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Original article

Results of a retrospective analysis to identify the causes of nephropathologies in prenatal children exposed to maternal inflammatory process of bacterial etiology of the genitourinary system

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Abstract. *Background and Aim:* Urinary tract infection during pregnancy is one of the most common infections in women. Nearly two-thirds of babies are born with kidney disease due to prenatal exposure to inflammation in the mother. Determining the risk of developing kidney disease is important to prevent complications. The aim of this study is to determine the causes and criteria for the occurrence of specific manifestations of nephropathology in children of different ages and genders, based on a retrospective analysis of archival documentation. *Methods:* Retrospective cohort study included archival documentation of 76 cases of kidney disease in children of various ages born to mothers whose pregnancies occurred against the background of inflammatory diseases of the genitourinary system of bacterial etiology. *Results:* The occurrence of kidney diseases in children depends on age and gender. Kidney diseases were detected in girls of the older age group in 67.1% of cases. The debut of nephropathy from birth was detected in 28.4% of cases. Manifest kidney disease at an early age was detected in 23.7% of cases. In 93.4% of cases combined kidney pathologies were registered. *Conclusions:* The frequency of nephropathology in children of different ages is associated with the presence of an infectious process of the genitourinary system of bacterial etiology in women during pregnancy. The early risk of nephropathology in children is associated with an infectious disease of the genitourinary system of the mother during pregnancy. The manifestation of inflammation in the presence of a complex perinatal history occurs at birth or in early childhood. (www.actabiomedica.it)

Key words: nephropathology, children, inflammatory process, genitourinary system, bacterial factors

Introduction

The occurrence of inflammatory diseases of the genitourinary system of bacterial etiology in pregnant women is an urgent medical problem and is a generally recognized risk factor for adverse pregnancy outcomes (1,2). Although the mortality rate for this pathology has decreased in recent decades, professional studies still record a high risk of adverse outcomes for the fetus and mother (3). According to the literature, urinary tract infections in pregnant women occur in approximately one in three pregnant women (4). Bacterial inflammatory diseases of the genitourinary system in pregnant women are the result of the invasion of pathogens into the previously sterile genitourinary system. Favorable factors for their development during pregnancy are characteristic anatomical and functional changes in the urinary system. Among them, the most

important are the decrease in the tone of the ureters, bladder, hormonal changes, as well as mechanical compression of the urinary tract by the uterus, which increases in volume in the II and III trimesters. In addition, due to the increasing glomerular filtration during pregnancy, there is an increase in the concentration of glucose, protein, and steroid hormone metabolites in the urine, which promotes the reproduction of bacteria and reduces the resistance of the uroepithelium to infection, and the urine acquires a persistent alkaline reaction (5). Urogenital tract infections in pregnant women can manifest as cystitis, urethritis, asymptomatic bacteriuria, acute pyelonephritis or exacerbation of chronic pyelonephritis, salpingo-oophoritis, etc. The manifestations of diseases depend on the pathogenicity and virulence factors of pathogens, their resistance to antimicrobial drugs (6,7). It is known that inflammatory diseases of the genitourinary system of bacterial etiology can increase the risk of developing serious obstetric and neonatal complications of pregnancy and childbirth: anemia, arterial hypertension, premature rupture of amniotic fluid, and the birth of children with low body weight (8,9). However, the influence of inflammatory diseases of the genitourinary system of bacterial etiology in the mother during pregnancy on the development of kidney pathology in the fetus and newborn is poorly studied. Although there are reports of the relationship of the infectious-inflammatory process of the urinary tract in the mother's body with the occurrence of an inflammatory process in the fetoplacental complex and in the urinary system of the fetus (10). This dictates the need for close attention of researchers to the problem of inflammatory diseases of the genitourinary system of bacterial etiology in pregnant women. The renal system plays a major role in the development of children, especially at an early age. The function and physiological adaptation of the kidneys under the influence of maternal inflammatory process of the genitourinary system on the child's body in the prenatal period have been considered extremely insufficiently. It is known that maternal diseases during pregnancy affect the nephrogenesis of the newborn due to the action of drugs or toxic substances consumed by a pregnant woman suffering from inflammatory process of the genitourinary system (11). Specialists have identified pathological situations, such as congenital anomalies of the kidneys and urinary tract, other kidney diseases (12,13), which occur not only at an early age, but also in adulthood. But there is no information about the risk of developing nephropathology in children of different age groups depending on the combination of kidney disease in order to implement preventive strategies. The debut of nephropathies in young children is currently an urgent problem worldwide. Despite the great interest of domestic and foreign specialists in the study of this pathology (14,15), many issues related to its steady increase in children of different ages, the complexity of diagnosis, especially in early childhood, prevention of the formation of nephropathologies and tactics of dispensary observation of this category of patients remain relevant to this day due to the lack of pathognomonic criteria for the risk of developing kidney pathology in the prenatal period and at birth. Currently, the issue of identifying previously unaccounted for or poorly studied risk factors for the formation of nephropathology in children, as well as finding ways to prevent the development and timely diagnosis of kidney diseases, which will help prevent the progression of the pathological process and the development of complications, is acute. All of the above determines the relevance of this study. The aim of this study is based on a retrospective analysis of archival documentation of children born to mothers whose pregnancies occurred against the background of inflammatory diseases of the genitourinary system of bacterial etiology, to determine the causes and criteria for occurrence and to establish the features of the manifestation of nephropathology in children of different ages and genders.

