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

Thesis

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Publications

I Tálosi G, Streitman K, Surányi A, Pinter S, Horvath I, Mulugeta Z:
The possible role of uric acid in renal hyperechogencity in neonatal hypoxic acute shock. J Perinat Med 1996;24:693-697

II Surányi A, Pál A, Streitman K, Pintér S, Kovács L:
Fetal renal hyperechogenicity in pathological pregnancies.
J Perinat Med 1997;25:274-279

III Surányi A, Streitman K, Pál A, Nyári T, Retz C, Foidart JM, Schaaps JP, Kovács L:
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Contents

1. Abbreviations

AMP	adenosine monophosphate
ADP	adenosine diphosphate
AIDS	acquired immune deficiency syndrome
ATP	adenosine triphosphate
Ca	calcium
DNA	desoxyribonucleic acid
EPH-gestosis	oedema, proteinuria and hypertension during pregnancies
g	gram
GMP	guanosine monophosphate
GDP	guanosine diphosphate
GTP	guanosine triphosphate
Hadlock weight estimation	$\log_{10}$(estimated foetal weight)=1.3598+0.051(abdominal circumference) +0.1844(femur length)-0.0037(femur length)(abdominal circumference)
HELLP syndrome	haemolysis, elevated liver enzymes, low platelets syndrome
HGPRT	hypoxanthine guanine phosphoribosyl transferase
HMD	hyaline membrane disease
H_2O	water
IMP	inosine monophosphate
IRDS	idiopathic respiratory distress syndrome
IUGR	intrauterine growth retardation
i.v.	intravenous
K	potassium
kg	kilogram
NICU	neonatal intensive care unit
NST	non-stress test
P_{10}	ten percentile
P_3	three percentile
pCO_2	partial carbon dioxide pressure
pH	negative logarithm of hydrogen ion concentration of a solution
P.I.	pulsatility index
pO_2	partial oxygen pressure
R.I.	resistance index or Pourcelot index
SD	standard deviation
SGOT/ASAT	serum glutamate-oxaloacetic-transaminase / aspartate aminotransferase
SGPT/ALAT	serum glutamate-pyruvate-transaminase / alanine aminotransferase
GGT	gamma-glutamyl transferase
urea-N	urea nitrogen
UV	ultraviolet

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 0.05 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, 118). 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.

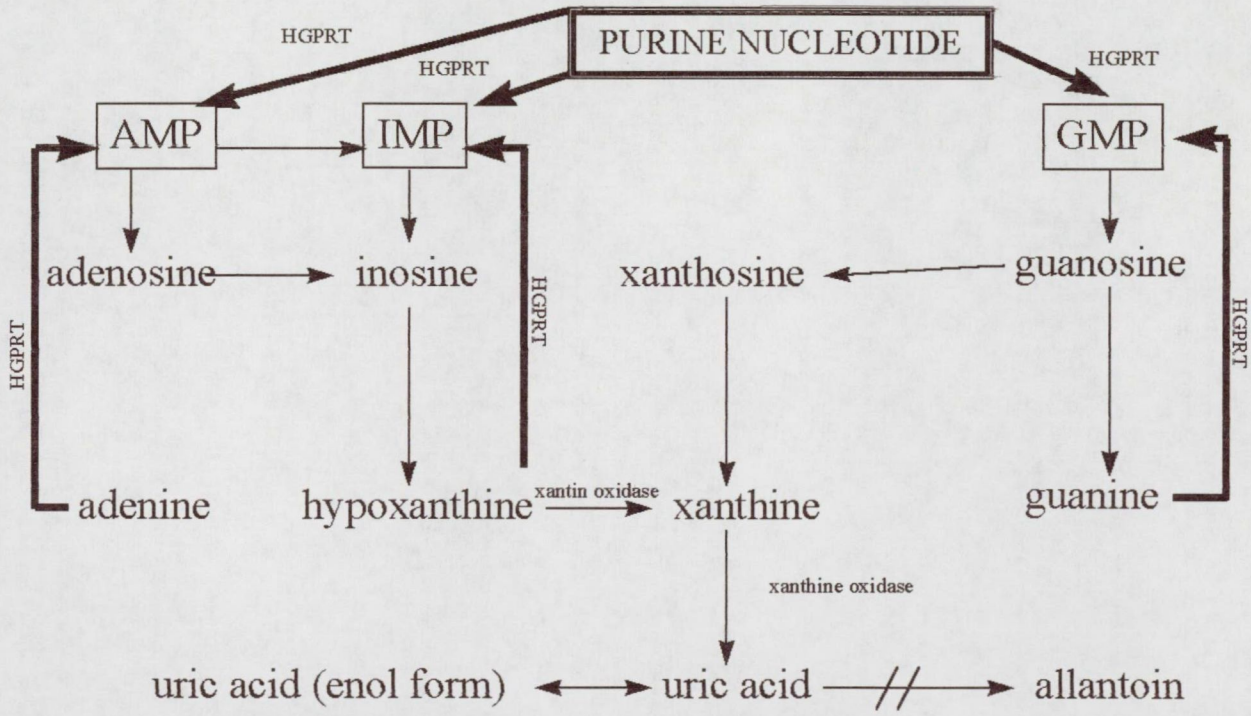

Figure 1. Schematic representation of metabolism of purine nucleotides (53)

Non-invasive monitoring is very important. Perinatal asphyxia causing organ damage is an appreciable neonatal problem (113, 124 , 126). Endogenous stress is caused by pathological conditions such as intrauterine hypoxia, perinatal asphyxia, respiratory distress syndrome, congestive cardiopathy, polycytaemia, diabetic foetopathy 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 respiratory acidosis (54). The renal perfusion is damaged, and the glomerular fitration and tubular functions are therefore reduced (9, 37, 68, 115, 125). 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, free radicals, nitric oxide, etc.(23, 28, 49, 51, 64, 67, 76, 101, 106, 119)

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 distal tubules, i.e. urate-caused nephropathy.

Neonates always have hyperuricaemia in a severe hypoxic condition (7, 28, 38, 112), 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 normalization 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 (120) 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.

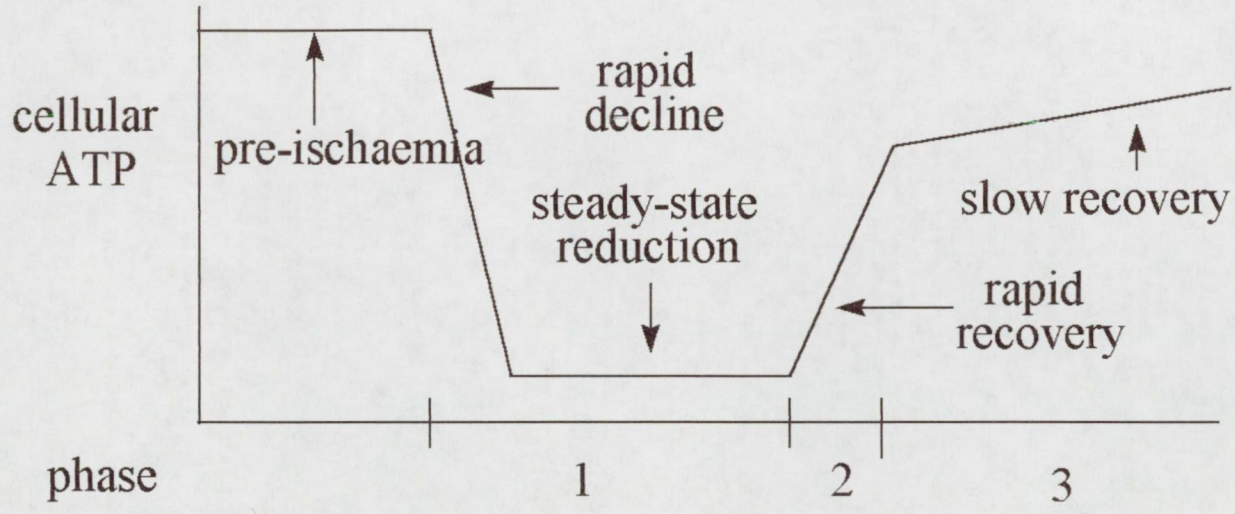

Figure 2. Schematic representation of alterations in cellular ATP that occur during and after renal ischaemia as determined by *in vivo* nuclear magnetic resonance spectroscopy (101).

