechogenicity of the renal 109).

On the basis of these experimental results a study protocol was first designed for hypoxic neonates. We then extended the project in the prenatal field. We investigated foetuses in a chronic hypoxic condition (e.g. EPH-gestosis and IUGR).
The animal model of urate precipitation in the kidney allowed a study of the ultrasonography image characteristics of the phenomenon.

Boda et al. studied the pathological role of hyperuricaemia in experimental work and the animal results confirmed their findings on hypoxaemic neonates (7).

One link of the chain was missing however, how can extensive uric acid precipitation in the kidney be demonstrated non-invasively?

30 minutes after administration of a 1% uric acid infusion i.v. 0.8 g/kg once in a large volume, severe dyspnoea, tachycardia and bradycardia were observed. After 4 hours, the hypoxanthine, uric acid and urea-N levels were increased significantly (p<0.05, p<0.01 and p<0.001), while the creatinine and uric acid level increases were not significant.

Ultrasonographic examination did not demonstrate formed uric acid precipitation in the kidney.

The sudden death can be explained by a circulatory insufficiency. In animals given 0.4 g/kg uric acid i.v. 4 times during 8 hours, together with tourniquet shock, after 4 hours the hypoxanthine levels were higher than in group I, which was negative to uric acid with renal ultrasonography.

The average uric acid level increase in this group revealed to the 0-time level was not significant after 4 hours, but it was significant after 8 hours. Ultrasonographic examination revealed extensive nodular reflectivity, which is proportional to the urate precipitation observed in the pyramids on both sides at autopsy. Uric acid nephropathy caused by a high blood uric acid level is a well-known phenomenon. Exogenously administered urate is accumulated in the tourniquet-shocked sensitive kidney within half an hour. Uric acid nephropathy in rabbits had not been examined by ultrasonography prior to our study (111).

In the postnatal study, we examined 4 cases. Neonates with severe hyaline membrane disease display various degrees of hyperuricaemia, which very sensitively reflects the severity of the disease (111). The uric acid level was 560±156.4 μmol/l (mean ±SD), which was about 3.5 times more than the normal neonatal concentration. The hypoxanthine level in our asphyxia patients was 43.5±34.5 μmol/l (mean ±SD), while the normal level is <5 μmol/l. Very high
hypoxanthine levels are predictors of a poor prognosis (94, 95), as was shown in 2 of our patients, who died at the ages of 4 and 10 days. The urea-N concentration in these two neonates was 12±5.3 mmol/l (mean ±SD), which was slightly elevated. The creatinine level was 145±26.4 μmol/l (mean ±SD), double the normal level. Case 4, an immature newborn, had the highest values: urea-N 19.5 mmol/l, creatinine 172 μmol/l. Three of the 4 babies had oliguria of various degrees, and the osmolality of the urine was increased. There was no hypercalcaemia in any of the patients. Although furosemide was given to every patient, the low urine Ca/creatinine ratio (maximum 0.4 mg/mg, normal range: 0.32-0.78 mg/mg) practically excludes the possibility of nephrocalcinosis. On the other hand, all newborns were hyperuricosuric.

Hyperechogenicity of the medulla of different grades was found in all of the cases. The increased renal parenchyma echogenicity was transient in every case. Uric acid was considered to be a possible cause of transient renal insufficiency of neonates in the 1970s (1), but hyperechogenicity of the kidneys could not be diagnosed at that time. With the introduction of ultrasonography the echogenicity of the kidneys during the first days of life is often found to be increased (12, 28, 41). In an Italian study (12), 90 of 103 newborns suffered from medullary hyperechogenicity secondary to perinatal asphyxia, but renal function parameters and pathophysiology was not discussed in that article. Alteration in medullary hyperechogenicity is often thought to explain the presence of Tamh-Horsfall protein (87, 93), a mucoprotein excreted by the distal tubules (74).

Opinions in the literature, however, are divided as to whether this protein causes transient renal failure or merely physiological hyperechogenicity of the pyramids. In our opinion, medullary hyperechogenicity of the neonatal kidney seems to be a pathological phenomenon.

We consider that ultrasonographic examination of the kidneys and the measurement of hypoxanthine and uric acid levels should be used as sensitive indicators in the diagnosis and grading of hypoxic injury in the neonate.

7.2. Discussion of perinatal investigations
7.2.1. EPH-gestosis

Foetal and neonatal renal hyperechogenicity was first examined by Estroff et al. (20). Foetal and neonatal renal hyperechogenicity has different causes from those in paediatric and adult patients. Chiara et al. identified different types of neonatal hyperechogenicity (12). Diffuse renal hyperechogenicity is caused by polycystic kidney, renal candidiasis, dysplastic
kidney and thrombosis of the renal vein. They observed an increased cortical echogenicity in a neonate with haemolytic-uraemic syndrome. Medullary hyperechogenicity was found in renal disease secondary to perinatal asphyxia (12, 99).

Neonatal renal hyperechogenicity may have different causes, but the cause is unknown in 20%. We investigated this latter group in both the intrauterine and postnatal periods. It is our opinion that increased medullary echogenicity is an early sign of intrauterine hypoxia, if there are no other anatomical disorders. This is not a normal variant, because it has associative signs of an intrauterine hypoxic condition.

The present results, in accord with literature findings, indicate that there are indirect signs of an intrauterine hypoxic state (13, 15, 61, 62, 70, 73, 80, 88, 89, 121.) These are decreased flow parameters in the umbilical artery and the renal artery, oligohydramnion and IUGR (3, 66, 69, 75, 81). A pathological renal artery and/or umbilical artery flow should induce retarded growth development (13, 92).

In 6 of the 15 renal hyperechogenic cases IUGR was found (40%), whereas there were only 3 cases in the control group (2.8%).