Material and Methods

This retrospective cohort study was designed to conduct a comprehensive analysis by studying archival documentation of disease histories, medical records of hospitalized sick children, extracts from medical records of sick children, and collecting anamnesis of mothers of these children who suffered from urogenital infections of bacterial etiology during pregnancy. Inclusion criteria: children of different ages with kidney pathologies who were examined and treated in the

nephrology department of the KNP KOR "Regional Children's Clinical Hospital" in order to determine the structural characteristics of nephropathology in children of the Kharkiv region. These children were born to mothers whose pregnancies occurred against the background of inflammatory diseases of the genitourinary system of bacterial etiology. The analysis included medical records of 76 children who were exposed to the inflammatory process of the mother's genitourinary system in the prenatal period in different trimesters of pregnancy, which provides valuable information about risk factors for the development of nephropathology and about the onset of diseases in children depending on gender. The child's age category, gender, combination of kidney pathology, mother's age, trimester of pregnancy when diagnosing inflammatory disease of the genitourinary system, and the debut of nephropathology in the child were analyzed.

Data collection

Anamnestic data were collected: data of the mother during pregnancy (age, chronic inflammatory diseases of the genitourinary system present in the mother before or during pregnancy, trimester of pregnancy when an exacerbation of a chronic disease of the genitourinary system occurred or an inflammatory disease of the urogenital tract first occurred, the causative agent of the disease). The history of the infants (diagnosis of kidney disease, age, sex, onset of disease) was retrospectively extracted from medical records. In the study, we included all cases of kidney disease in children, regardless of whether the mother had inflammatory diseases of the urogenital tract during pregnancy, symptomatic or asymptomatic (bacteriuria). This decision was based on the understanding that both symptomatic and asymptomatic (bacteriuria) genitourinary inflammatory diseases can have significant consequences for neonatal health, including the potential for long-term development of nephropathology. By including all cases, we aimed to provide a comprehensive assessment of risk factors for renal pathology in infants exposed prenatally to maternal genitourinary inflammatory disease. The diagnosis was made on the basis of diagnostic tests: laboratory - clinical and biochemical analysis of blood and urine, microscopy (bacteriological culture) of urine; instrumental - ultrasound examination of the kidneys and bladder, results of X-ray examination - micturition cystography (16,17,18). Routing of pregnant women with pathology of the genitourinary system was organized as follows: pregnant women were admitted to the admission department according to the disease profile, then to the obstetrics and gynecology department regardless of the primary diagnosis, where an obstetrician-gynecologist examined the pregnant woman, excluding obstetric and gynecological disease, and then the examination was conducted by a urologist. The examination standards included: laboratory tests - clinical and biochemical blood tests, general urine analysis; instrumental examination - ultrasound examination of the pelvic organs and fetus. If surgical pathology was suspected, the patient was consulted by a surgeon. To assess the outcome of acute or chronic pyelonephritis during pregnancy or other urogenital infection, as well as the outcome of gestation itself, patients in the retrospective group were asked to answer the following questions. Based on these questions, a questionnaire was further developed to analyze factors affecting the risk of kidney pathology in offspring. The age, gestational age at which the inflammatory disease of the genitourinary system of bacterial etiology occurred, the number of relapses and severity of the disease, acute or chronic form of the disease, the causative agent of the inflammatory disease of the genitourinary system, complications, the therapy performed, the regimens of which were prescribed individually taking into account the sensitivity of the uropathogen to antimicrobial drugs, the individual sensitivity of pregnant women to drugs in accordance with the current unified clinical protocols of medical care, approved by the Orders of the Ministry of Health of Ukraine “On approval of clinical protocols in the specialty “Urology”, which are comparable to international standards. The sensitivity of pathogens of infectious diseases of the urogenital tract to antimicrobial drugs was necessarily taken into account. Recommended first-line therapy (drugs of choice): ciprofloxacin (400 mg 2 times/day, cefotaxime (2 g 3 times/day). Second-line therapy: cefepime (1 g/day), amikacin (15 mg/kg 1 time/day). Alternative antibacterial therapy: imipenem/cilastatin (0.5 g 3 times/day), ceftolozane/tazobactam

(1.5 g 3 times/day), if there was no response to antibiotic therapy within 72 hours, then carbapenems, cephalosporins III, IV, V generations, new aminoglycosides were used (19,20,21,22). The control group consisted of 20 healthy women who gave birth to healthy children. According to obstetric and gynecological anamnesis, the main group and the comparison group were comparable.

Statistical analysis

Statistical analysis and data management were performed using Statistica 7 (23). This study was approved by the meeting of the Department of General and Clinical Pathological Physiology named after D.O. Alpern at Kharkiv National Medical University and Department of Microbiology, Virology and Immunology named after D.P.Grynyov, Kharkiv National Medical University (Protocol No.2, 01/30/2024).