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, 123). 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, 123).

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).

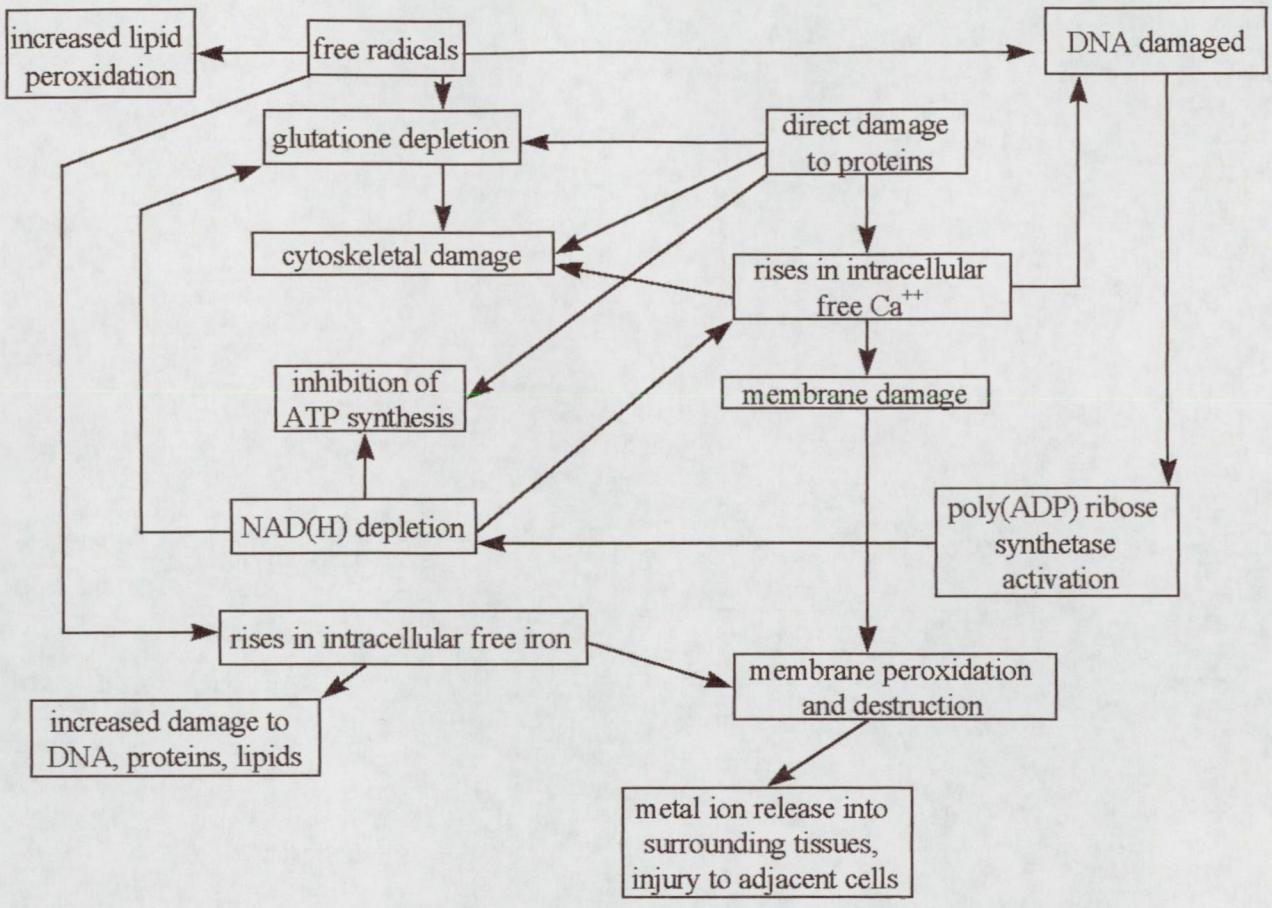

Figure 3. Interacting mechanisms of cell injury by free radicals (11, 48, 49, 50)

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.

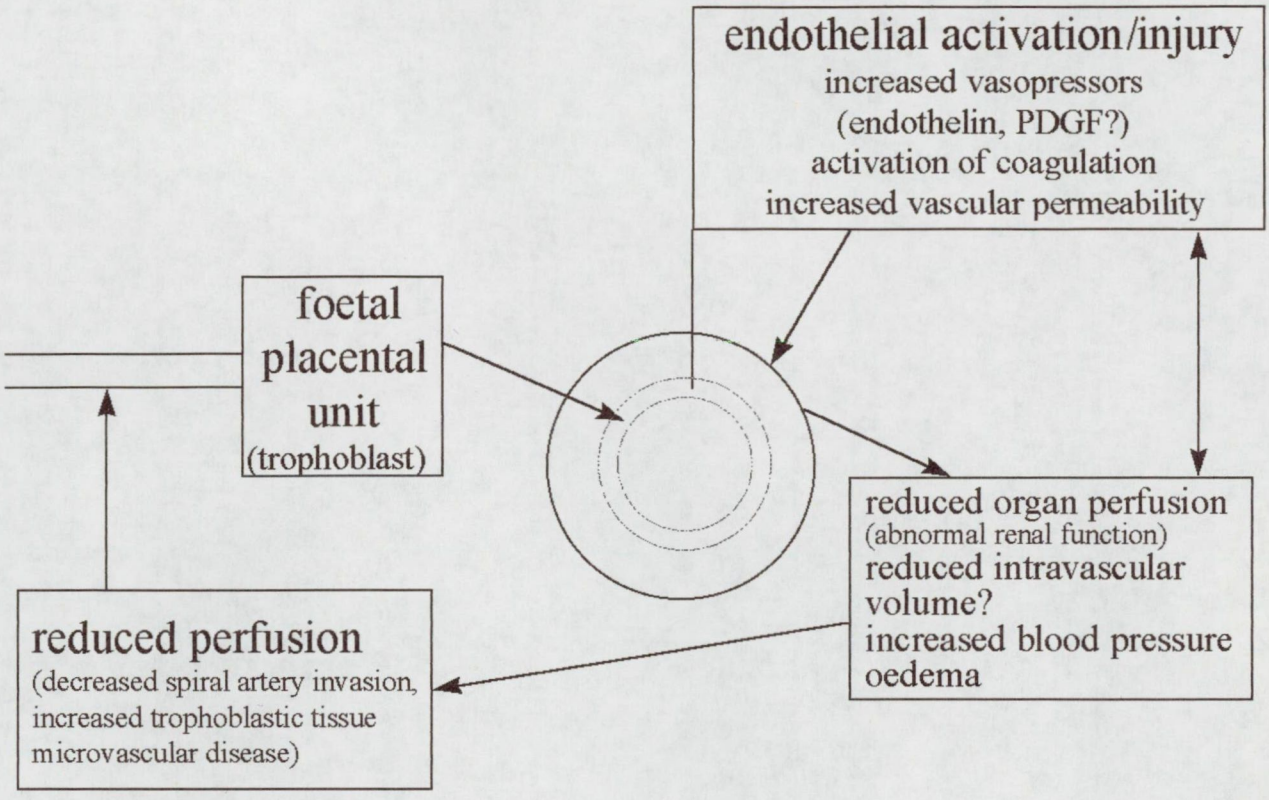

Figure 4. Model of the pathogenesis of pre-eclampsia based on enthothelial cell and injury as the key factor (121).

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 hypoechogenic 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. Aims of the investigation

The aims of our study were:

1. To reproduce experimental urate nephropathy and to detect pyramidal by renal ultrasonographyic 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 whe ther 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 controll 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 paO_2 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 Gynecologie et d'Obstetrique (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 Naegele rule and the first-trimester ultrasonographyic 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 cholesterin) 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, pCO_2, pO_2 and O_2 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 hypoechogenic 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 hypoechogenic 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, postsystolic ischaemia 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).

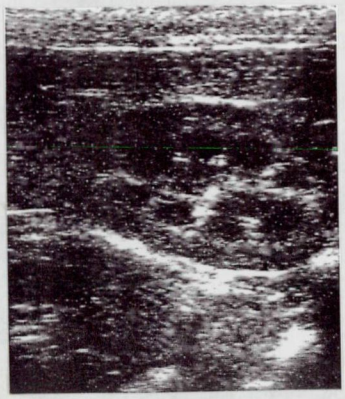

Fig.5. Control ultrasonography examination in rabbits. No pathological change was detected in any case.