Besides the ultrasonography signs (echogenicity and flow parameter), we also examined blood samples from the cubital vein of the pregnant women for electrolytes and for kidney and liver functions. These investigations revealed a pathological kidney function in the mothers. This suggests an abnormal purine metabolism, which is an indirect sign of intrauterine hypoxaemia (27, 30, 82).

The measured blood parameters of the 15 foetal renal hyperechogenic cases suggest a pathological renal function connected with a chronic hypoxic state in the foetuses. We found the following alterations in the newborns: high urea-N, pathological creatinine and increased uric acid levels. The foetal liver enzyme levels were normal. Estroff et al. observed a slightly increased serum creatinine level 1 week after birth (20). Prolonged regional hypoperfusion results in a hyperechogenic kidney. However, the chronic hypoxic state is balanced by a brain-sparing effect (.39, 51). This relationship is a feature of the redistribution of the cardiac output that has been reported in hypoxic human foetuses. It has been noted in IUGR foetuses, presumably as a result of the associated hyperechogenicity. It occurs in 40% of the cases of foetal hyperechogenic kidney. It is an early and subtle sign of mesenteric vasoconstriction secondary to a haemodynamic redistribution (21).

It has been demonstrated that caesarean section for the delivery of growth-retarded foetuses has an increased incidence because of foetal distress (26, 31). In our study, caesarean section for foetal distress was performed in 6 cases (40%).
The statistical approach demonstrates a significant relation between foetal renal hyperechogenicity and a pathological postnatal clinical outcome (p<0.01). The statistical results suggest a good relation between the diagnostic method and the clinical outcome. The specificity is low, because we investigated only simple foetal renal hyperechogenicity with no anatomical disorders.

Foetal renal hyperechogenicity appears to be a good predictive sign of intrauterine hypoxia. The clinical outcome supported this.

Attention is drawn to the importance of examining the foetal renal echogenicity. We consider that ultrasonographic investigation of foetal renal echogenicity is necessary during the routine scan. It is important to direct pregnant women to the NICU to detect this pathological foetal state in time.

7.2.2. IUGR

Foetal and neonatal renal hyperechogenicities can be due to causes that are different from those in paediatric and adult patients. Chiara et al. identified the types of neonatal hyperechogenicity (12). Diffuse renal hyperechogenicity may be due to polycystic kidney, renal candidiasis, dysplastic kidney and renal venous thrombosis. They observed increased cortical echogenicity in neonates with the haemolytic-uraemic syndrome. Medullary hyperechogenicity was observed with renal disease secondary to perinatal asphyxia (12, 47, 113). Shulman summarized the possible cases of neonatal hyperechogenicity in an editorial letter (98). Calcium deposition, the precipitation of Tamm-Horsfall proteins or other crystalloids. The precipitations of proteins or uric acid, papillary necrosis, vascular congestion, sickle cell anaemia, medullary fibrosis, lymphcell infiltration, dehydration, intrarenal reflux and renal vein thrombosis, have a common ultrasonographic appearance as multiple aetiology factor pathways in renal hyperechogenicity (78, 98, 113). For the first time, foetal and neonatal renal hyperechogenicity was examined by Estroff et al., who identified that the hyperchoic renal parenchyma in the foetus was associated with ultrasonographic or functional abnormalities in 74% of the cases (20). We set out to examine the medullary hyperechogenicity in the foetus and follow up the postnatal clinical outcome, to detect the correlation and/or connection between foetal medullary hyperechogenicity, intrauterine growth retardation and the neonatal outcome.

In our study we detected 25 cases of foetal renal pyramidal hyperechogenicity in 382 normal and pathological (hypertension, HELLP syndrome, IUGR, parvovirus infection or multicystic kidney) pregnancies. We consider the foetal condition of chronic hypoxia in this pathological state to be the cause of the IUGR outcome.
According to our study and the literature, there are different diagnoses for the foetal and neonatal renal hyperechogenicity. The prenatal diagnoses of IUGR connected with renal hyperechogenicity suggest a more serious pathological state.

In 8 of 25 renal hyperechogenic studies IUGR was found. The birth weight of the newborns was lower (mean±SD: 2634±741 g) than the IUGR cases without foetal renal hyperechogenicity. The delivery age was 37.5±2.2 weeks in IUGR and renal hyperechogenic cases.

In small-fo-r-gestation-age foetuses, there is relationship between hypoxia and the redistribution of cardiac output (14, 17, 19, 26). This relationship would be part of the brain-sparing effect that has been reported to produce IUGR in hypoxic human foetuses. This mechanism may result in transient renal insufficiency, as a benign prognosis (5, 35, 36, 37, 46). Ultrasonographic examination can in addition reveal the modified echogenic parenchyma during a short postnatal oliguric period (6, 47).

Hyperechoic pyramids were compared with the renal cortex, liver or spleen because the normal medullary pyramids are hypoechogenic in infants, so the ultrasonographic finding of hyperechogenicity is striking (43). After the postnatal period, it is possible to identify the different aetiologies in cases of foetal hyperechogenicity in the kidney (nephrocalcinosis, Bartter syndrome, renal tubular acidosis, etc.) or sometimes already in utero (polycystic kidney). In transient hyperechogenic case, the cause is transient renal insufficiency. The increased echogenicity may represent tubular blockage caused by occlusion of Tamm-Horsfall protein precipitation in tubules (5, 86, 99). It is correlated with Tamm-Horsfall proteinuria (5). The complication is benign if it is transitory. Therefore, renal failure does not always incur necrosis. The aetiology and clinical condition of acute necrosis and acute blockage of the tubules are the same. They are differentiated by the degree and the course of the disease (8, 77).

In our foetal cases, the medullary echogenicity could be explained by the same mechanism, which started in the last period of intrauterine life. The protein blocking disappears with the start of urinary production after birth (107). This ultrasonographic sign is less sensitive in transitory renal failure than in conditions involving serious disease, such as acute tubular necrosis (58). However, a high positive predictive value calls attention to the examination of this less sensitive sign together with the evident characteristic features.