Results

As a result of the analysis of the questionnaire data and medical records of the mothers, it was found that the age of the women during pregnancy was from 19 to 38 years. The age group from 19 to 29 years included 44 pregnant women (57.9%), and the age group from 30 to 38 years included 32 pregnant women (42.1%). Thus, mainly inflammatory diseases of the genitourinary system were detected in young pregnant women. The average age of the mother was 28.5 years. The diagnosis of inflammatory disease of the urogenital tract of bacterial etiology in the I trimester of pregnancy was established in 40.8% of pregnant women (n=31). Of these, 38.7% (n=12) of patients with acute pyelonephritis, cystitis and urethritis. 41.9% (n=13) of women had chronic pyelonephritis and salpingo-oophoritis. Asymptomatic bacteriuria was detected in 19.4% (n=36) of pregnant women. In the II trimester, inflammatory diseases of the genitourinary system of bacterial etiology were detected in 44.7% (n=34) of women. Acute pyelonephritis, cystitis and urethritis were detected in 11.8% (n=4) of cases. Chronic pyelonephritis was detected in 50% (n=17) of women (of which, a combination of chronic pyelonephritis and polycystic kidney disease in 29.4% (n=5) of cases). Asymptomatic bacteriuria was detected in 38.2% (n=13) of pregnant women. In the III trimester of pregnancy, inflammatory diseases of the genitourinary system were detected in 14.5% (n=11) of women. Acute pyelonephritis, cystitis and urethritis were detected in 27.3% (n=3) of cases. Chronic pyelonephritis was detected in 54.5% (n=6) of women (of which, a combination of chronic pyelonephritis and polycystic kidney disease in 33.3% (n=2) of cases). Asymptomatic bacteriuria was detected in 18.2% (n=2) of pregnant women. In pregnant women of the retrospective group, the duration of the course, the degree of severity, and the features of the clinical picture of inflammatory diseases of the genitourinary system during pregnancy depended on the virulence of the pathogen, the degree of spread of infection, the gestational age, the presence and severity of impaired urine passage, as well as the presence or absence of purulent-destructive changes in the renal tissue. Recurrences of inflammatory diseases of the genitourinary system after treatment of the first episode of exacerbation during pregnancy were registered in 12 (15.8%) women in the III trimester, which was due to impaired urine outflow. Of these, in 9 (11.8%) pregnant women, it was an indication for stenting of the ureters. When analyzing bacteriological culture of urine of pregnant women, it was found that the selected spectrum of etiological factors of urinary system infections in pregnant women aged 19 to 29 years and after 30 years had no significant differences. A retrospective analysis of the etiological structure of urinary system infections, taking into account the trimester of pregnancy, established that in the I, II and III trimesters of pregnancy, the 1st and 2nd rank places in most cases fell on *Escherichia coli* and *Proteus mirabilis*. The 3rd place in the I trimester was occupied by *Enterococcus faecalis*, in the II trimester by *Proteus vulgaris* and *Streptococcus pyogenes*, in the III trimester by *Streptococcus pyogenes*. The etiological structure of urinary tract infections in pregnant women, taking into account the topography of the inflammatory process of bacterial genesis, had certain features. In women with asymptomatic bacteriuria, the 1st place was occupied by *Proteus mirabilis*, the 2nd place by *Escherichia coli*, the 3rd place by *Proteus vulgaris* and *Enterococcus faecalis*. In chronic pyelonephritis, the 1st place was occupied by *Proteus*

mirabilis, the 2nd place by *Streptococcus pyogenes*, the 3rd place by *Escherichia coli* and *Proteus vulgaris*. In acute pyelonephritis (in combination with cystitis and urethritis), 1st place was given to *Escherichia coli*, *Proteus mirabilis*, 2nd place – *Streptococcus pyogenes*, *Klebsiella pneumoniae*, 3rd place – *Enterococcus faecalis, Klebsiella pneumoniae, Proteus vulgaris* and *Pseudomonas aeruginosa*. The most important factor in the virulence of uropathogenic strains is their ability to attach to the urothelium due to adhesins and antigens, which allows bacteria not only to colonize the surfaces of the mucous membranes of the urinary tract, but also to penetrate the tissue, form biofilms, especially when the local and general protective mechanisms of the pregnant woman's body are weakened, especially in the II and III trimesters. The most common complications of pregnancy in inflammatory diseases of the genitourinary system during pregnancy were: gestosis in 10 pregnant women in the III trimester (13.2%), anemia in 31 pregnant women (40.8%), placental insufficiency in 28 pregnant women (36.8%), intrauterine fetal hypoxia was registered in 8 cases (10.5%). Premature rupture of the membranes occurred in 9 (11.8%) women in labor, but in all women who participated in the survey, the pregnancy ended in childbirth, the average gestation period did not significantly differ from the control group (Figure 1).

When studying archival material of medical histories and medical records of children (n=76) who were exposed to an inflammatory process of the genitourinary system in the prenatal period. It was found that the occurrence of kidney diseases in children varies and depends on age and gender aspects. Namely: most often kidney diseases were detected in girls in 67.1% of cases (n=51), more often in girls of the older age category (n=22) and in boys, nephropathology was most often detected in two age categories: 4-8 years and 9-16 years - 40% each. More often kidney diseases in children were registered in the older age category from 9 to 16 years - in 42.1% of cases (n=32). In 34.2% of cases (n=26) nephropathies were registered in children of the age category from 4 to 8 years and in 23.7% of cases (n=18) - in children of early age (Figure 2).

It has been established that the frequency of kidney pathology in a child depends on the uropathogen of inflammatory diseases of the genitourinary system during the mother's pregnancy. Thus, in children of the age group 0-3 years in 39% of cases kidney pathology is associated with the uropathogen *Proteus mirabilis*, in 33% - *Streptococcus pyogenes*, in 17% - *Enterococcus faecalis* and in 6% of cases - *Escherichia coli* and *Proteus vulgaris*. In children of the age group 4-8 years, the development of nephropathology is associated with the action of pathogenic factors of uroisolates *Proteus mirabilis* and *Proteus vulgaris* - in 27% each, in 23% of cases - *Escherichia coli*, in 15% of cases - *Streptococcus pyogenes*. In children aged 9-16 years, the development of kidney pathology is caused by the action of the uropathogen *Escherichia coli* in 53% of cases, *Proteus*

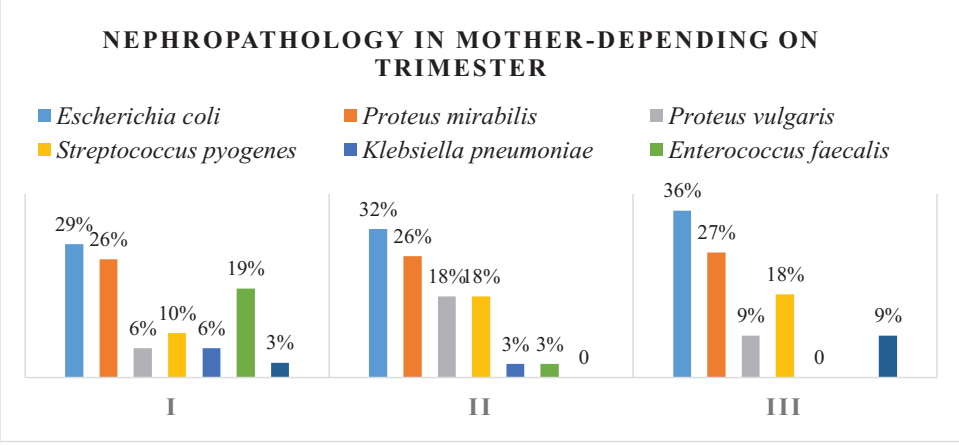

Figure 1. The spectrum of etiological factors of inflammatory diseases of the genitourinary system during pregnancy depending on the trimester.