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)

Time (hour)	Hypoxanthine (μmol/l)	Uric acid (μmol/l)	Creatinine (μmol/l)	Urea nitrogen (mmol/l)	Kidney sonography	Patho-histology
0	3.8±2.7	12.8±3.4	121±19	8.5±1.5	negative	negative
4	15.7±10.2	89±10	243±20	11.4±2.9	negative	negative
8	-	-	-	-	-	-

Table II.

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

Time (hour)	Hypoxanthine (μmol/l)	Uric acid (μmol/l)	Creatinine (μmol/l)	Urea nitrogen (mmol/l)	Kidney sonography	Patho-histology
0	4.5±2.5	13.9±3.9	117.0±5.0	8.3±1.0	negative	negative
4	15.7±6.7	21.4±8.4	124.0±3.0	7.5±1.8	positive	negative
8	34.9±9.9	36.2±9.2	204.0±9.0	6.9±1.5	positive	positive

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

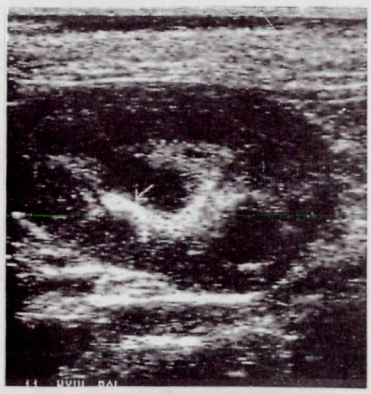

Fig.6 In group II renal hyperplasia and pyramidal hyperechogenicity were detected at 4 hours.

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

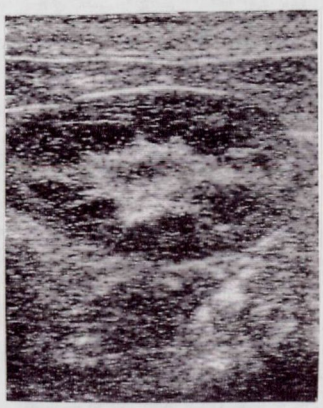

Fig.7. In group II a renal enlargement was not detected, but the cortex and pyramid hyperechogenicity was unambiguous.

After 24 hours the increased echogenicity of the pyramids was unchanged (Fig. 8).

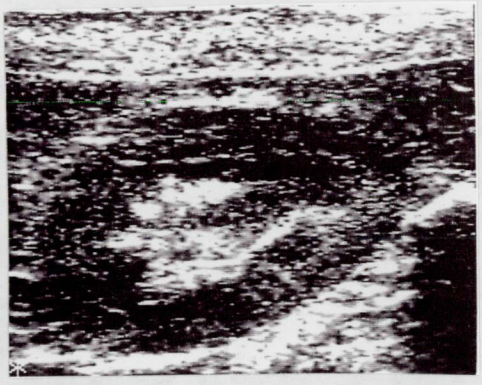

Fig. 8. After 1 day, pyramidal hyperechogenicity was still detected.

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).

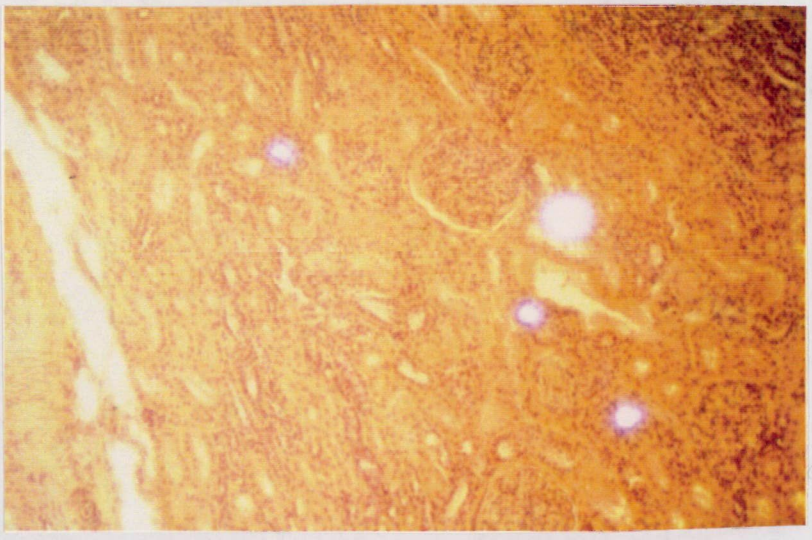

Fig. 9. In the kidney of rabbits, tubular uric acid precipitation was visualized by polarized light microscopy.

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 pO_2 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.

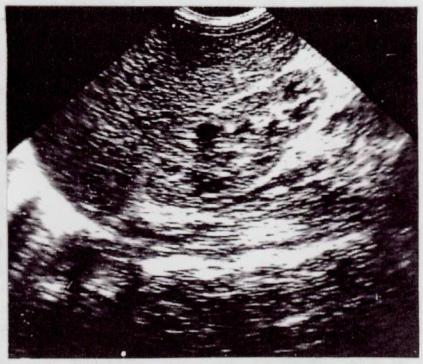

Fig. 10. Renal hyperechogenicity in the weighing 2950 g (case 2).

Table III

Purine metabolites and renal hyperechogenicity in neonatal hypoxic acute shock

Case number	Diagnosis	Sex	Gestation age (weeks)	Delivery weight (g)	Apgar score (1'5'10')	pa O2 (mmHg)	Serum pH	Uric acid (mmol/l)	Hypoxanthine (mmol/l)	Pathological renal ultrasound
1	MAS	m	40	4100	2,6,8	48	7.18	337	8.4	1st day of life
2	SIDS	f	38	2950	4,7,9	39	7.12	570	81.4	2nd day of life
3	foetal distress	f	36	3850	0,1,1	50	7.17	645	64.4	4th day of life
4	IRDS	f	27	720	1,1,3	44	7.2	688	20.1	1st day of life

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

Case number	Urea-N (mmol/l)	Creatinine (umol/l)	UA/Creatinine (mg/mg)	Ca (mmol/l)	CA/Creatini-ne (mg/mg)	Quantity of urine (ml/kg/h)	Osmolality of urine (mosm/kg)
1	9.9	142.5	2.7	1.68	0.11	0.3	366
2	7	110	2.9	2.2	0.06	1.4	392
3	11.4	154	6.2	1.82	0.4	0.2	286
4	19.5	173	2.1	1.06	0.22	0.6	175

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 pregnants 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 V

The pregnants' data in cases of foetal renal hyperechogenicity

Case number	Diagnosis	Gestation age (weeks)	RR (mmHg)	Protein- uria	Uric acid (mmol/l)	CN (mmol/l)	Creatinin (umol/l)	SGOT (mmol/l)	SGPT (mmol/l)	GGT (mmol/l)
1	EPH gestosis I.4 Oligohydramnion I.u.distress	35	170/120	3+	381	5.8	64	54	76	83
2	EPH gestosis I.3 Diabetes mellitus	32	140/85	1+	390	3.9	75	35	25	30
3	EPH gestosis I.3 IUGR Oligohydramnion	36	140/90	1+	268	3.6	70	18	12	25
4	EPH gestosis I.5 I.u.distress Oligohydramnion	31	170/100	1+	414	9.1	162	43	52	49
5	EPH gestosis I.3	32	130/90	1+	192	2.6	79	22	17	30
6	EPH gestosis I.3	24	100/60	-	273	3	48	31	12	5
7	EPH gestosis I.3 gestation diabetes mellitus	34	130/90	1+	266	1.4	57	14	9	10
8	EPH gestosis I.3 hyperthyreosis	30	140/80	-	161	5.2	52	19	18	7
9	EPH gestosis I.3	36	120/80	1+	365	8.9	127	37	25	18
10	EPH gestosis I.4 nephrosis sy., glomerulonephritis	38	160/110	3+	374	5.4	53	10	7	5
11	IUGR Oligohydramnion	37	110/60	-	321	3.7	71	32	24	17
12	EPH gestosis I.3 hyperthyroidism	36	130/90	-	391	4.2	102	34	30	27
13	EPH gestosis I.4 praeeclampsia	28	190/120	3+	280	3.7	49	47	40	41
14	EPH gestosis I.2 IUGR Oligohydramnion	38	145/90	-	190	2.8	53	14	10	3
15	EPH gestosis I.7 oligohydramnion	28	150/90	3+	145	5.9	116	43	36	24

