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Urinary Tract Infection (UTI) in Newborns: Risk Factors, Identification and Prevention of Consequences

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ABSTRACT

The aim of the study is identification of urinary tract infections (UTI) and urinary tract anomalies (UTA) already in the perinatal period. The authors attempted to prevent serious consequences of the above conditions in the examined children. Family history data, certain conditions in pregnancy and appertaining symptoms in children were elaborated to specify selective distinctive criteria for children at risk. Newborns (1200) were selected for potential existence of a UTI. All the examined newborns underwent a urinalysis. Those with significant bacteriuria were taken urine specimens, C-reactive protein (RVP), Complete Blood Count (CBC) and bilirubin. The newborns with a UTI and a suspected UTA were sent to ultrasound examination, direct radio nuclide cystography and Tc^{99m} MAG3 dynamic scanning. The frequency of a UTI in the perinatal period amounted to 4.5%. A UTA was found in 29.6% of the examinees. The infection was more likely to appear among newborns with a UTA in their families, a UTI, pre-eclampsia and a febrile infection in mother, intrauterine growth retardation, premature rupture of membranes (RVP), umbilical cord strangulation, jaundice, cyanosis, breathing difficulties, seizures and asphyxia.

Key words: urinary tract anomalies, perinatal period, newborns at risk, ultrasound

Introduction

Next to respiratory infections, urinary tract infections (UTI) are the most common infections in childhood. Their incidence in children under 14 ranges from 5 to 10%. If inadequately cured or not treated at all, they could lead to permanent renal impairment and disability. The incidence of chronic renal failure in children amounts to approximately 27%. The failure may result from an unrecognised or incompletely cured UTI, urinary tract obstruction (16%) and vesicourethral reflux (VUR) – 7%^{1–4}.

A UTI is perfidious in its nature. Sometimes, only the first infection is clinically detectable while subsequent attacks may occur quietly or only with scarce symptoms. However, they still damage kidneys. It is important to detect the first, symptomatic infection which can ensue even perinatally in children with a UTA^{5,6}. If the first, early UTI has not been diagnosed, a severe UTA might remain unidentified too. One third of children with a UTI suffer from a UTA, in most cases they develop vesicourethral reflux (VUR). Only in newborns, obstruc-

tion of the pyelourethric junction is the most common anomaly. Considering that VUR itself is not associated with other symptoms, UTI detection seems to be crucial for its discovery. An obstructive UTA can severely and at early stage damage the urinary system. Early recognition of a UTA facilitates efficient chemo prophylaxis and thus prevents UTI recidivism^{7–11}.

The perinatal age is characterized by very subtle symptoms of a UTI. The same symptoms can be found in healthy newborns. The symptoms are seldom prominent. The line between a healthy and an ill newborn is the thinnest at that age.

The authors tried to isolate newborns at risk. Achievement of this goal required a search for a UTI and a severe UTA as early as in perinatal period. Specification of particular factors in family history, pregnancy and delivery, and in clinical presentation of children, served as a method for selection of newborns who are more likely to develop a UTI and UTA and then be treated. The ulti-

mate goal was prevention of renal damage and disability in affected children.

Patients and Methods

There were a total of 1200 children examined during the period of 6 months (every newborn). A clinical prospective study was conducted at the newborn department and neonatal intensive care unit. All newborns were taken samples for urine culture on the second day of their life. Those with positive results of urinalysis were taken two additional samples. When the same agent grows in three cultures, the sensitivity rises above 95%¹². The newborns whose all three tests had been positive for bacteria were taken native urine and were tested for CBC, CRP and total bilirubin (if they have jaundice). The newborns with a UTI underwent ultrasound examination of the urinary system, direct radionuclide cystography, perfusion DMSA Tc^{99m} and dynamic radionuclide scanning. Intravenous pyelography (IVU) was performed only exceptionally in children who needed imaging examination of anatomic details.

The criteria for a UTI included significant bacteriuria and at least one of the following laboratory abnormalities (considering the fact that newborns react systemically to infections): leukocytes above $30 \times 10^9/L$, leucopenia below $8 \times 10^9/L$, increased proportion of non-segmented granulocytes (5% and higher), toxic neutrophilic granulations, increased CRP value (more than 20 g/L). A UTI is not always accompanied with a high CRP¹³. There were 54 newborns with a diagnosed UTI.