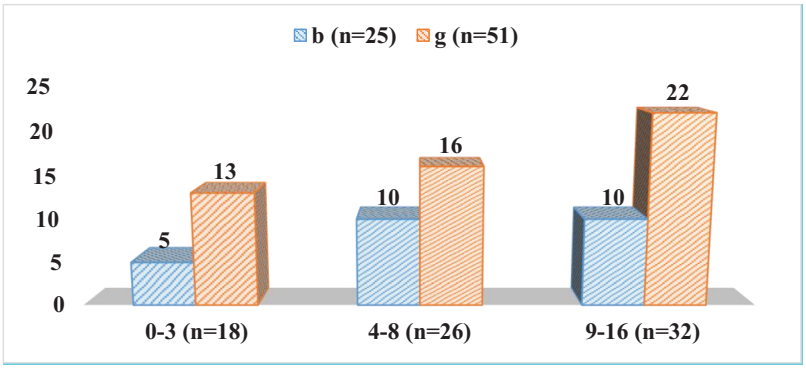

Figure 2. The frequency of nephropathology depending on the age and gender of the child.

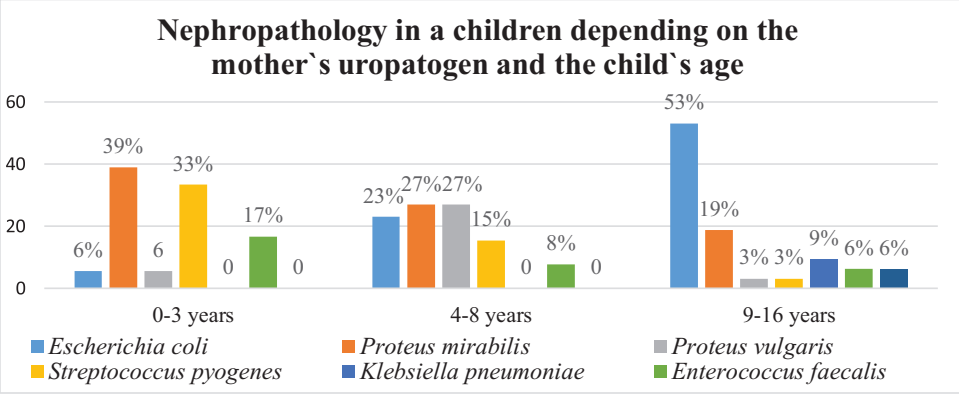

Figure 3. Frequency of nephropathology in children depending on age and uropathogen of inflammatory diseases of the genitourinary system during the mother's pregnancy.

mirabilis in 19% of cases, *Klebsiella pneumoniae* in 9% of cases, *Enterococcus faecalis* and *Pseudomonas aeruginosa* in 6% of cases, and *Proteus vulgaris* and *Streptococcus pyogenes* in 3% of cases (Figure 3).

Moreover, the debut of nephropathy from birth was detected in 22 (Figure 4) cases (28.4%). The highest frequency of manifestation among children aged 1 month to 3 years - among 18 examined, half (50%) were found with a debut at birth, of which 55.6% were girls and 44.4% boys. Among all children aged 4 to 8 years (n=26), kidney disease was first diagnosed at birth in 6 children (23.1%), of which 55.6% were girls and 44.4% were boys. Among all children aged 9 to 16 years (n=32), the debut of the disease at birth was registered in 7 children (21.9%), of which 57.1% were girls and 42.9% were boys.

Manifestation of kidney disease at an early age was found in 23.7% of cases (n=18, of which 66.7% were girls and 33.3% were boys). Among children of all age categories: the highest rate was registered in children aged 4 to 8 years – 34.6%, of which 44.4% were girls and 55.6% were boys. The debut of nephropathies at an early age in children aged 1 month to 3 years was observed in 27.8% of cases, of which 80% were girls and 20% were boys. The debut of kidney disease at an early age was found among children aged 9 to 16 years (n=4 – all girls) (Figure 5).

As a result of the analysis conducted to compare the manifestation of kidney disease in a child and the etiological factor of inflammatory diseases of the genitourinary system during the mother's pregnancy, it was found that nephropathology was detected at birth in

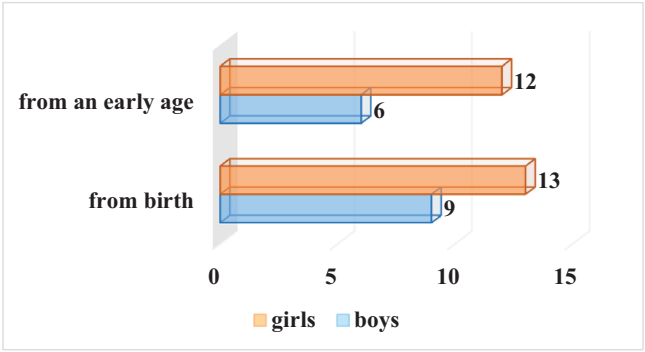

Figure 4. Debut of nephropathology depending on the sex of the child.

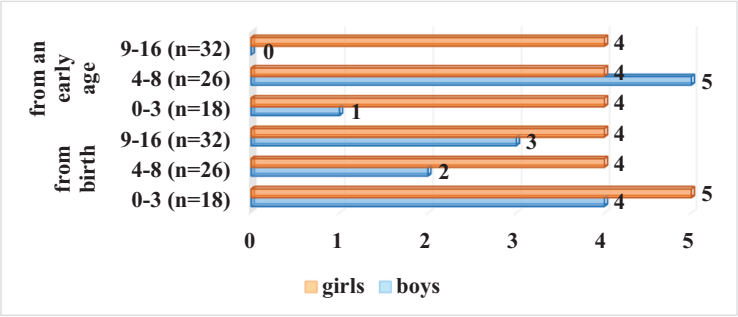

Figure 5. The onset of nephropathology depends on the age and gender of the child.