Table VI

Characterization of cases when foetal renal hyperechogenicity was present

Case number	Delivery age (weeks)	Delivery weight (g)	Apgar score (1'5'10')	Acid-base parameters pH-st.bicarb-CO2-O2	Uric acid (umol/l)	CN (mmol/l)	Creatinine (umol/l)	Notes
1	35	1600	4,7,9	7,32-24,2-44,3-60,1	419	4.9	148	sectio c., IUGR, uricosuria, azotemia, anuria, postnatal renal hyperechogenicity
2	32	3600	7,9,9	7,34-21,3-43,6-64,4	242	2.8	56	sectio c., WAC
3	36	2200	7,9,10	7,26-19,3-45,2-67,3	269	3.4	75	PVN, IUGR
4	31	1460	2,4,7	7,24-21,7-39,2-47,1	399	8.2	153	sectio c., PRH, renal hypoplasia on right side, NEC
5	39	2980	10,10,10	7,36-21,0-42,2-71,3	174	3	67	PVN, WAC
6	39	2750	10,10,10	7,37-17,2-30,6-43,9	259	3.4	66	PVN, IUGR, PRH on left side
7	38	3740	9,10,10	7,30-22,3-46,1-33,0	210	3.2	79	PVN, WAC
8	31	1500	5,7,8	7,33-24,1-46,9-63,8	372	4.1	101	sectio c., IRDS
9	38	3010	9,10,10	7,20-22,1-48,8-30,0	357	8.9	119	PVN, WAC
10	38	2940	10,10,10	7,39-18,4-31,3-79,3	401	5.2	123	PVN, WAC
11	40	3170	10,10,10	7,31-20,3-41,5-38,3	376	3.7	92	sectio c., IUGR, PRH
12	38	2870	10,10,10	7,14-13,4-40,1-35,3	324	4.2	97	PVN, WAC
13	28	1130	7,9,10	7,36-25,0-45,7-27,1	240	2.7	56	sectio c., part.praemat., IRDS, PRH
14	40	2180	10,10,10	7,43-23,2-35,7-66,4	224	2.9	57	PVN, IUGR, part.praemat
15	32	1440	2,8,9	7,21-21,6-56,0-57,0	365	3.6	69	sectio c., IUGR, part.praemat., IRDS, PRH

PRH: postnatal renal hyperechogenicity
PVN: per vias naturales
IUGR: intrauterine growth retardation
IRDS: idiopathic respiratory distress syndrome
sectio c.: cesarean section
part.praemat.: 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 (χ^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).

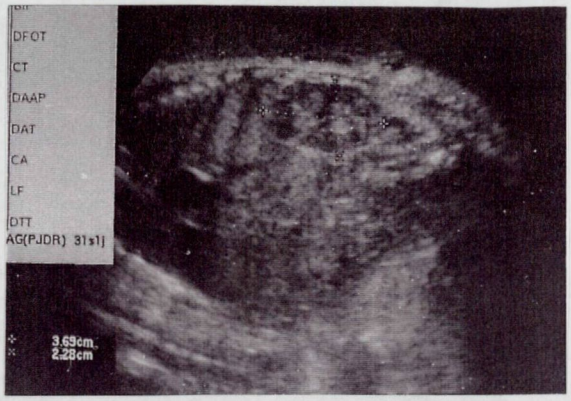

Fig. 11. Longitudinal view of a normal-sized hyperechogenic fetal kidney (31st week of gestation). The kidney gives pattern B (78).

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 P_3 at birth. The others were located between P_3 and P_{10} or above P_{10} (Fig. 12,13).

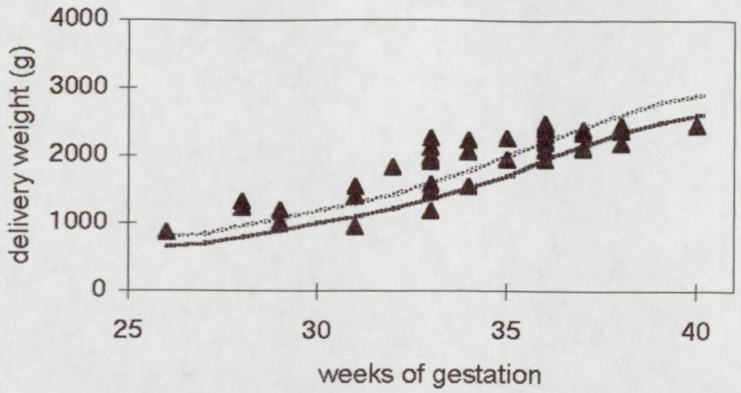

Figure 12. Intrauterine non diagnosed IUGR cases (N=68)

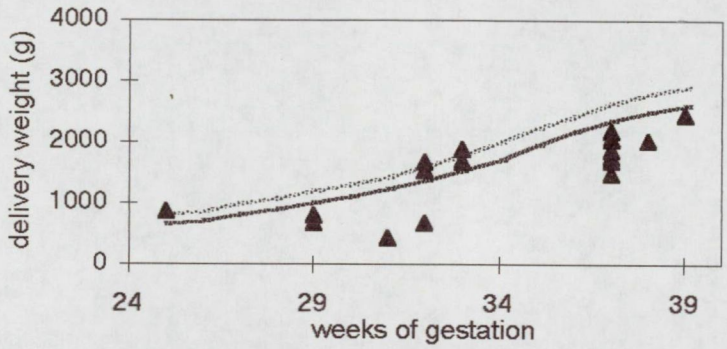

Figure 13. Intrauterine diagnosed IUGR cases (N=22)

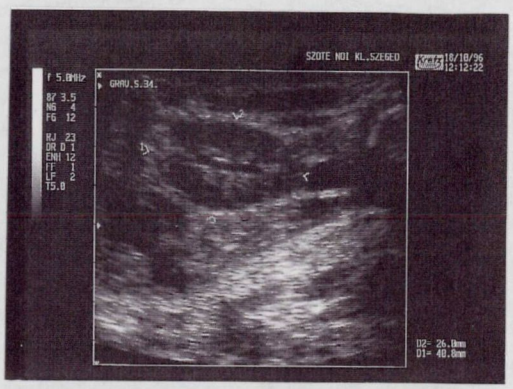

Figure 14. Longitudinal view of a normal echoic fetal kidney (34st week of gestation).

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 accured 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 VII

Cases of foetal renal hyperechogecity in IUGR cases

Case	Mother	Pregnancy	Sex	Weight (g)	Getational age (weeks)	Apgar score (1' 5')	Renal hyperechogenicity detected (weeks)	Notes	NICU
1	A.M.	IUGR	f	2170	40	9;10	35	without any problem	+
2	B.N.A	hypertension	f	3035	40	8;9	35	perinatal infection, tachycardia	+
3	B.S.	hypertension	f	3030	39	8;9	37	without any problem	-
4	B.J.	normal	f	3600	40	9;10	37	perinatal infection	+
5	B.F.	normal	m	3320	39	9;10	26	perinatal infection	+
6	B.M.J.	hypertension	m	3100	38	8;9	34	caesarean section	-
7	B.CH.	IUGR, toxicoman	m	2030	35.5	9;10	34	caesarean section	+
8	B.A.	renal malformation	m	3260	38	7;8	18	multicystical kidney	+
9	B.CH.	IUGR	f	2020	38	8;9	36	foetal infection?	+
10	C.C.	IUGR, hypertension	m	950	31	1;6	30	bradycardia, apnoea, met.acid., cataract, intraventr. haemorrhagia, death on 2nd day	+
11	C.R.	hypertension	f	3260	41	5;7	37	without any problem	-
12	F.B.	hypertension	f	1690	37	8;9	34	gemini "A"	+
13	F.B.	hypertension	f	1870	37	4;8	34	gemini "B"	+
14	G.C.	IUGR, HELLP-sy	f	1580	33	7;9	32	caesarean section	+
15	K.P.	IUGR, i.u.parvovirus inf., hydrops fetalis	f	2260	33	4;8	31	caesarean section, reanimation, meconial amnial fluid	+
16	L.F.	hypertension	f	3455	39.5	7;9	24	caesarean section	+
17	L.J.	normal	f	3800	40	8;9	36	without any problem	+
18	P.M.	normal	f	2860	37	9;9	35	caesarean section	-
19	P.J.	normal	m	2910	38	9;10	36	without any problem	-
20	P.N.	normal	f	3720	39	8;8	32	perinatal infection	+
21	R.FR.	hypertension	f	2460	36	8;9	33	without any problem	-
22	S.G.FR.	IUGR, hypertension, oligohydramnion	f	2260	38	7;9	37	perinatal infection?	+
23	S.C.	normal	f	3600	39	9;9	35	caesarean section	-
24	T.C.	hypertension	f	3190	41	9;10	32	without any problem	-
25	W.K.	IUGR	m	420	31	0;0	27	stillborn	no transfer