Urine specimens for culture were collected using urine collecting bags. The bags were kept attached to the newborns for 1 hour (after the morning bath). If a newborn did not urinate, a new bag was installed. The collected urine was analysed immediately or it was kept in a refrigerator for not more than 2 hours.

A two-dimensional apparatus performed ultrasound, using a probe of 5 Hz. VUR was diagnosed by means of direct radionuclide cystography while detection of other anomalies involved perfusion and dynamic radionuclide scanning.

The control group consisted of 77 newborns randomly selected among the examined children with no UTI. If a

selected newborn was treated at the neonatal department for a pulmonary, cardiologic or neurological illness, then it was not included into the group but replaced by the following randomly selected baby.

The authors put efforts into determination of potential features of newborns with a UTI that made them different from those in the control group. Those characteristics should represent selective criteria for newborns at risk of renal impairment. A UTA in close relatives, maternal pathology during pregnancy (UTI, pre-eclampsia), and child-related complications in utero (intrauterine growth retardation (IUGR), oligohydramnion, premature rupture of membranes (RVP) and complications during delivery (signs of a febrile infection in mother, umbilical cord anomalies, green amniotic fluid) were all taken into account. The mothers of both groups of children underwent urinalysis as well. UTA data in close relatives were based on an interview with the mothers. UTI data in mother and delivery complications referred to medical records of the mother and child. Capillary specimens were taken for biochemistry analyses which comprise common procedures. Statistical significance was based on the chi-square test.

Results

Differences in pregnancy, family history and clinical and laboratory findings

A UTI was found in 54 newborns or in 4.5% of the examinees. In terms of gender distribution of infections, 33 boys (61.1%) and 21 girls (38.9%) were affected by the infections.

The difference between the two groups in the incidence of bacteriuria was statistically significant. Concerning the mothers of children with a UTI, they suffered from the infections thrice as often as the mothers of the children from the control group. Pre-eclampsia was seven times more frequent in the mothers of children with a UTI than in those of the children from the control group. Seven mothers of children with a UTI only one mother from the control group showed prepartal systemic signs of an infection (Table 1).

TABLE 1
MATERNAL COMPLICATIONS DURING PREGNANCY

	Mothers of newborns with a UTI		Mothers of newborns without a UTI		χ^2	p value
	Number	%	Number	%		
Bacteriuria	21	38.9	8	10.4	13.35	<0.001
UTI	12	22.2	4	5.2	7.07	<0.01
Prenatal systemic signs of infection	7	13	1	1.3	4.63	<0.05
Pre-eclampsia	7	13	1	1.3	4.63	<0.05
No complications	14	25.9	63	81.8		
Total	54		77			

TABLE 2
INTRAUTERINE CHILD-RELATED COMPLICATIONS

	Newborns with a UTI		Newborns without a UTI		χ^2	p value
	Number	%	Number	%		
IUGR	13	24.1	6	7.8	3.93	<0.05
Oligohydramnion	4	7.4	1	1.3	1.78	>0.05
UTA diagnosed in uteri	2	3.7	0	0.0		
No complications	35	64.8	70	9.9		
Total	54		77			

TABLE 3
OBSTETRIC COMPLICATIONS

	Mothers of newborns with a UTI		Mothers of newborns without a UTI		χ^2	p value
	Number	%	Number	%		
Bacteriuria	21	38.9	8	10.4	13.35	<0.001
UTI	12	22.2	4	5.2	7.07	<0.01
Prenatal systemic signs of infection	7	13	1	1.3	4.63	<0.05
Pre-eclampsia	7	13	1	1.3	4.63	<0.05
No complications	14	25.9	63	81.8		
Total	54		77			

TABLE 4
SIGNS OF A UTI IN THE PERINATAL PERIOD

	Newborns with a UTI		Healthy newborns		χ^2	p value
	Number	%	Number	%		
Jaundice	26	48.1	10	13.0	17.96	<0.001
Diarrhoea, vomiting, weak suck, (non-specific signs of infection)	17	31.5	5	6.5	12.42	<0.001
IUGR	13	24.1	6	7.8	3.93	<0.05
Peripheral cyanosis	9	16.7	0	0	8.56	<0.001
Dyspnoea	8	14.8	2	2.6	4.21	<0.05
Asphyxia	7	13.0	1	1.3	4.63	<0.05
Fever	5	9.3	0	0		
Seizures	4	7.4	0	0		
Total number of signs	89*	>100*	24		59.6	<0.05
No signs	0	0	53	68.8		

* Some signs were present at the same time

The newborns with a UTI suffered from IUGR twice as often as their peers do. Oligohydramnion was found four times more frequently in the children with a UTI than in the healthy babies, but there is no statistic significance between the two groups (Table 2).