36% of cases due to the action of the uropathogen *Proteus mirabilis*, in 27% of cases - *Streptococcus pyogenes*, in 18% of cases - *Escherichia coli*, in 14% of cases - *Enterococcus faecalis* and in 5% of cases - *Proteus vulgaris* - etiological factors of the mother's urogenital infection. The manifestation of kidney pathology in children at an early age (from 1 month to 3 years) was due to the action of pathogenic factors of pathogens of inflammatory diseases of the genitourinary system during the mother's pregnancy. In 39% of cases - *Proteus mirabilis*, in 28% - *Proteus vulgaris*, in 17% - *Streptococcus pyogenes*, in 11% - *Escherichia coli* and in 6% - *Enterococcus faecalis*. The debut of nephropathology in children after 3 years of age was observed under the influence of the inflammatory process of the genitourinary system in the prenatal period, caused by a uropathogen: in 50% of cases - *Escherichia coli*, in 14% of cases - *Proteus mirabilis*, in 8% of cases - *Proteus vulgaris*, *Streptococcus pyogenes*, *Enterococcus faecalis* and in 6% of cases - *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (Figure 6).

More often, children were diagnosed with combined nephropathologies and only in 5 cases was a mono diagnosis established. In children of the age group 0-3 years - 3 cases: a girl aged 11 months was diagnosed with "dysmetabolic nephropathy", a girl aged 8 months - "acute uncomplicated pyelonephritis" and a girl aged 1 year 4 months was diagnosed with "renal dysplasia"; a boy aged 6 years - "chronic kidney disease" and a boy aged 9 years - "renal dysplasia". In 93.4% of cases (n=71), combined renal pathologies were recorded in children of different age groups. Thus, in the age group 0-3 years, pyelonephritis was most often recorded, which was combined with renal dysplasia, solitary renal cyst, initial phase of urolithiasis, reduced glomerular filtration rate (GFR) and congenital kidney defects, and chronic kidney disease (CKD), which was

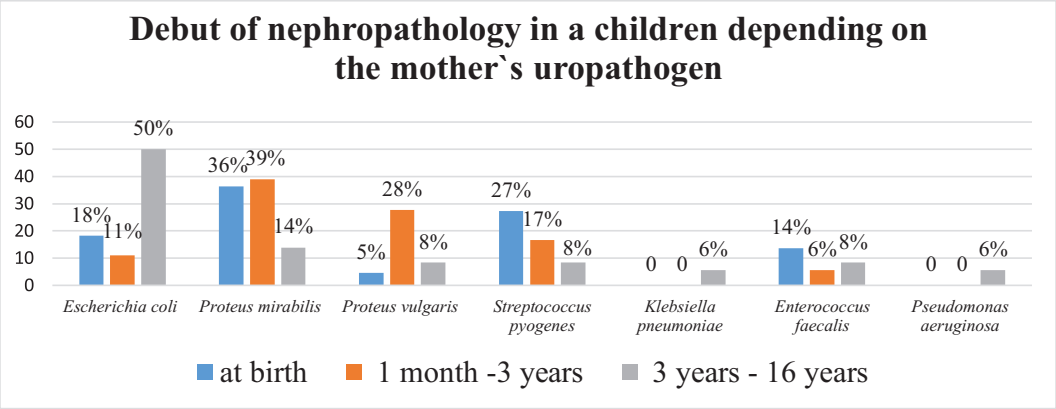

Figure 6. The debut of nephropathology in a child depends on the uropathogen of inflammatory diseases of the genitourinary system during the mother's pregnancy.

Table 1. Incidence rate (%) of kidney diseases in children aged 0-3 years (n=18)

Diagnosis	Concomitant diagnosis	Case ratio	Gender of the child
Acute pyelonephritis	renal dysplasia	22,2%	girl
	urolithiasis	11,1%	girl
	reduced GFR	11,1%	girl
Chronic pyelonephritis	renal dysplasia	22,2%	girl
	solitary cyst	5,5%	boy
	reduced GFR	22,2%	girl, boy
	congenital defect	11,1%	boy
Chronic kidney disease	reduced GFR	5,5%	boy
	congenital defect	11,1%	girl, boy

combined with congenital kidney anomaly (right-sided hydronephrosis) with reduced GFR (Table 1).

As a result of the conducted retrospective study, it was found that with prenatal exposure to the inflammatory process of the genitourinary system of bacterial etiology in children aged 0-3 years, the development of pyelonephritis in combination with renal dysplasia with prenatal exposure to *Streptococcus pyogenes* was detected in 44.5% of cases. With the influence of *Proteus mirabilis* - 33.3% of cases, with the influence of *Escherichia coli* and *Enterococcus faecalis* 11.1% of cases each. The development of pyelonephritis with a decrease in glomerular filtration rate was observed in 50% of cases under the prenatal influence of the inflammatory process of the genitourinary system caused by *Proteus mirabilis* and in 25% of cases under the influence of *Streptococcus pyogenes* and *Enterococcus faecalis*. The development of pyelonephritis in combination with a congenital kidney anomaly - uterohydronephrosis was registered in 50% of cases under the influence of *Proteus mirabilis* and 50% of cases - under the influence of *Streptococcus pyogenes*, but the development of the congenital defect was manifested by right-sided hydronephrosis. The development of dysmetabolic nephropathy was due to the influence of *Proteus mirabilis* (mono diagnosis) and *Proteus vulgaris* - in combination with chronic complicated pyelonephritis. And the only case of chronic pyelonephritis in combination with a solitary renal cyst was registered due to prenatal exposure to *Enterococcus faecalis* (Figure 7).