The intrauterine states have ultrasonographic signs. Our study suggested that medullary hyperechogenicity was a pathological sign of a hypoxic state (96, 97, 116). The kidney parenchyma is very sensitive to hypoxia, and hypoxic renal failure is accompanied by hyperechogenicity of the kidneys (113).
We would like to compare intrauterine growth with physical conditions apart from medullary hyperechogenicity. We believe that there is a correlation between abnormal intrauterine growth, the necessity for neonatal intensive care and medullary hyperechogenicity, which indicates the intrauterine hypoxic state, often the cause of neonatal renal failure. Therefore, if the sonographer detects renal parenchymal hyperechogenicity, it is important to direct the pregnant woman to the NICU in order to detect the possible pathological foetal state in time.

7.2.3. Renal artery investigation

Visualization of small foetal vessels such as the renal artery was described by Campbell et al. in 1988 (10). 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 foetal renal artery (10, 90, 91). During hypoxaemia, 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 (81). This would imply that, instead of a local vasoconstriction of the renal vasculature, the foetal 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 haemodynamic change (88). A direct relationship has been reported between hypoxia and the renal artery pulsatility index (e.g. resistance) (59, 104). Abnormal umbilical and venous pulsation is probably a late sign of hypoxia (33).

Perinatal renal hyperechogenicity may have different causes, but in a considerable proportion of the cases (about 20%), there is no anatomical alteration (21). Intrauterine and/or neonatal renal hyperechogenicity has been interpreted as a sign of intrauterine hypoxia (12, 110).

We investigated intrauterine hypoxia by using indirect ultrasonographic signs: renal hyperechogenicity, and decreased flow parameters in the umbilical artery and the renal artery (12, 81, 121). The screened pregnancies were those with chronic hypoxia caused by pregnancy-associated hypertension and/or proteinuria and intrauterine growth retardation. We selected these cases, because they are well defined and diagnosis is possible in the prenatal period (96, 97, 100). There is a similarity between these two populations in terms of the causes of the intrauterine chronic hypoxia. We examined these two types of pathological pregnancies in order to eliminate other chance differences or identity in our analysis of 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 foetal 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 the renal artery flow parameters were significantly different.

There is a good correlation between the progressive increase in renal vascular resistance and the decreased organ perfusion (73, 102, 105). By Doppler methods, both foetal and uterine blood flow can be measured, thereby permitting an assessment and detection of a dysfunction affecting the uteroplacental circulation (22, 31, 57). In foetuses 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 analyse the association between the prenatal pathological renal echogenicity and the postnatal clinical outcome. A 6 times higher risk of a pathological outcome was demonstrated by the odds ratio method when the kidneys were hypechoic in pregnancy-associated hypertension and/or proteinuria. In intrauterine growth retardation, the risk was revealed by an odds ratio of 1.5 times the normal. This intrauterine growth retardation group is a very heterogeneous population. One cause of retardation can be intrauterine hypoxia. This explains why the risk of a pathologic 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/chronic intrauterine hypoxia such as retarded growth (birth weight below $P_{10}$) and caesarean section as the mode of delivery There were higher rates of caesarean section (12 times), perinatal infection (8 times), transfer to the NICU (11 times), perinatal mortality (45 times) and necrotizing enterocolitis (3 times) among babies with hypechoic medullae than in the control group, where there was a suspected chronic hypoxic state with a normal-echoic foetal kidney. Of course, these conditions arise with much lower rates in the normal population.

The redistribution of the foetal circulation results in an abnormal renal flow. The redistribution of the blood flow is due to foetal hypoxaemia. During this process, the foetal kidneys are among those organs which are sometimes compromised, leading to transient renal insufficiency, usually a benign disease (5). In theory, foetal hypoxia triggers a discordant vasmotor 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 the 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 (121). The increased resistance index of the descending thoracic aorta could be a component of the centralization of the foetal circulation due to chronic hypoxia. The foetal renal blood flow may similarly be affected as a result of an elevated intravascular resistance, leading to a decline in renal perfusion (117).

In those neonates where there had been renal hyperechogenicity due to foetal hypoxia, this modified echogenicity of the renal medulla is preserved during the short postnatal oliguric period (6, 47). These ultrasonographic signs disappear quickly after the first postnatal urinary evaluation. In our investigations the hyperechoic features were found to be lost by day 2 in 51% and by the end of the second 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 aetiologies of foetal renal hyperechogenicity (nephrocalcinosis, Barter syndrome, renal tubular acidosis, etc.) (72). The aetiology is sometimes already clear during the foetal period (e.g. polycystic kidney) (60).

In contrast, renal hyperechogenicity due to foetal hypoxia develops in the last period of pregnancy, in our cases between the week 25 and 39 weeks of gestation. Our results show that the foetal 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 (5, 86, 99). There is a consistent body of evidence supporting the idea that the transient renal insufficiency is correlated with Tamm-Horsfall proteinuria in the postnatal period (5, 6).

Renal hyperechogenicity as a complication of foetal hypoxia is benign if transitory. Foetal renal failure of hypoxic origin does not automatically lead to tubular necrosis. The aetiology 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 (8, 77). 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 in the Doppler data than change in the 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 of foetal renal hyperechogenicity is a simple examination, and should therefore be performed during a routine scan. It is a sensitive sign, and measurement of the foetal renal artery blood flow is essential because the changes in the flow parameters are more characteristic. However, measurements on the foetal renal artery are difficult. For this reason, we suggest the detection of renal echogenicity first. Then, if hyperechogenicity is found, the blood flow is measured with the Doppler method in order to detect the redistribution of the foetal circulation, as an early sign of an intrauterine hypoxic state. Therefore, it is important to direct pregnant women to a NICU in order to detect the possible pathological foetal state.