Premature rupture of membranes happened to members of the group with a UTI twice as often ($p < 0.01$) as to the children from the control group. Umbilical cord anomalies (strangulation around the neck or body, umbilical node) were identified thrice less often in the healthy ba-

bies. The children from the control group were twice as prone to green amniotic fluid as the children with a UTA. A UTA in close relatives was found in the group of children with a UTI in 10 cases, which compares to one case of the infection in the control group, $\chi^2 = 7.85$, $p < 0.01$ (Table 3).

More than one sign of illness were found in some ill newborns and there was no newborn with any sign of illness. Some signs lasted only shortly or ensued periodically, i.e. periodical attacks of peripheral cyanosis, a low

Apgar score in the 5th minute, but were eliminated soon. Jaundice was found 2.6 times more often in the newborns with a UTI than in their healthy peers. Furthermore, jaundice in the newborns with a UTI appeared at very early stage, was prolonged or characterized by unusually high concentrations of total bilirubin. Non-specific infective symptoms (vomiting, diarrhoea, weak suck) were noticed in the newborns with a UTI thrice more often than in control group members. The examined newborns with a UTI suffered from dyspnoea four times more frequently than healthy babies do. Asphyxia ensued in seven children with and in one child without UTI symptoms. Nine examinees with a UTI were associated with periodic attacks of peripheral cyanosis, which compares to none of the children from the control group. Seizures (due to hypocalcaemia) ensued in four babies with a UTI whereas no seizures were detected among control group members (Table 4).

Ultrasound findings and major anomalies of the urinary tract

About 63% of the newborns were connected with some pathologic ultrasound findings. In a group of neonates with the pyelon width ranging from 7 to 10 mm, some had changes in the echogenicity of the kidney parenchyma and in the thickness of the urinary bladder and some did not. If the hyperechogenicity of a kidney

TABLE 5
ULTRASOUND FINDINGS IN NEWBORNS WITH A UTI

	Number	%
Mild dilatation of the renal pelvis (7–10 mm)	12	22.2
Hyperechogenicity of the renal parenchyma	7	13
Thickened wall of the urinary bladder	6	11.1
Hydronephrosis with megaureter	4	7.4
Hydronephrosis	2	3.7
Hypotrophic kidneys	2	3.7
Ureter duplex	1	1.9
Without any changes	20	37
Total	54	

TABLE 6
ANOMALIES OF THE URINARY TRACT IN NEWBORNS WITH A UTI

	Number	%
Vezicoureteral reflux (VUR)	6	11.1
Obstruction of the pelviureteric junction	5	9.3
Megaureter	4	7.4
Ureter duplex	1	1.9
No anomalies	38	70.4

was the only ultrasound finding, it was indicated separately. The same thing was done with newborns with the thickened wall of the urinary bladder. The most frequent finding was pyelectasis (Table 5).

After nephrology examination, a UTA was diagnosed in 16 (29.6%) newborns with a UTI. The most usual anomaly was VUR, followed by obstruction of pelviureteric junction. Among the examined newborns, boys were more prone to UTAs (75%) than girls (75%) (Table 6).

Discussion

Most children with serious urinary system impairment could be recognised as early as in the neonatal age (due to a diagnosed UTA). A UTI during pregnancy is three to four times more likely to be found in mothers of newborns with a UTI. Presence of uropathogenic bacteria in mother enables their transfer into the newborn during delivery. At the very moment of birth, the child has a very close contact with mother by blood and mother's secretion. It can be extremely dangerous if mother of a susceptible child experiences prepartal symptoms of a febrile infection. Uropathogenic bacteria are of even greater importance in newborns with a more severe UTA due to impaired urine voiding. It is vital to identify subtle symptoms of a UTI, though on some occasions, only the first UTI presents clinically while others keep on existing with few or with no symptoms at all. One can conclude that even severe UTAs may exist without being detected. More frequent UTIs in mothers of children with a UTI could also implicate genetically caused predilection for a UTI. Developed countries perform screening of pregnant women for bacteriuria due to its possibility to jeopardise the child^{14,15}.