When analyzing the medical histories of children aged 4-8 years, the ratio of cases of kidney

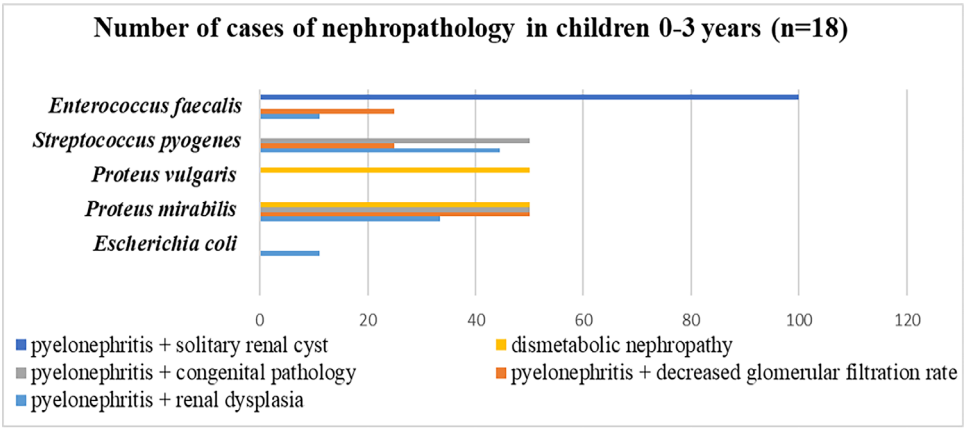

Figure 7. Frequency of nephropathology in a child (age group 0-3 years) depending on the uropathogen of inflammatory diseases of the genitourinary system during the mother's pregnancy.

pathologies depending on gender was revealed. It was established that the most frequently recorded cases were cases of combination of dysmetabolic nephropathy with renal dysplasia in girls (15.4%). The course of chronic pyelonephritis was accompanied by a decrease in GFR in 15.4% of cases, and in 11.5% of cases - with renal dysplasia in girls. It is noteworthy that CKD in 11.5% of cases is combined with the development of congenital defects (anomalies) of the kidneys (Table 2).

Analysis of the conducted study revealed that with prenatal exposure to the inflammatory process of the genitourinary system of bacterial etiology in children aged 4-8 years, the development of pyelonephritis in combination with renal dysplasia was detected in 33.4% of cases with prenatal exposure to *Escherichia coli*, 22.2% of cases with *Proteus mirabilis* and *Proteus vulgaris*, and 11.1% of cases with *Streptococcus pyogenes* and *Enterococcus faecalis*. The development of pyelonephritis with a decrease in glomerular filtration rate has been observed with prenatal exposure to an inflammatory process of the genitourinary system caused by *Proteus mirabilis*. The combination of pyelonephritis with urolithiasis is most often caused by the influence of *Enterococcus faecalis* (50% of cases) and in 25% of cases by the influence of *Streptococcus pyogenes* and *Proteus mirabilis*. The development of chronic kidney disease is due to prenatal exposure to the uropathogens *Proteus mirabilis* and *Proteus vulgaris*. Glomerulonephritis in combination with renal dysplasia, decreased glomerular filtration rate, and congenital kidney defects has been reported with *Proteus mirabilis* and *Streptococcus pyogenes*, and chronic tubulointerstitial nephritis with *Streptococcus pyogenes*. The development of dysmetabolic nephropathy with renal dysplasia was caused by the influence of *Escherichia coli* (60% of cases) and *Proteus vulgaris* (40% of cases) (Figure 8)

Retrospective analysis of data from children aged 9-16 years revealed a combination of chronic pyelonephritis with renal dysplasia in girls in 18.8% of cases, in combination with the initial phase of urolithiasis in 15.6% of cases, and with reduced GFR in 9.4% of cases. In 3.1% of cases, a combination of acute pyelonephritis with urolithiasis and renal dysplasia was recorded in girls. In boys, chronic pyelonephritis was combined with congenital kidney disease. The course of chronic glomerulonephritis was accompanied by the addition of initial urolithiasis with reduced GFR, nephrotic syndrome and dysmetabolic nephropathy in both girls and boys. Toxic-metabolic nephropathy in boys, and hereditary nephritis in girls were combined with renal dysplasia and urolithiasis (Table 3).

Retrospective analysis revealed that with prenatal exposure to an inflammatory process of the genitourinary system of bacterial etiology in children aged 9-16 years, the development of pyelonephritis in combination with renal dysplasia was detected in 53.8% of cases with prenatal exposure to *Escherichia coli*, 15.4% with *Proteus mirabilis*, and

Table 2. Incidence rate (%) of kidney disease in children aged 4-8 years (n=26)

Diagnosis	Concomitant diagnosis	Case ratio	Gender of the child
Acute pyelonephritis	renal dysplasia	7,6 %	girl, boy
	urolithiasis	7,6 %	girl
Chronic pyelonephritis	renal dysplasia	11,5 %	girl
	urolithiasis	7,6 %	girl
	reduced GFR	15,4 %	girl
Acute glomerulonephritis	renal dysplasia	3,8 %	girl
	reduced GFR	3,8 %	girl
	renal dysplasia	3,8 %	boy
	dysmetabolic nephropathy	3,8 %	boy
	reduced GFR	3,8 %	boy
	congenital defect	3,8 %	boy
Chronic kidney disease	renal dysplasia	7,6 %	girl, boy
	urolithiasis	3,8 %	girl
	reduced GFR	3,8 %	boy
	congenital defect	11,5%	boy
Chronic tubulointerstitial nephritis	reduced GFR	3,8 %	girl
	congenital defect	3,8 %	girl
Dysmetabolic nephropathy	renal dysplasia	15,4 %	girl
	reduced GFR	11,5%	girl