Table VIII

Comparison of two groups of prenatally diagnosed IUGR cases: with or without renal medullae hyperechogenicity

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

Table IX

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

	IUGR with renal medullae hyperechogencity (25 cases)	IUGR without renal medullae hyperechogencity (65 cases)	rate (hyperechoic to normoechoic)
neonatal mortality	2 (8%)	3 (4.6%)	1.7
neonatal morbidity	17 (68%)	30 (42%)	1.6
NICU stay	16 (64%)	38 (55%)	1.2

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 Apgar 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 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 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 bradycardyia, 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), agenesia 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 [χ^2=2.049 ($p<0.05$) in pregnancy-associated hypertension and/or proteinuria cases, and χ^2=0.075 ($p<0.05$) in intrauterine growth-retarded cases] (Figs. 15 and 16).

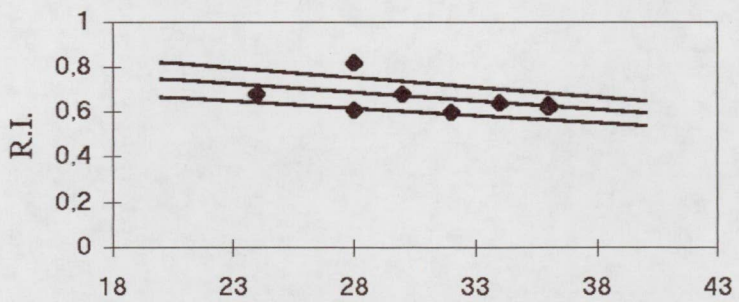

Figure15. Resistance index of umbilical artery in cases with foetal renal hyperechogenicity in EPH-gestosis (N=15)

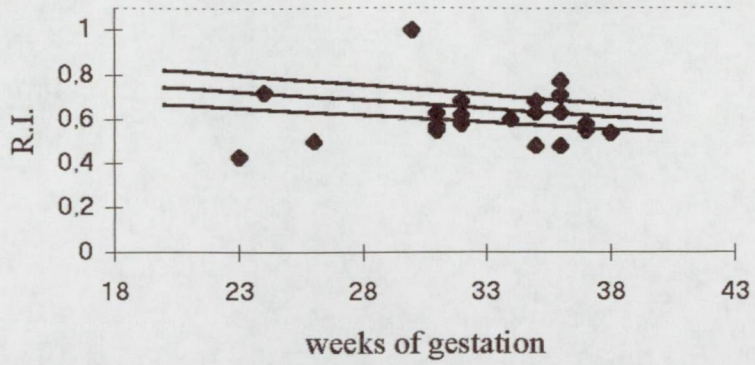

Figure 16. Resistance index of umbilical artery in cases with foetal reanal hyperechogenicity in IUGR (N=22)

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).

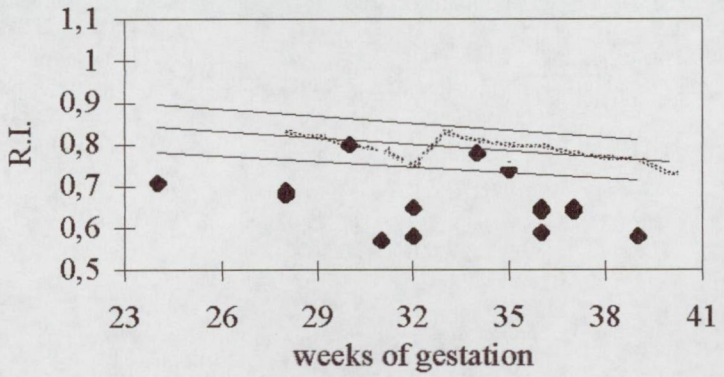

Figure 17. Resistance index of renal artery in cases with foetal renal hyperechogenicity in EPH-gestosis (N=15)

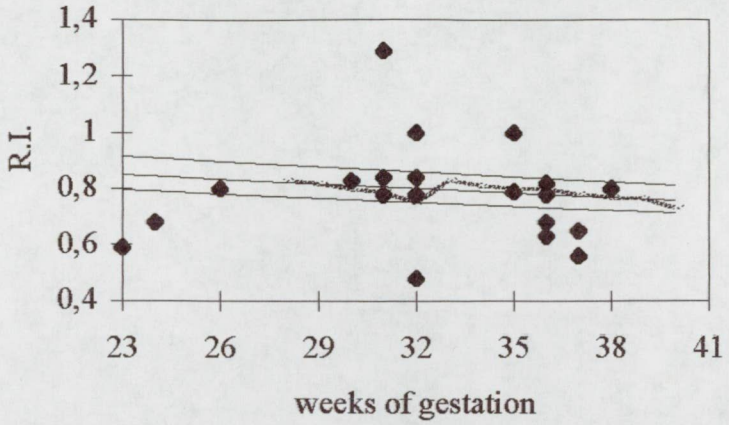

Figure 18. Resistance index of renal artery in cases with foetal renal hyperechogenicity in IUGR (N=22)

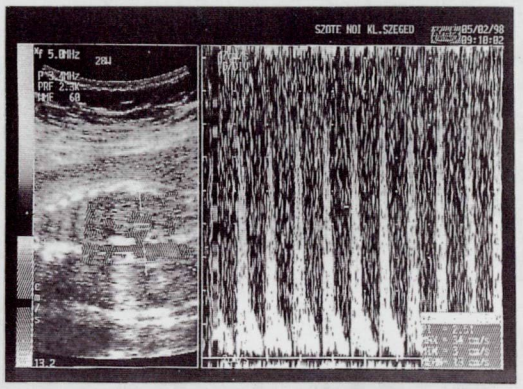

Figure 19. Normal blood flow-velocity waveforms in the foetal renal artery at 28th week of gestation. The Doppler gate is positioned over the main renal artery.

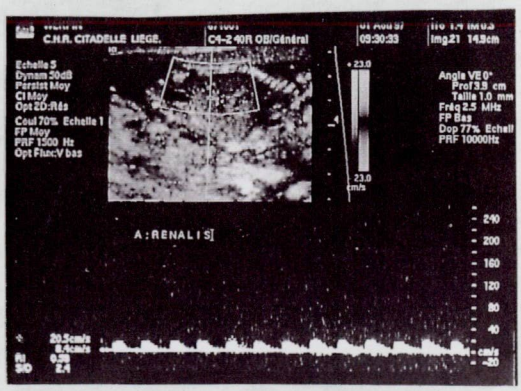

Figure 20. Decreased blood flow-velocity waveforms in the renal artery at 32nd week of gestation. The Doppler gate is positioned over the main renal artery.

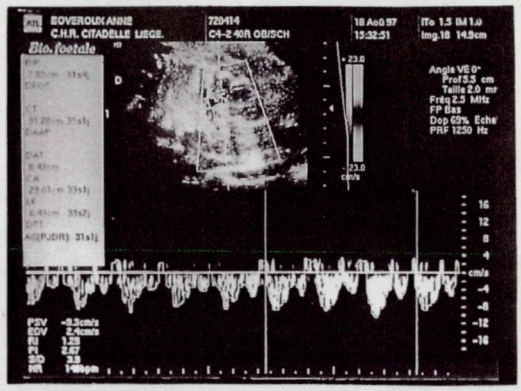

Figure 21. Flow-velocity waveforms with postsystolic incisura in the renal artery at 31st week of gestation. The Doppler gate is positioned over the main renal artery.