Pre-eclampsia was 10 times more common in mothers of children with a UTI. Sometimes, urinary tract problems remain undetected until oedema or proteinuria appears. Pre-eclampsia has effect on the concentration of beta 2 micro globulin in mother and leads to further renal impairment. Hypoxia of the child ensues. One should refer here to a report on the relation between pre-eclampsia and a UTI in mother during pregnancy^{16,17}. These women suffer from immune disturbances and in such cases it can also come to appearance of auto antibodies while the children frequently suffer from IUGR. The peripheral circulation is limited; the child's proneness to hypoxia, weakening of its immune competence and resistance to infection may be attributed to placental hypo perfusion. Children with a UTI are three times more exposed to IUGR than healthy children (see data from a report on IUGR as a risk factor for renal damage and scars¹⁸, IUGR was also reported in one fourth of children with a UTA. Due to hypoxia in utero, babies are more susceptible to asphyxia, aspiration of amniotic fluid and delivery channel contents, thus acquiring infection¹⁹. Firm links between oligohydramnion and a UTI were not proved and the reference data suggest its relation only with UTAs²⁰.

RVPs encourage spreading of uropathogenic bacteria. They could enter a child through the delivery channel, favouring UTI development. Umbilical cord anomalies (strangulation, various nodes) are responsible for appearance of urinary infections. Hypoxia in utero causes intrauterine asphyxia (due to maternal complications – praeeclampsia and a UTI, it reflects on the child in the form of UTAs and immune incompetence).

There is a chance of detection of symptoms of a UTI (fever), but mostly these symptoms are hardly noticeable. Newborns presenting such symptoms can sometimes »infiltrate« into fit newborns. This can be explained by short duration or periodicity of the symptoms or by their possible presence in healthy newborns. Some appear only for a short period of time after the delivery and then disappear. The references suggest that a UTA in close relatives is a relevant risk factor for a UTI and a UTA in children²¹. Fever is not such a permanent and specific symptom of a UTI in the perinatal period as it is later in the child's life, i.e. during infancy. In fact, it appears very seldom and its occurrence results from the newborn's immune incompetence. Seizures ensued in four examinees with a UTI. One child had urosepsis and meningitis while other seizures were metabolic in origin (hypocalcaemia).

Almost half of the newborns with a UTI had pathological jaundice. The references enlist jaundice as a possible single symptom of a UTI²². This may be associated with hem concentrations (as an adaptive mechanism to hypoxia) or with haemolysis caused by bacterial toxins.

Non-specific symptoms of a UTI involved diarrhoea, vomiting, weakened suck, inappropriate weight gain, malaise and pain. They were found in a third of the newborns with a UTI. The same symptoms were seen five times less frequently in the control group^{23,24}.

Periodical attacks of peripheral cyanosis appeared in every sixth child with a UTI. Sometimes, cyanosis ensued only in the first minutes after the delivery, causing a lower vitality score at birth. Some babies experienced periodical attacks of cyanosis during the whole perinatal period. Cyanosis could also be a single observed symptom of a UTI. It is a consequence of impaired blood supply of tissues and organs, i.e. of hypoxia. Dyspnoea came as a symptom of a UTI in 15% of the newborns. It can ensue in children that have an obstructive UTA, for example in case of hydronephrosis when a huge kidney compresses the diaphragm and lungs. In case of mother's infection, maternal interleukins can contribute to breathing impairment by limiting the placental and umbilical circulation, which can result in hypoperfusion of organs, hypoxia and asphyxia^{25–27}. Mechanical obstacles during prolonged and complicated delivery also predispose newborns with a UTI to neonatal dyspnoea, especially if the mother has an infection. Healthy newborns compensate for such impairments by tachypnea while a newborn with a UTI

has peripheral cyanosis, dyspnoea and a low Apgar score. Asphyxia at birth appeared more often in the newborns with a UTI than in the control group. The main cause thereof is hypo perfusion of tissues and organs and foetal hypoxia due to a UTI in mother, pre-eclampsia and obstetric (RVP, strangulation of the umbilical cord) or child – related complications (oligohydramnion, UTA). During infection in pregnancy, mother's proinflammatory cytokines (IL1, IL6) can pass transplacentally onto the child and centrally depress cardio respiratory function²⁵. An asphyxiated child reacts insufficiently to invasion of microorganisms. Its immune competence is inadequate favouring development of infections which, by their systemic effects, contribute to the cardio respiratory burden itself. These circumstances imply development of the »circulus viciosus« of hypoxia, hypo perfusion and inflammatory response.