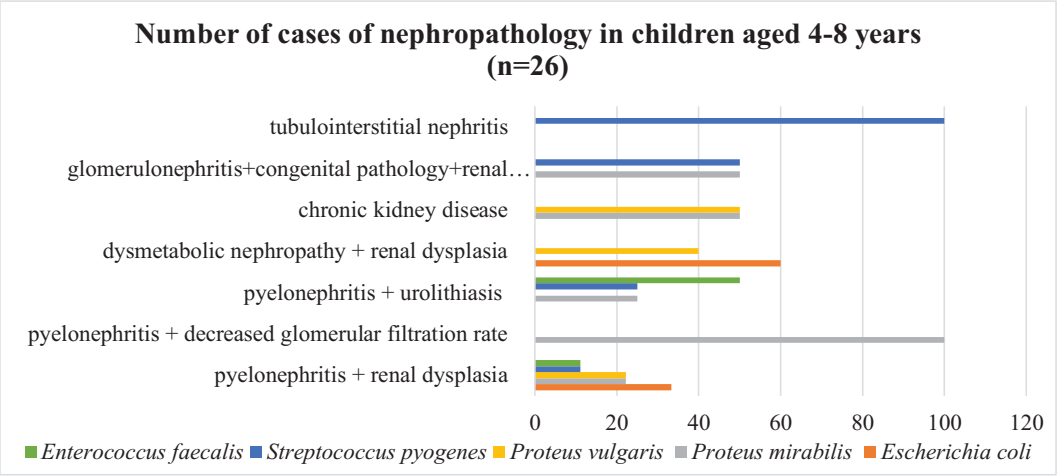

Figure 8. Frequency of nephropathology in a child (age group 4-8 years) depending on the uropathogen of inflammatory diseases of the genitourinary system during the mother's pregnancy.

7.7% with *Proteus vulgaris*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*. The development of chronic tubulointerstitial nephritis is caused by prenatal exposure to *Escherichia coli* and *Proteus vulgaris*. The development of congenital malformations (hydronephrosis) of the kidneys has been recorded under the influence of *Proteus mirabilis* and *Streptococcus pyogenes*. The development of

Table 3. Incidence rate (%) of kidney disease in children aged 9-16 years (n=32)

Diagnosis	Concomitant diagnosis	Case ratio	Gender of the child
Acute pyelonephritis	renal dysplasia	3,1 %	girl
	urolithiasis	3,1 %	girl
Chronic pyelonephritis	renal dysplasia	18,8 %	girl
	urolithiasis	15,6 %	girl
	reduced GFR	9,4 %	girl
	congenital defect	3,1% 6,3%	boy girl
Acute glomerulonephritis	renal dysplasia	3,1 %	boy
Chronic glomerulonephritis	renal dysplasia	3,1 % 3,1 %	boy girl
	solitary cyst	3,1 %	girl
	dysmetabolic nephropathy	3,1 %	girl
	reduced GFR	3,1 %	boy
	nephritic syndrome	3,1 %	boy
	urolithiasis	3,1 % 3,1 %	boy girl
Toxic-metabolic nephropathy	renal dysplasia	3,1 %	boy
	urolithiasis	3,1 %	boy
Chronic tubulointerstitial nephritis	congenital defect	3,1 %	girl
Dysmetabolic nephropathy	renal dysplasia	3,1 %	boy
	urolithiasis	3,1 % 3,1 %	boy girl
	congenital defect	3,1 %	girl
Hereditary nephritis	renal dysplasia	3,1 %	girl
	urolithiasis	3,1 %	girl

dysmetabolic nephropathy with renal dysplasia was caused by exposure in 71.4% of cases to *Escherichia coli* and in 14.3% of cases to *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The development of toxic-metabolic nephropathy with urolithiasis was observed under the prenatal influence of the inflammatory process of the genitourinary system caused by *Proteus mirabilis*.The development of glomerulonephritis in combination with renal dysplasia, dysmetabolic nephropathy, nephritic syndrome, urolithiasis, and other concomitant diagnoses is due to prenatal exposure to *Proteus mirabilis* in 57.1% of cases and to *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* in 14.3% of cases (Figure 9).

It should be noted that all mothers had infectious diseases of bacterial etiology of the genitourinary system during pregnancy. 75% of mothers of these children had pyelonephritis during pregnancy. Of these, 36.8% had acute pyelonephritis and 63.2% had chronic pyelonephritis. Thus, as a result of a retrospective study of archival material from medical records and medical histories of children with nephropathology, as well as data from a questionnaire survey of mothers who suffered from inflammatory diseases of the genitourinary system during pregnancy, it was established that the leading criteria by which the risk of developing kidney pathology can be identified depending on the child's age, the debut of the disease and the concomitant diagnosis are: uropathogen, trimester of pregnancy in which the disease occurred or worsened in the pregnant woman, and the sex of the child.

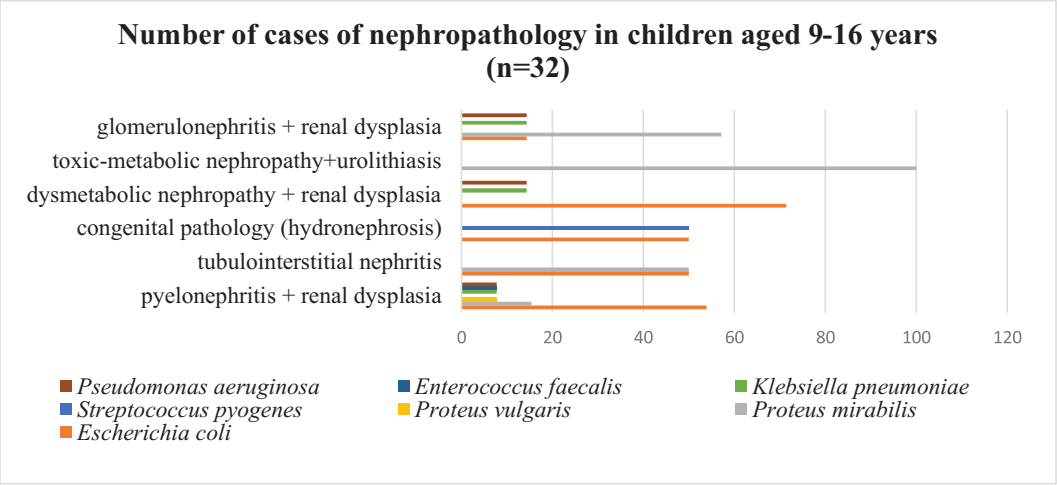

Figure 9. Frequency of nephropathology in a child (age group 9-16 years) depending on the uropathogen of inflammatory diseases of the genitourinary system during the mother's pregnancy.