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

Since the majority of foetal renal hyperechogenic cases are complicated by a foetal and/or neonatal pathological condition, we suggest foetal renal ultrasonography for use for the screening of all risk pregnancies. The conception is as above:

1. Investigation of intrauterine hypoxia is possible by using indirect ultrasonographic signs: foetal renal hyperechogenicity and decreased flow parameters in the renal artery.

2. Besides the routine scan renal ultrasonography is important in the diagnosis of foetal hypoxia at an early state.

3. The EPH-gestosis and IUGR cases are a high-risk group for chronic foetal hypoxia, and therefore foetal renal ultrasonographic examination is essential.

4. The combined use of echogenicity of the foetal renal parenchyma and Doppler flow study of the foetal renal artery, in order to detect pathologic changes renal artery, because the aetiology of foetal renal hyperechogenicity is different.

5. Change in the renal artery flow resistance is seen sooner in the Doppler data than change in the umbilical artery, because of the redistribution of the blood circulation.

6. Furthermore, we suggest the testing of the kidneys of the neonates after a foetal renal hyperechoic ultrasound finding.

7. In every case of detected foetal renal hyperechogenicity, we suggest that pregnant women should be directed to a perinatal intensive care centre in order to detect the possible pathological foetal state.
Whether there is a quantitative relation between the magnitude of the hypoxia and the amplitude of the renal flow reduction reflected by the hyperechogenicity of the foetal renal medulla remains to be elucidated.
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Short communications

The possible role of uric acid in renal hyper-echogenicity in neonatal hypoxic acute shock

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1 Introduction
Perinatal asphyxia frequently causes renal injury [9]. Normally, rather than being hypo-echogenic, the echogenicity of the cortex of the neonatal kidney is equal to that of the liver and spleen. In contrast, the medullary pyramids are normally hypo-echogenic and prominent [4, 5, 7]. Hyper-echogenicity of the renal cortex, and especially of the renal pyramids is a well-known phenomenon. It is common in newborns with anatomical abnormalities (e.g., polycystic kidneys) [12], however, opinions vary about its importance in cases without any underlying anatomical abnormality. In a report from Germany it was considered to be a physiologic sign of adaptation, while in an Italian study of a larger population of neonates with hyper-echogenic renal pyramids, patients with no anatomical abnormality were found to have had fetal asphyxia [12].

In this paper we describe a number of newborns with hypoxic episodes of different etiology and severity. Ultrasonicographic examination was performed and the pathophysiological background was investigated.

2 Patients and methods
2.1 Patients
Four newborns were examined after perinatal asphyxia. Three of them were mature and one of them was immature. In every case the following criteria were fulfilled: Apgar score (1. minute)

Curriculum vitae

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was born in 1969 in Nagykántza, Hungary. During his university training he spent three months in the Department of Physiology of the Free University of Amsterdam. In 1993 he graduated with “summa cum laude” at the Albert Szent-Györgyi University Medical School, Szeged. In the same year he started his residential training at the Pediatric Clinic of the university. His main field of interest is pathophysiology of hypoxic states during the perinatal neonatal period.

< 4, umbilical artery pH < 7.2 and PaO₂ < 50 mmHg. Patients were observed in the Neonatal Intensive Care Unit (NICU).

2.2 Methods
The kidneys were examined ultrasonographically using a Hitachi EUB-450 real-time equipment and its 5 MHz transducer within the first 24 hours after the hypoxia was noted, and examinations were continued for 14 days.

Blood samples were collected immediately right after arrival of the baby at the NICU. Determination of uric acid (UA) and hypoxanthine (HX)
were performed with High Pressure Liquid Chromatography using a method elaborated by Harkness et al. [6]. Other parameters were determined using conventional laboratory techniques.

Urine output was measured and urine calcium/creatinine (creat.) and UA/creat. ratios [15] were calculated.

3 Case report

Case 1: Male infant born at 40 weeks gestation weighing 4100 g. Apgar scores at 1, 5 and 10 minutes were 2, 6 and 8 respectively. Meconium aspiration syndrome (MAS) was present. After successful resuscitation nasal Continuous Positive Airway Pressure (CPAP) was started using 60% oxygen. Arterial pO2 was 48 mmHg, pH was 7.18 at the age of 12 hours (tables 1 + II). Sonographic examination of the kidneys was performed on the first day of life. Hyper-echogenicity was detected in the spires of the medullary pyramids of the right kidney. This was no longer visible from day 3.

Case 2: Female infant born at 28 weeks gestation weighing 2950 g. Apgar scores at 1, 5 and 10 minutes were 4, 7 and 9 respectively. At 17 hours, the baby unexpectedly collapsed with "near miss" Sudden Infant Death Syndrome. Resuscitation was partially successful. She was having repeated convulsions and was intubated and ventilator treatment was started. The hypoxic state lasted three hours (tables 1 + II). On day 2 reflectivity of the renal cortices was increased. Increased reflectivity could also be confirmed to be present in the pyramids of both kidneys. By day 3 no hyper-echogenicity of the cortices nor of the medulla could be detected any more. This patient died at the age of 10 days (figure 1).

Case 3: Female infant born at 36 weeks gestation weighing 3680 g. The clinical diagnoses were fetal distress and diabietic fetopathy. Comprensive resuscitation was required because asphyxia was severe, with Apgar scores of 0, 1 and 1 at 1, 5 and 10 minutes. After intubation ventilation was commenced. Her oxygen requirement was 55% (tables I + II). At the age of 4 days marked echogenicity was found to be present in the medulla of both kidneys. By day 14 the renal medullary hyper-reflectivity had disappeared.