The chi-square test was applied for statistical analyses [χ^2=3.71 ($p<0.05$) in pregnancy-associated hypertension and/or proteinuria cases, and χ^2=3.76 ($p<0.05$) in intrauterine growth-retarded cases]. In cases without 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 achronic 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 Tamm-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 hyperechoic 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-for-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 identity 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. 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 pulsatily 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 pulsatily 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 hyperechoic 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 (4.5 times) and necrotizing enterocolitis (3 times) among babies with hyperechoic medullae than in the control group, where there was a suspected chronic hypoxic state with a normal-echoic 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 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

pulsatily 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 ultrasnographic 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 directedto 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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9. Bibliography

1. Ahmadian Y, Lewi PR: Possible urate nephropathy of the newborn infant as a cause of transient renal insufficiency J Pediatrics 1977;91:96-100
2. Almstrom H, Axelsson O, Cnattingius S, Ekman G Maesel A, Ulmsten U, Arstrom K, Marsal K: Comparision of umbilical artery velocymetry and cardiotocography for surveillance of SGA foetus. Lancet 1992;340:936-940
3. Arabin B, Bergman PL, Saling E: Simultaneous assessment of blood flow velocity waveform in uteroplacental vessels, the umbilical artery, the foetal aorta and the foetal common carotid artery. Foetal Ther 1987;2:17-21
4. Avison MJ, van Waarde A, Stromski ME, Gaudio KM, Siegel NJ: Metabolic alterations in the kidney during ischaemic acute renal failure Semin Nephrol 1989;9:98-101
5. Avni EF, Spehl-Robberecht M, Lebrun D, Gomes H, Garel L: Transient acute tubular disease in the newborn: carasteristic ultrasound pattern. Ann Radiol (Paris) 1983;26:175-182
6. Avni EF, Van Sinoy ML, Hall M, Stallenberg B, Matos C: Hypothesis: reduced renal mass with glomerular hyperfiltration a cause of renal hyperechogenicity in children. Pediatr Radiol 1989;19:108-110
7. Boda D: Role of hyperuricaemia in critical ill patients especially newborns. A Pediatr Hung 1984;25:23-32
8. Brenner MH, Meyer TW, Hostetter TH: Dietary protein intake and the progressive nature of kidney disease. N Eng J Med 1982;307:652-659
9. Brocklebank JT: Renal failure in the newly born. Arch Dis Childh 1988;63:991-994
10. Campbell S, Vyas S: Color flow mapping in measurements of flow velocity in foetal renal arteries. First International Meeting, In: Foetal and neonatal color flow mapping. Dubrovnik, 1988 pp136-142
11. Chaen DP: Determination of erythrocyte superoxide dismutase, catalase, glucose-6-phosphate dehydrogenase, reduced glutatione and malonylaldehyde in uremia. Clin Chim Acta 1982;123:153-159
12. Chiara A, Chirico G, Comelli L: Increased renal echogenicity in the neonate. Early Hum Dev 1990;22:29-33
13. Clapp JFIII, Szeto HH, Larrow R, Hewitt J, Mann LJ: Umbilical blood flow response to embolization of the uterine circulation. Am J Obstet Gynecol 1980;138:60-67
14. Crane JP, Mazie M Kopta Prediction of intrauterine growth retardation via ultrasonically measured head/abdominal circumference ratios. Obstet Gynecol 1979;54:597-601

15. Creasy RK, Swiet M, Kahanpaa KV, Yoong WP, Rudolph AM: Pathophysiological changes in the foetal lamb with growth retardation. In: Foetal and Neonatal Physiology, Cambridge, Cambridge University Press 1973 p.641
16. Davey DA, MacGillivray I: The classification and definition of the hypertensive disorders of pregnancy. Clin and Exper Hyper in Pregnancy 1986;B5:97-133
17. Dawes G: Size at birth. Ciba Foundation Symposium 27th, Amsterdam, Associated Scientific Publishers, 1974 p393
18. Diard F, Nicolau A, Bernard S: Intra-renal reflux: a new cause of medullary hyperechogenicity? Pediatr Radiol 1987;17:154-155
19. Epstein FH, Agmon Y, Brezis M: Physiology of renal hypoxia. Ann N Y Acad Sci 1994;718:72-81
20. Estroff JA, Mandell J, Benacerraf BR: Increased renal parenchymal echogenicity in foetus: importance and clinical outcome. Radiology 1991;181:135-139
21. Ewer AK, McHugo JM, Chapman S, Newell SJ: Foetal echogenic gut: a marker of intrauterine gut ischemia? Arch. Dis. Childh. 1993;69:510-516
22. Fay RA, Ellwood D: Doppler investigation of uteroplacental blood flow resistance in the second trimester: a screening study for pre-eclampsia and uterine growth retardation. Br J Obstet Gynecol 1992;99:527-528
23. Fickling SA, Williams D, Vallance P, Nussey SS, Whitley GS: Plasma concentrations of endogenous inhibitor of NO synthesis in normal pregnancy and pre-eclampsia. Lancet 1993;342:242-243
24. Forstermann U, Closs EI, Pollock JS, Nakane M, Schwarz P, Gath I, Kleinert H: Nitric oxide synthase isoenzymes, characterization, purification, molecular cloning, and function. Hypertension 1994;23:1121-1131
25. Furchgott RF, Zawadzki JV: The obligatory role of endothelial cells in the relaxation arterial smooth muscle by acetylcholine. Nature 1980;288:373-376
26. Galbraith RS, Karchmar EJ, Piercy Wn, Low JA: The clinical prediction of intrauterine growth retardation. Am J Obstet Gynecol 1979;133:281-286
27. Geirsson RT: Arngrimsson R, Apalset E, Einarsson A, Snaedal G: Falling population incidence of eclampsia. A case control study of short term outcome. Acta Obstet Gynecol Scand 1994;73:465-467
28. Gottlieb RP, Roeloffs S, Galler-Rimm G, Gross GW: Transient renal insufficienciency in the neonate related to hyperuricaemia and hyperuricosuria. Child Nephr Urol 1991;11:111-114

29. Gouyon JP, Guignard JP: Functional renal insufficiency: role of adenosine. Biol Neonate 1978;53:237-242

30. Gouyon JP, Guignard JP: Theophylline prevent the hyperuricaemia-induced renal haemodinamic changes in rabbits. Kidney Int 1988;33:1078-1082

31. Grannum PAT, Berkowitz RL, Hobbins JC: The ultrasonic changes in the maturing placenta and their relation to foetal pulmonic maturity. Am J Obstet Gynecol 1979;133:915-22

32. Griffin D, Cohen-Overbeek T, Campbell S: Foetal and utero-placental blood flow. Clin Obstet Gynecol 1993;10:596-602

33. Gudmundsson S, Gunnarsson GO, Hokegard KH, Kjellmer I, Marsal K: Foetal lamb ductus venousus and umbilical venousus blood velocity during hypoxia. J Matern Foetal Invest 1993;2:197

34. Gudmundsson S, Tulzer G, Hunta JC, Masal K: Venous Doppler velocimetry in foetus with absent and diastolic blood velocity in the umbilical artery. J Matern Foetal Invest 1993;2:196

35. Guignard JP: Renal function in the newborn infant. Pediatr Clinics of North America 1982;29:777-787

36. Guignard JP: Clinical implications of a low glomerular filtration rate. Proceedings of the Sixth International Symposium of Paediatric Nephrology, Hannover, Pediatrics Nephrology Edited by Brodehl J and Ehrich JHH, Springer-Verlag Ltd. 1983 Chapter 2.2.1. pp.60-68

37. Guignard JP: Renal function in the tiny, premature infant. Clin Perinatol 1986;13:377-401

38. Guignard JP: Can we protect the neonatal stressed kidney? 3rd International Workshop on Neonatal Nephrology Rome,1992, Abstract pp.49-56

39. Guignard JP, Gouyon JB, John G: Vasoactive factors in the immature kidney. Pediatr Nephrol 1991;5:443-446

40. Hadlock FP, Harrist RB, Carpenter RJ, Deter RL, Park SK: Sonographic estimation of fetal weight. Radiology 1984;150:535-540