The most frequent ultrasound finding referred to mild dilatation of the renal pelvis (22.2% of the neonates). It is not a very specific finding, but it allowed us to select newborns at risk^{28–31}. Ultrasound findings in VUR were not specific. Similar to other references, the authors also revealed mild dilatation of the renal pelvis and thickening of the wall of the urinary bladder^{32,33}. Urinary tract anomalies seemed to occur more often in boys (75%) than in girls (25%). Two thirds of the newborns with a UTI were boys, which could be explained by a greater share of boys with a UTA. Approximately one third of the newborns with a UTI also developed a UTA while the respective incidence of VUR totalled 11.1%. The same percentage is mentioned in references^{34–37}. The newborn urine screening brought to the discovery that only six out of 1200 newborns suffered from VUR. Only sterile refluxes were omitted³⁸. The incidence stated in the references amounted from 0.4 to 1.8%³⁹.

Conclusion

It is important to diagnose a UTI in newborns in the perinatal period. Occasionally, the most serious urinary tract anomalies can severely damage kidney and they can only be disclosed by detection of UTI symptoms. Newborns at risk for a UTI should be regularly monitored. These are the newborns with a UTA in close relatives and with mothers having experienced a UTI during pregnancy, pre-eclampsia or prepatal symptoms of a febrile infection. This risk group also includes those with IUGR, RVP or strangulation of the umbilical cord at birth. Presence of jaundice (if not caused by blood groups or Rh incompatibility), periodical attacks of peripheral cyanosis and dyspnoea, asphyxia and seizures of a metabolic origin (if the conditions are not caused by a lung, heart or neurological illness) carry such a risk as well. Children with non-specific infective symptoms belong to the group at risk for a UTI too.

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INFEKCIJA MOKRAČNOG SUSTAVA U NOVOROĐENČADI: RIZIČNI ČIMBENICI, PREPOZNAVANJE I SPRJEČAVANJE POSLJEDICA

SAŽETAK

Cilj ove studije je prepoznavanje novorođenčadi s prirođenim manama mokraćnog sustava radi sprječavanja posljedica tih mana. Prepoznavanje je vršeno putem otkrivanja novorođenčadi s infekcijom mokraćnog sustava u perinatalnom razdoblju. Nastojali smo pronaći osobitosti u anamnezi majke te odrediti karakteristike trudnoće i simptome kod novorođenčadi pomoću kojih bi izdvojili onu djecu kod koje su infekcija i mana mokraćnog sustava vjerojatnije. U istraživanje smo uključili 1200 novorođenčadi. Svima smo uzeli urinokulturu. Ako im je dijagnostificirana značajna bakteriurija, ispitali smo im nativni urin, C-reaktivni protein, kompletnu krvnu sliku i ukupni bilirubin. Novorođenčad s infekcijom mokraćnog sustava podvrgnuta je ultrazvučnom pregledu, direktnoj radionuklidnoj cistografiji i Tc^{99m} MAG3 dinamičkoj scintigrafiji. Učestalost infekcije mokraćnog sustava u perinatalnom razdoblju iznosila je 4,5%. Manu mokraćnog sustava imalo je 29,6% novorođenčadi s infekcijom. U pogledu perinatalnog razdoblja, takva novorođenčad češće pati od žutice (nejasne), periferne cijanoze, problema s disanjem, konvulzije i asfiksije. Osobitosti u anamnezi i trudnoći majki koje su rodile djecu s manama mokraćnog sustava su ljeđeće: mane mokraćnog sustava u užoj obitelji, pre-eklampsija ili febrilna infekcija majke pred porod, intrauterina hipotrofija ploda, prerano prsnuće plodovih ovoja te pupkovina omotana oko vrata ili tijela djeteta.