Case 4: Female infant born at 27 weeks gestation weighing 720 g. Apgar scores were 1, 1 and 3 at 1, 5 and 10 minutes. She was intubated and

Table I. Purine metabolites and renal hyper-echogenicity in neonatal hypoxic acute shock

<table>
<thead>
<tr>
<th>Case</th>
<th>Birth weight (g)</th>
<th>Gest. age (week)</th>
<th>Apgar score</th>
<th>pO2 mmHg</th>
<th>Uric acid (mmol/l)</th>
<th>Hypoxanthine (mmol/l)</th>
<th>UA/Creat. in urine (mg/mg)</th>
<th>Renal sonography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4100</td>
<td>40</td>
<td>2/6/8</td>
<td>48.0</td>
<td>337.0</td>
<td>8.4</td>
<td>2.7</td>
<td>Pathologic on lifeday 1.</td>
</tr>
<tr>
<td>2</td>
<td>2950</td>
<td>38</td>
<td>4/7/9</td>
<td>39.0</td>
<td>570.0</td>
<td>81.4</td>
<td>2.9</td>
<td>Pathologic on lifeday 2.</td>
</tr>
<tr>
<td>3</td>
<td>3850</td>
<td>36</td>
<td>0/1/1</td>
<td>50.0</td>
<td>645.0</td>
<td>64.4</td>
<td>6.2</td>
<td>Definitely pathologic on lifeday 4.</td>
</tr>
<tr>
<td>4</td>
<td>720</td>
<td>27</td>
<td>1/1/3</td>
<td>44.0</td>
<td>688.0</td>
<td>20.1</td>
<td>2.1</td>
<td>Pathologic on lifeday 1.</td>
</tr>
</tbody>
</table>

Table II. Blood and urine values in neonatal hypoxic acute shock on the 1st day after birth

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>pH (mmol/l)</th>
<th>BUN (mmol/l)</th>
<th>Creatinine (mmol/l)</th>
<th>Ca (mmol/l)</th>
<th>Quantity of urine (ml/kg h)</th>
<th>Osmolality of urine (mosm/kg)</th>
<th>Ca/Creat. in urine (mg/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>MAS</td>
<td>7.18</td>
<td>9.9</td>
<td>142.5</td>
<td>1.68</td>
<td>0.3</td>
<td>366</td>
<td>0.11</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>SIDS</td>
<td>7.17</td>
<td>7.0</td>
<td>110.0</td>
<td>2.20</td>
<td>1.4</td>
<td>392</td>
<td>0.06</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>Fetal Distress</td>
<td>7.17</td>
<td>11.4</td>
<td>154.0</td>
<td>1.82</td>
<td>0.2</td>
<td>286</td>
<td>0.40</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>IRDS</td>
<td>7.2</td>
<td>19.5</td>
<td>173.0</td>
<td>1.06</td>
<td>0.6</td>
<td>175</td>
<td>0.22</td>
</tr>
</tbody>
</table>

transferred to our hospital immediately because of extreme prematurity and IRDS. Respirator treatment was started immediately after her arrival (tables I + II). At 1 day of age, increased echogenicity of the renal parenchyma was found. This very immature infant died of intraventricular hemorrhage on the fourth day of life.

4 Discussion

In our previous animal experiment, UA nephropathy due to acute shock could be induced, and sonographic examination showed hyper-echogenicity of the renal medulla [14]. According to these experimental results a study protocol was designed for hypoxic neonates. So far we have examined 4 cases, who fulfilled all the criteria of our protocol. UA level was 560 ± 156.4 µmol/l (x ± SD), which was about 3.5 times higher than the normal neonatal concentration found in our laboratory (160 µmol/l). HX level in our asphyxial patients was 43.6 ± 34.9 µmol/l (x ± SD), while the normal level found in our laboratory is < 5 µmol/l. Very high HX levels predict a bad prognosis [13], which was also shown in two of our patients, who died at the age of 4 and 10 days. BUN concentration was 12.0 ± 5.3 mmol/l (x ± SD), which was slightly elevated (normal: 2–9 mmol/l). Creat. level was 145.0 ± 26.4 µmol/l (x ± SD), while the normal level is 10–70 µmol/l. Case 4, the immature newborn with a birthweight of 720 g had the highest values (BUN 19.5 mmol/l, creat. 172 µmol/l). 3 of the 4 patients had oliguria of various degrees, and osmolality of the urine was increased. There was no hypercalcemia in any of the patients. Although furosemide was given to every patient, the low urine Ca/creat. ratio (maximum 0.4 mg/mg, normal = 0.32–0.78 mg/mg) practically excludes the possibility of nephrocalcinosis. On the other hand, all newborns were hyper-uricosuric (normal range: 0.79 mg/mg, patients data in the tables).

Hyper-echogenicity of the medulla was found of different grades in all of the cases. In two cases the entire parenchyma was hyper-reflective. The increased renal parenchymal echogenicity was transient in all of the cases.

UA was considered to be a possible cause of transient renal insufficiency of the neonate as early as the 70’s [1], however, hyper-reflectivity of the kidneys could not be diagnosed at that time. With the introduction of ultrasonography echogenicity of the kidneys during the first days of life is often found to be increased [2, 3, 4]. In a study from Italy [2], 90 newborn infants out of 103 had med-

![Figure 1. On the 2nd day of life, increased reflectivity of both kidneys occurred, either in the cortical, or in the medullary parenchyma.](image)

ullary hyper-echogenicity secondary to perinatal asphyxia, however parameters of renal function and pathophysiology are not discussed in this article. Alteration in medullary hyper-echogenicity is often thought to explain the presence of Tamm-Horsfall protein [10, 11], a mucoprotein, excreted by the distal tubulus [8]. Opinions in the literature are, however divided as to whether this protein causes transient renal failure or just physiological hyper-echogenicity of the pyramids. In two of our cases, we found hyper-echogenicity of either the cortices or the medulla, which cannot be explained by deposition of Tamm-Horsfall protein.

In our opinion medullary hyper-echogenicity of the neonatal kidney seems to be a pathological phenomenon. In addition, we consider that sonographic examination of the kidneys and measurement of hypoxanthine and uric acid levels should be used as sensitive indicators in the diagnosis and grading of hypoxic injury in the neonate.