41. Haller JO, Berdon WE, Friedman AP: Increased renal cortical echogencity: a normal finding in neonates and infant. Radiology 1982;142:173-174

42. Harkness RA, Simmonds RJ, O'Connor MC, Webster ADB: Purine metabolism studied with high pressure liquid chromatography. Biochemical Society Transaction, 583rd Meeting, Cambridge 1979;7:654-656

43. Hayden CK, Santa-Cruz FR, Amparo EG, Brouhard B, Swischuk LE, Ahrendt DK: Ultrasonographic evaluation of the renal parenchyma in infancy and childhood. Radiology 1984;152:413-417

44. Hecker K, Spernol R, Szalay S: Doppler blood flow velocity waveforms in the foetal renal artery. Arch Gynecol Obstet 1989;246:133-137

45. Herman TE, Siege MJ: Pyramidal hyperechogenicity in autosomal recessive polycystic kidney disease resembling medullary nephrocalcinosis. Pediatr Radiol 1991;21:270-271

46. Hijazi Z, Keller MS, Gaudio KM: Transient renal dysfunction of the neonate. Pediatrics 1988;82:929-930

47. Howlett DC, Greenwood KL, Jarosz JM, Macdonald LM, Saunders AJS: The incidence of transient renal medullary hyperechogenicity in neonatal ultrasound examination. Brit J Radiol 1997;70:140-143

48. Hunley TE, Iwasaki S, Homma T, Kon V: Nitric oxide and endothelin in pathophysiological settings. Pediatr Nephrol 1995;9:235-244

49. Ignarro LJ, Buga GM, Wood KS, Byrnes RE, Chauduri G: Endothelium-derived relaxing factor produced and released from artery and vein nitric oxide. Proc Natl Acad Sci USA 1987;84:9265-9269

50. Ignarro LJ: Biosynthesis and metabolism of endothelium-derived nitric oxide. Ann Rev Pharmacol Toxicol 1990;30:535-560

51. Jensen A, Künzel W, Hohmann M: Dynamic of foetal organ blood flow redistribution and catecholamine release during acute asphyxia. In: Jones CT and Nathanielsz PW (eds.): The Physiological Development of the Foetus and Newborn. Academic Press, London 1985 p.605

52. Joshua AC, Reed KL: Doppler ultrasound in Obstetrics and Gynecology. Reed Raven press.Ltd., New York 1995 pp.131-132

53. Karloson P: Schematic representation of metabolism of purin nucleotides. Pathobiochemie, Medicina Ltd. p.110

54. Karlowicz MG, Adelman RD: Nonoliguric and oliguric acute renal failure in asphyxiated term neonates. Pediatr Nephrol 1995;9:718-722

55. Kastner PR, Hall JE, Guyton AC: Controll of glomerular filtration rate: role of intrarenally formed angiotensin II. Am J Physiology 1984;246:F897

56. Kaufman JM, Green ML, Seegmiller JE: Urine uric acid to creatinine ratio- a screening test for inherited disorders of purine metabolism. J Pediatr 1968;73:583-592

57. Kazzi GM, Gross TL, Sokol RJ, Kazzi NJ: Detection of intrauterine growth retardation: a new use for sonographic placental grading. Am J Obstet Gynecol 1983;145:733-737

58. Kensky AM, Reddish JM, Teele RL: Causes of increased renal echogenicity in pediatric patients. Pediatrics 1983;72:840-846

59. Kofinas AD, Penry M, Simon NV, Swain M: Interrelationship and clinical significance of increased resistance in the uterine arteries in patients with hypertension or pre-eclampsia or both. Am J Obstet Gynecol 1992;166:601-606

60. Korantzis A, Cardamakis E, Apostolidis C: Prenatal diagnosis of fetal urinary pathology with ultrasound. Eur J Obstet Gynecol Reprod Biol 1993;52:169-174

61. Kurjak A, Kirkinen P, Latin V: Biometric and dynamic ultrasound asssessment of small-for-dates infants: report of 260 cases. Obstet Gynecol 1980,56:281-284

62. Kurjak A, Kirkinen P, Latin V, Ivankovic D: Ultrasonic assessment of foetal kidney function in normal and complicated pregnancies. Am J Obstet Gynecol 1981;141:266-270

63. Lorentz WB, Burton BK, Trillo A, Browning MC, Winston-Salamon NC: Failure to thrive, hyperuricaemia, and renal insufficiency in early infancy secondary to partial hypoxanthine-guric acidenine phosphoribosyl transferase deficiency. J Pediatr 1984;104:94-97

64. Malee MP, Malee KM, Azuma SD, Taylor RN, Roberts JM: Increases in plasma atrial natriuretic peptide concentration antedate clinical evidence of pre-eclampsia. J Clin Endocrinol Metab 1992;74:1095-1100

65. Manzke H, Eingster G, Dörner D, Grünitz J: Uric acid infarctions in the kidneys of newborn infants. (Study on the changing incidence and on oxypurine ratios.) Eur J Pediatr 1977;126:29-35

66. Mari G, Kirshon B, Abuhamad A: Foetal renal artery flow velocity waveforms in normal pregnancies and pregnancies complicated by polyhydramnions and oligohydramnions. Obstet Gynecol 1993;81:560-564

67. Matkovics B, Karmazsin L, Kalász H (editors): Radicals, ions and tissue damage. Akademia Ltd. Budapest 1990 pp. 177-181

68. Mayor G, Genton N, Torrado A, Guignard JP: Renal function in obstructive nephropathy. Pediatrics 1975;56:740-747

69. McCarthy AL, Wolfson RG, Raju SK, Poston L: Abnormal endothelial cell function of resistance arteries from women with pre-eclampsia. Am J Obstet Gynecol 1993;168:1323-1330

70. McInnis AN, Felman AH, Kaude JV, Walker RD: Renal ultrasound in neonatal period. Pediatr Radiol 1982;12:15-20

71. Nathan C: Nitric oxide as a secretory product of mammalian cells. FASEBJ 1992;6:3051-3064

72. Nayir A, Kadioglu A, Sirin A, Emre S, Tongue E, Bilge I: Causes of increased renal medullary echogenicity in Turkish children. Pediatr Nephrol 1995;9:729-733

73. Norris CS, Barnes RW: Renal artery flow velocity analysis, a sensitive measure of experimental and clinical renovascular resistance. J Surg Res 1984,36:230-236

74. Ollier-Hartmann MP, Pouget-Abadie C, Boullie J, Hartmann L: Variations of urinary Tamm-Horsfall protein in humans during the first thirty years of life. Nephron 1984;38:163-166

75. Ott WJ, Doyle S: Normal ultrasonic foetal weight curve. Obstet Gynecol 1982;59:603-606

76. Palmer RMJ, Ferrige AG, Moncada S: NO release accounts for the biological activity of endothelium-derived relaxing factor. Nature 1987;327:524-526

77. Patel R, McKenzie JK, Mcqueen EG: Tamm-Horsfall urinary mucoprotein and tubular obstruction by casts inacute renal failure. Lancet 1964;1:457-461

78. Patriquin H, Robitaille P: Renal calcium deposition in children: sonographic demonstration of the Anderson-Carr progression. AJR 1986;146:1253-1256

79. Pearce JM, Campbell S, Cohen-Overbeek, T, Hackett G, Hernandez J, Royston JP: Reference ranges and sources of variation for indices of pulsed Doppler flow velocity waveforms from the uteroplacental and fetal circulation. Br J Obstet Gynecol 1988;95:248-256

80. Perlman JM, Tack ED, Martin T, Shackelford G, Amon E: Acute systemic organ injury in term infants after asphyxia. AJDC 1989;143:617-620

81. Peters LLH, Sheldon RE, Jones MD Jr., Makowski EL, Meschia G: Blood flow of foetal organs as a function of arterial oxygen content. Am J Obstet Gynecol 1979;135:637-646

82. Porter KB, O'Brien WF, Benoit R: Comparison of cord purine metabolites to maternal and neonatal variables of hypoxia. Obstet Gynecol 1992;79:394-397

83. Pourcelot L: Application cliniques de l'examen Doppler transcutané. In: Perroneau P (ed.) Vélocimetrié Ultrasonoré Doppler. Séminaire INSERM, Paris, 1974 pp 213-240).