Abstract

Sonographic examinations as well as blood and urine chemistry tests were carried out in 4 neonates (3 mature, 1 premature) with transient renal failure, who were suffering from the effects of neonatal asphyxia of varying etiology. The first ultrasound examinations of the kidneys were performed within 24 hours after the hypoxic event. Simultaneously, blood and urine tests for parameters of renal function and purine metabolites were also carried out. Transient insufficiency of renal function could be detected in all cases with hyper-uricemia and hyper-uricosuria with no hypercalciuria. Ultrasonographic examinations showed hyper-echogenicity of the renal pyramids in all of the cases and hyper-reflectivity of the renal cortex in cases 2 and 4. In 3 cases, hyper-echogenicity appeared within 24 hours and disappeared in a short time, while in case 3 it could be detected from day 4 until day 14. These findings demonstrate, that the neonatal kidney is very sensitive to hypoxia and that hypoxic renal failure is accompanied by hyper-echogenicity of the kidneys. Uric acid is a possible cause of the renal hyper-echogenicity.

Keywords: Hypoxia, neonate, renal hyper-echogenicity, uric acid.

Zusammenfassung

Die mögliche Rolle von Harnsäure bei renaler Hyper-Echogenität bei neonatalem akutem hypoxischem Schock


Schlüsselwörter: Harnsäure, Hypoxie, Neugeborenes, renale Hyper-Echogenität.

Résumé

Rôle possible de la l'acid urique dans le choc hypoxique néonatale aigu

Nous avons effectué les examens échographiques, les examens chimiques du sang et de l'urine sur 4 nouveau-nés (3 matures, 1 immature) présentant une altération du passage rénal et souffrant des séquelles d'une asphyxie néonatale d'étiologie diverse. Le premier examen échographique a été réalisé dans les 24 heures suivant l'événement hypoxique. Nous avons effectué dans le même temps les examens du sang et de l'urine pour établir

les paramètres de la fonction rénale et les métabolites urinaires. Nous avons détecté sur tous une insuffisance de passage de la fonction rénale avec hyperuricémie et hyperuricurie mais sans hypercalcurie. Les examens échographiques ont révélé un rein hyper-échogène au niveau des pyramides rénales dans tous les cas et une hyper-réflectivité du cortex rénal dans les cas 2 et 4. Dans 3 cas, le rein hyper-échogène est apparu dans les 24 heures mais a disparu rapidement alors que dans le cas 3, il a été détecté du jour 4 au jour 14. Ces résultats montrent que le rein néonatal est extrêmement sensible à l’hypoxie et que l’hypoxie rénale s’accompagne d’un rein huper-échogénique. Il est possible que l’acide urique soit à l’origine de ce rein hyper-échogénique.

Mots-clés: Acide urique, hypoxie, nouveau-né, rein hyper-échogénique.

References

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Fetal renal hyperechogenicity in pathological pregnancies

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1 Introduction

Estroff et al. examined the fetal and neonatal hyperechogenicity. Neonatal renal hyperechogenicity is a characteristic feature in chronic or acute perinatal hypoxia [2, 18]. The cause of fetal renal hyperechogenicity in hypoxic cases is presumed to be the accumulation of ATP depletion products.

Neonatal hyperechogenic kidneys have been reported in connection with urinary tract obstruction, polycystic and glomerulocystic kidney disease, obstructive nephrolithal disease and nephrocalcinosis [5, 9, 11, 17]. In about 20% of cases of fetal renal hyperechogenicity, the cause is unknown [7]. The possibility of a connection between intrauterine growth retardation and hyperechogenicity has not been examined so far. Hyperechogenic kidney is diagnosed when the fetal kidney displays an echogenicity higher than that of the liver or the spleen [6]. Hyperechogenicity of the renal cortex and especially the renal pyramids is a well-known phenomenon, but opinions differ appreciably as to its importance in cases involving no anatomical alterations. Chiara et al. examined a large population of neonates with hyperechogenic pyramids, but no anatomical abnormality was ever found to accompany fetal asphyxia [2].

We have investigated the echogenicity of the fetal kidneys during the last period of intrauterine life in normal and pathological pregnancies, focusing on pregnancies complicated by chronic fetal hypoxia (pregnancy-induced hypertension and preeclampsia). Pregnancy-induced hypertension does not always involve intrauterine hypoxia, but in our cases this was the case.

These fetal examinations were designed to screen for medullary hyperechogenicity, and to examine whether there is a connection between the hyperechogenicity of the fetal kidney and the presence of an intrauterine hypoxic state (figures 1 + 2).

2 Patients and methods

One hundred and twenty pregnancies were investigated between the 28th and 36th weeks of gestation. All these women had toxemia, as defined by the Fédération Internationale de Gynecologie et d’Obstetrique (FIGO); EPH gestation has edema, proteinuria and hypertension. The gestation age was calculated according to NAEGLE’s rule and the first trimester ultrasound examination. In the positive group (15 cases), fetal renal hyperechogenicity was diagnosed, without other fetal ana-
ornal abnormalities. The control group comprised of the other 105 cases of the 120 pathological pregnancies.

The maternal liver and kidneys and the fetal brain, heart, bowel, liver and renal parenchyma were screened by ultrasound. The blood flows of the fetal renal artery and the umbilical artery were measured by Doppler. Examinations were performed using Hitachi EUB-450 ultrasound equipment fitted with a 3.5 MHz transducer. Hyperechogenic kidney was diagnosed when the fetal renal medulla or cortex displayed an echogenicity similar to that of the surrounding bone, but higher than that of the liver or spleen (figures 1 + 2). The pathological waveforms of the renal arteries include diastolic zero flow, reverse flow, postystolic incisura or higher flow parameters than those of the normal field [18].