84. Ramkumar V, Nie Z, Rybak LP, Maggirwar SB: Adenosine, antioxidant enzymes and cytoprotection. TIPS, Elsevier Science Ltd. 1995;16:283-285

85. Raivio RO: Neonatal hyperuricaemia. J Pediatr 1976;88:625-630

86. Reinhart HH, Spencer JR, Zaki NZ, Sobel ID: Quantitation of urinary Tamm-Horsfall protein in children with urinary tract infection. Eur Urol 1992;22:194-199

87. Riebel TW, Abraham K, Wartner R, Müller R: Transient medullary hyperechogenicity in ultrasound studies of neonates: It is a normal phenomenon and what are the cause? J Clin Ultrasound 1993;21:25-31

88. Robillard JE, Weismann DN, Herrig JE, Avres NA, Gomez RA, Nakamura KT: Effects of hypoxaemia on renal function during maturation. U.S. Public Heath Service Grants and American Heart Association Grant, Proceedings of the Sixth International Symposium of Paediatric Nephrology, Hannover, In: Brodehl J, Ehrich JHH: Pediatrics Nephrology, Springer-Verlag Ltd.1983 Chapter 2.1.2. pp. 51-55

89. Robillard JE, Weitzman RE, Burmeister L, Smith FG Jr: Developmental aspects of the renal response to hypoxemia in the lamb foetus. Circ Res 1981;48:128-137

90. Rudolph AM, Heymann MA: The circulation of the fetus in utero. Circ Res 1967;21:163-184

91. Rudolph AM, Heymann MA: The fetal circulation. Ann Rev Med 1968;19:195-206

92. Rudolph AM, Heymann MA: Circulatory changes during growth in the foetal lamb. Circ Res 1970;26:289-299

93. Salisz JA, Kass EJ, Cacciarelli AA: Transient renal failure in the neonate. Urology 1993;41:137-140

94. Saugstad OD, Gluck L: Plasma hypoxanthine levels in newborn infants: specific indicator of hypoxia. J Perinat Med 1982;10:266-272

95. Saugstad OD, Tubman RJ, Gloppestad K, Halliday HL, Oyasdaetter SS, Curstedt T, Robertson B: Raised plasma hypoxanthine levels as a prognostic sign in preterm babies with respiratory distress syndrome treathed with natural surfactant. J Perinat Med 1992;20:379-385

96. Seeds JW: Impaired foetal growth: definition and clinical diagnosis. Obstet Gynecol 1984;64:303-10

97. Seeds JW: Impaired foetal growth: ultrasonic evaluation and clinical management. Obstet Gynecol 1984;64:577-84

98. Shulman MH: Hyperechoic renal medullary pyramids in infants and children. Radiol 1991;181:9-11

99. Shultz PK, Strife JL, Stife CF, Mcdanie JD: Hyperechoic renal medullary pyramids in infants and children. Pediatric Radiol 1991;181:163-167

100. Sibai BM, Kustermann L, Velasco J: Current understanding of severe pre-eclampsia, pregnancy associated hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, hemolysis, elevated liver enzymes, and low platelet syndrome, and postpartum acute renal

failure: different clinical syndromes or just different names? Curr Opin Nephr Hypertens 1994;3:436-445

101.Siegel NJ, Devarajan P, Van Why S: Renal cell injury: metabolic and structural alterations. Pediatr Res 1994;36:129-135

102.Sinclair RJ, Randall JR, Wise GE, Jones CE: Response of isolated renal artery rings to adenosine and inosine. Drug Dev Res 1985;6:391-394

103.Solhaug MJ, Ballévre LD, Guignard JP, Granger JP, Adelman RD: Nitric oxide in the developing kidney. Pediatr Nephrol 1996;10:529-539

104.Soothill PW, Nicolaides KH, Campbell S: Prenatal asphyxia, hyperlacticemia, hypoglycemia and erytroblastosis in growth retarded foetuses. Br Med J 1987;1:1051-3

105.Spielman WS, Osswald H: Characterization of the postocclusive response of renal blood flow in the cat. Am J Physiology 1978;235:F286-290

106.Stapleton FB: Renal uric acid clearance in human neonates. J Pediatr 1983;103:290-294

107.Starinsky R, Vardi U, Batasch D, Goldberg M: Increased medullary echogenicity in neonates. Pediatr. Radiol. 1995;25:S43-S45

108.Stark JM: Pre-eclampsia and cytokine induced oxidative stress. Br J Obstet Gynecol 1993;100:105-109

109.Streitman K, Pintér S, Horváth I, Zewdu M: Sonographic morphology of acut shock uric acid nephropathy in rabbits. 2nd World Congress of Perinatal Medicine, Rome 19-24 Sept,1993 In: Cosmi EV, Di Renzo GC, Monduzi E (eds): Processings of Communications and Posters Vol.II, Editore Ltd., Bologna, 1993 pp. 869-874

110.Surányi A, Pál A, Streitman K, Pintér S, Kovács L: Fetal renal hyperechogenicity in pathological pregnancies. J Perinat Med 1997;25:274-279

111.Surányi A: Experimentális és neonatalis acut shockos urathos nephropathia pathophysiologiája és sonographiás morphologiája. (Pathophysiology and sonographycal morphology of experimental and neonatal urathe-caused nephropathy in acute shock.) (Thesis) Albert Szent-Györgyi Medical University, 1994

112.Szakolczai I, Ötvös L: Hypoxias újszülöttek vizeletének húgysav kreatinin hányadosa (Uric acid/creatinine ratio of hypoxic neonates). Orv Hetil 1981;12:1181-1182

113.Tálosi G, Streitman K, Surányi A, Pinter S, Horvath I, Mulugeta Z: The possible role of uric acid in renal hyperechogencity in neonatal hypoxic acute shock. J Perinat Med 1996;24:693-7

114.Thompson RS, Tudinger BJ, Cook CM: Doppler ultrasound waveform incides: A/B ratio, pulsatily index and Pourcelot ratio. Br J Obstet Gynecol 1988;95:581-588

115.Torrado A, Guignard JP: Hypoxaemia and renal function in newborns with respiratory distress syndrome. Helv Pediatr Acta 1974;85:443-444

116.Toyoda K, Miyamoto Y, Ida M, Tada S, Utsunomiya M: Hyperechoic medulla of the kidneys. Radiol 1989;173:431-434

117.Veille JC, Kanaan C: Duplex Doppler ultrasonographic evaluation of the foetal renal artery in normal and abnormal fetuses. Am J Obstet Gynecol 1989;161:1502-1507

118.Verma UL, Tejani NA, Chatterjee S, Weiss RR: Screening for SGA by the roll-over test. Obstet Gynecol 1980;56:591-594

119.Villy Y, Proudler A, Abbas A, Nicolaides K: Atrial natriuretic factor concentration in normal, growth retarded, anemic and hydropic foetuses. Am J Obstet Gynecol 1994;171:777-783

120.Voight MT, Farber E: On the molecular pathology of ischaemic renal cell death. Am J Pathol 1968;53:1-26

121.Vyas S, Nicolaides KH, Campbell S: Renal artery flow-velocity waveforms in normal and hypoxemic fetuses. Am J Obstet Gynecol 1989;161:168-172

122.Wallenburg HCS, Visser W: Pregnancy-induced hypertensive disorders. Curr Opin Obstet Gynecol 1994;6:19-29

123.Weinberg JM: The cell biology of ischemic renal injury. Kidney Int 1991;39:476-500

124.Willis F, Summers J, Minutillo C, Hewitt I: Indices of renal tubular function in perinatal asphyxia. Archiv of Disease in Childhood 1997;77:F57-60

125.Yamai T, Hirai N, Ishibasi M: Atrial natriuretical peptide in umbilical cord blood for a circulating hormone in human foetus. J Clin Endoc Metab 1986;63:1414-1418

126.Zamella P, Zorzi C, Pavanello L, Rizzoni G, Zacchello G, Rubaltelli FF, Cantarutti: The prognostic significance of acute neonatal renal failure. Child Nephrol Urol. 1991;11:11-15

127.Zeeman GG, Dekker GA: Pathogenesis of preeclamsia: a hypothesis. Clin Obstet Gynecol 1992;35:317-337