Between the 28th and 36th weeks of gestation, at the same time as the ultrasound examinations, blood was taken from the mothers for determination of electrolytes (Na, K, Ca, Cl) and kidney (creatinine, urea-N, uric acid, triglyceride, cho- lesterol) and liver (SGOT, SGPT, GGT, bilirubin) functions. Blood was also collected after delivery, from the pulsating umbilical artery and from the cubital vein of the mothers for the same reasons. Blood was collected from the non-pul- sati ng umbilical artery within the first 15 minutes of life for determination of acid-base parameters (pH, st. bicarb., PCO₂, PO₂, O₂ saturation) as a usual investigation. Blood samples were examined by standard laboratory techniques.

The liver and kidneys of the neonates were screened with Hitachi EUB-450 ultrasound equipment fitted with a 3.5 MHz transducer during the first 5 days after birth.

The results were analysed by the chi-square test with the Yates correction.

3 Results

Fifteen out of 120 pathological pregnancies involved fetal renal hyperechogenicity without any other fetal anatomical abnormalities. In the control group, 21 of the 105 cases displayed some pathological fetal and neonatal states, but no fetal renal hyperechogenicity. The pregnant women in the hyperechogenic group developed toxemia after the 28th week of gestation. Serious hypertension was detected in 9 mothers. The pregnant women had normal electrolyte levels. The kidney function was abnormal in 3 mothers. In 2 cases there were abnormal urea-N levels and in 3 cases abnormal creatinine levels. Two women had pathological urea-N and creatinine levels, and one had abnormal uric acid, urea-N and creatinine levels. A pathological uric acid level was observed in 4 cases. All of the investigated maternal cases exhibited increased liver enzyme levels.

Table I lists the umbilical artery serum parameters at delivery. The 15 newborns had hyperuricemia, especially the first and the fourth case. In 4 cases, there was an elevated creatinine level and in 7 cases a high urea-N level. In the control group, there were no kidney function abnormalities. Similarly, no abnormalities were found in the blood samples taken for determination of acid-base parameters within the first 15 minutes in the two groups of newborns. In the postnatal period, ultrasonography revealed a pathological renal morphology (renal hypoplasia) in 1 case and transitory renal hyperechogenicity in 6 cases, but there were no renal lesions in the other cases in the hyperechogenic group. In the control group, 3 polycystic kidneys were identified in the intrauterine state. In the hyperechogenic group, there were 6 cases of IUGR (40%), whereas in the control group there were only 3 cases (3%). The mode of delivery was Cesarean section in 7 cases in the hyperechogenic group (46%), and in 6 cases in the control group (6%).

The results were evaluated statistically by the chi-square test with the Yates correction (χ² test 9.16, p < 0.01), sensitivity: 93%, specificity: 30%, positive predictive value: 60%, negative predictive value: 80%, validation: 77%.

4 Discussion

Fetal and neonatal renal hyperechogenicity was first examined by ESTROFF et al. [6] Fetal and neonatal renal hyperechogenicity has different causes from those in pediatric and adult patients. CHIARA et al. identified different types of neonatal hyperechogenicity [2]. Diffuse renal hyperechogenicity is caused by polycystic kidney, renal

candidiasis, dysplastic kidney and thrombosis of the renal vein. They observed an increased cortical echogenicity in a neonate with hemolytic-uremic syndrome. Medullary hyperechogenicity was found in renal disease secondary to perinatal asphyxia [2, 18]. Neonatal renal hyperechogenicity may have different causes, but the cause is unknown in 20%. We investigated this group in both the intrauterine and postnatal states. It is our opinion that increased medullary echogenicity is an early sign of intrauterine hypoxia, if there are no other anatomical disorders. This is not a nor-

Figure 1. Longitudinal ultrasound view of a normal-sized hyperechogenic fetal kidney in the third trimester. Renal pyramids are hyperechogenic.

Figure 2. Longitudinal ultrasound view of the left and right kidneys in a 2-day-old infant. The left kidney gives pattern C, and the right kidney pattern D of hyperechogenic pyramids [13].
<table>
<thead>
<tr>
<th>Case number</th>
<th>Delivery age [weeks]</th>
<th>Delivery weight [grams]</th>
<th>Apgar score (1st, 5th, 10th)</th>
<th>Acid-base parameters pH-st bicarb-CO₂-O₂</th>
<th>Uric acid (mmol/l)</th>
<th>CN (mmol/l)</th>
<th>Creatinine (umol/l)</th>
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<td>153</td>
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<td>57</td>
<td>PNV, IUGR, part. praematur.</td>
</tr>
<tr>
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<td>32</td>
<td>1440</td>
<td>2, 8, 9</td>
<td>7.21−21.6−56.0−57.0</td>
<td>365</td>
<td>3.6</td>
<td>69</td>
<td>sectio c., IUGR, part. praematur., IRDS, PRH</td>
</tr>
</tbody>
</table>

PRH = postnatal renal hyperechogenicity  
PVN = per vías naturales  
IUGR = intrauterine growth retardation  
IRDS = idiopathic respiratory distress syndrome  
sectio c. = sectio caesarea  
part. praematur. = partus praematurus  
NEC = necrotic enterocolitis  
WAC = without any complication
Our results, in accord with literature findings, indicate that there are indirect signs of an intrauterine hypoxic state [3, 4, 16, 19]. These are decreased flow parameters in the umbilical artery and the renal artery, oligohydramnion and IUGR [1, 12, 14]. The pathological renal artery and/or umbilical artery flow should induce the retarded growth development [3, 15]. In 6 of the 15 renal hyperechogenic cases, IUGR was found (40%), whereas there were only 3 cases in the control group (2.8%).

Besides the ultrasound signs (echogenicity and flow parameters) we also examined blood samples from the umbilical vein of the pregnant women for electrolytes and for kidney and liver functions. These investigations revealed a pathological kidney function in the mothers. This suggests an abnormal purine metabolism, which is an indirect sign of intrauterine hypoxemia.

The measured blood parameters of the 15 fetal renal hyperechogenic cases suggest a pathological renal function connected with a chronic hypoxic state in the fetuses. We found the following alterations in the newborns: high urea-N, pathological creatinine and increased uric acid levels. The fetal liver enzyme levels were normal. Estroff et al. observed a slightly increased serum creatinine level 1 week after birth [6]. Regional prolonged hypoperfusion results in a hyperechogenic kidney. However, the chronically hypoxic state is balanced by a brain-sparing effect [8, 10]. This relationship is a feature of the redistribution of the cardiac output that has been reported in hypoxic human fetuses. It has been noted in IUGR fetuses, presumably as a result of the associated hyperechogenicity. It occurs in 40% of the cases of fetal hyperechogenic kidneys. It is an early and subtle sign of mesenteric vasoconstriction secondary to a hemodynamic redistribution [7]. Growth-retarded fetuses have been demonstrated to have an increased incidence of Cesarean section because of the fetal distress. In our study, Cesarean section for fetal distress was performed in 6 cases (46%).

The statistical approach demonstrates a significant relation between fetal renal hyperechogenicity and a pathological postnatal clinical outcome (p < 0.01). The statistical results suggest a good relation between the diagnostic method and the clinical outcome. The specificity is low, because we investigated only simple fetal renal hyperechogenicity with no anatomical disorders.

Fetal renal hyperechogenicity appears to be a good predictive sign of intrauterine hypoxia. The clinical outcome support this.

Attention is drawn to the importance of examining the fetal renal echogenicity. We consider that ultrasound investigation of fetal renal echogenicity is necessary during the routine scan. It is important to direct pregnant women to the perinatal intensive care unit to detect this pathological fetal state in time.

Abstract

A relationship was sought between renal hyperechogenicity and the hypoxic state of fetuses.

120 pathological pregnancies were examined between the 28th and 36th week. All of these women exhibited moderately increased levels of hepatic enzymes, 3 of them had a pathological kidney function, and 4 of them displayed hyperuricemia during the examination period. The echogenicity of the fetal kidneys was examined with Hitachi EUB-450 ultrasound equipment with a 3.5 MHz transducer. The kidney (creatinine, urea-N, uric acid, triglyceride, cholesterol) and liver (SGOT, SGPT, GGT, bilirubin) functions and plasma electrolytes (Na, K, Ca, Cl) of the mothers were also examined and blood was collected from the pulsating umbilical artery for determination of the same parameters. After delivery, the physical condition of the neonates was followed and their kidneys were examined with the same ultrasound equipment within the first 5 days.

There was a significant correlation between a pathological neonatal clinical outcome and the frequency of fetal and hyperechogenicity (chi-square test with Yates correction, p < 0.01).

The results demonstrate that fetuses exhibiting renal hyperechogenicity in pathological pregnancies require particularly careful obstetric control and neonatological consultation. It is important that hyperechogenic cases be admitted to a perinatal intensive care unit. Fetal renal hyperechogenicity is considered to be associated with an enhanced risk of an adverse perinatal outcome.

Keywords: Fetus, renal hyperechogenicity, ultrasound.

References


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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 hyperechogenic 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 hyperechogenic 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.
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 maximal 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 echogenicity was detected without any fetal anatomical abnormalities (103 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 pre-eclampsia 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, post-systolic 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 nectrotizing 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 multi-
### Table 1 Characterization of neonates with hyperechogenic medul lce in pregnancy-associated hypertension and/or proteinuria (NICU neonatal intensive care unit)

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Delivery weight (g)</th>
<th>Delivery age (weeks)</th>
<th>Apgar score (1st min)</th>
<th>Postnatal clinical outcome (5th min)</th>
<th>Transfer to NICU</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>1600</td>
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<td>4</td>
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<tr>
<td>2</td>
<td>M</td>
<td>3600</td>
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<td>7</td>
<td>9</td>
<td>Cesarean section, without any problem</td>
</tr>
<tr>
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<td>2200</td>
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**Mean**
- 2438.00
- 35.67
- 7.47
- 8.87

**SD**
- 740.8
- 3.33
- 2.44
- 1.26

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

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Delivery weight (g)</th>
<th>Delivery age (weeks)</th>
<th>Apgar score (1st min)</th>
<th>Postnatal clinical outcome (5th min)</th>
<th>Transfer to NICU</th>
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**Mean**
- 2683.18
- 37.55
- 7.23
- 8.50

**SD**
- 727.15
- 2.43
- 1.78
- 1.27
cystic 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 oligohydramnios (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, catacata 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 amniotic 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), agenesis of the corpus callosum (1 case), facial malformation (1 case), spina bifida (1 case), oesophageal atresia (1 case), gastoschisis (1 case) and single umbilical artery (1 case) (comprising 10.4% of the control group).

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 \( \chi^2 = 2.049 \) \((P < 0.05)\) in pregnancy-associated hypertension and/or proteinuria cases and \( \chi^2 = 0.075 \) \((P < 0.05)\) 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 \( \chi^2 = 3.71 \) \((P < 0.05)\) in pregnancy-associated hypertension
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 post-stolic incisura in the renal artery at 31st week of gestation. The Doppler gate is positioned over the main renal artery

and/or proteinuria cases, and $\chi^2=3.76$ ($P<0.05$) in intrauterine growth retarded cases. In cases without fetal renal hyperechogenicity, there was a reduced resistance index, but differences were not significant.

**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 hyperchogenicity 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 hyperchoic 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 P10) 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 hyperchoic 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 hyperchogenicity 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 hyperchoic 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 hyperchogenicity 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 hyperchogenicity in the postnatal period.

In the postnatal period it is possible to identify the different etiologies of fetal renal hyperchogenicity (nephrocalcinosis, Barter syndrome, renal tubular acidosis, etc.) [25]. The etiology is sometimes already clear during the fetal period (e.g., polycystic kidney) [26]. In contrast, renal hyperchogenicity 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 hyperchogenic 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 hyperchogenicity 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 hyperchogenicity 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 Doppler 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 concept 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.

References