Discussion

Kidney disease in children can occur with inflammatory diseases of the mother during pregnancy and manifest in utero, in childhood or in adolescence. Early onset of nephropathy creates a certain risk of early development of chronic kidney disease with loss of function. Especially in children with prenatal exposure to inflammatory diseases of the genitourinary system of the pregnant mother, dysplasia of renal tissue, congenital malformations and urodynamic disorders (24). Experts conducted an analysis of the impact of maternal prenatal infections on the fetus. It was found that possible predictors of the pathological process in children with early onset nephropathy are pregnancy complications, placental pathology, and fetoplacental insufficiency (25,26,27). The authors indicated that the leading risk factors for the development of chronic secondary pyelonephritis in children are fetoplacental insufficiency, intrauterine fetal hypoxia, and oxidative stress, which make a significant contribution to fetal programming of nephrogenesis and can further affect the structure and physiological characteristics of the kidneys. A burdened antenatal and neonatal history negatively affects the morphogenesis of the urinary system organs and creates conditions for the development of early nephropathies in the first months of life. Our study shows that the leading criteria by which the risk of developing kidney pathology can be identified depending on the child's age, the manifestation of kidney disease, and the concomitant diagnosis that complicates the course of the underlying disease and leads to chronic renal failure in the future are: uropathogen, trimester of pregnancy in which the disease occurred or worsened in the pregnant woman, and the child's gender.

Researchers from the Department of Obstetrics and Gynecology, Wuwei Hospital, Gansu, China, conducted a retrospective study on the risk factors for urinary tract infections in pregnant women. It was found that the common pathogenic bacteria in pregnant women with urogenital tract infections were mainly gram-negative bacteria. The experts noted that older pregnant women, low education level, gestational complications, and anemia may be risk factors for the development of bacterial urinary tract infections in pregnant women, but no analysis was conducted on the risk of nephropathy in children born to such mothers (8). Our study also shows that the leading role in the occurrence of bacterial inflammatory processes of the genitourinary system in pregnant women is played by gram-negative bacteria: *Escherichia coli, Proteus mirabilis, Proteus vulgaris, Klebsiella pneumoniae, Pseudomonas aeruginosa*. However, the significance of gram-positive bacteria such as *Streptococcus pyogenes* and *Enterococcus faecalis* in the development of urogenital infections in pregnant women in different trimesters is also

shown. In our previous study it was established (28) that the leading pathogens of urinary tract infections in pregnant women in the Kharkiv region are *Escherichia coli, Proteus mirabilis, Proteus vulgaris, Streptococcus pyogenes, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa*. Among which *Escherichia coli, Proteus mirabilis, Streptococcus pyogenes* are prevalent. The identified spectrum of etiological factors of urinary tract infections does not depend on the age of the pregnant woman and most often in the I-III trimesters of pregnancy the uropathogens are *Escherichia coli, Proteus mirabilis, Enterococcus faecalis, Proteus vulgaris* and *Streptococcus pyogenes*. The etiological structure of urinary tract infections in pregnant women is determined by the topography of the inflammatory process of bacterial genesis. In women with asymptomatic bacteriuria, *Proteus mirabilis* ranks first, *Escherichia coli* ranks second, *Proteus vulgaris* and *Enterococcus faecalis* ranks third. In chronic pyelonephritis, *Proteus mirabilis* ranks first, *Streptococcus pyogenes* ranks second, *Escherichia coli* ranks third and *Proteus vulgaris* ranks fourth. In acute pyelonephritis, *Escherichia coli* ranks first, *Streptococcus pyogenes* ranks third, *Proteus mirabilis, Enterococcus faecalis, Klebsiella pneumoniae* ranks fourth; in urethritis, *Escherichia coli* ranks second, *Enterococcus faecalis, Klebsiella pneumoniae* ranks fourth, *Proteus mirabilis*, *Proteus vulgaris* ranks fourth. In cystitis, *Escherichia coli* ranks first, *Proteus mirabilis, Proteus vulgaris, Enterococcus faecalis, Klebsiella pneumoniae* ranks fourth, *Pseudomonas aeruginosa* ranks fourth. Our findings are consistent with a regional meta-analysis of bacterial profiles and prevalence of urinary tract infections in pregnant women (29), which showed that pregnant women in Latin America had a higher prevalence of bacteriuria, urinary tract infections, and pyelonephritis than pregnant women worldwide. This finding highlights the importance of universal screening with urine culture during early prenatal care to ensure better outcomes. However, this study did not identify any risk of nephropathy in children born to these mothers. Further studies with larger and more diverse cohorts are needed to confirm our findings and further explore the risk factors for developing renal pathology in children exposed to maternal bacterial genitourinary inflammation during the prenatal period, at different gestational ages. We recommend that future studies validate the model in different regions of the country to assess this problem more broadly. As kidney disease in children is increasingly common with manifestations at different ages, it is important to consider prognostic risks and intervene promptly to address potential health problems in infants as early as possible. The results of this study are valuable for obstetricians-gynecologists, urologists, and pediatricians, as they provide valuable information. This may improve the care of pregnant women with bacterial urinary tract infections and infants born to these mothers. Further research in this area may improve pregnancy and delivery outcomes, as well as reduce the number of nephrological complications in newborns.

Conclusion

The retrospective analysis allowed us to draw a number of conclusions. The frequency of nephropathology in children of different ages is associated with the presence of an infectious process of the genitourinary system of bacterial etiology in women during pregnancy, which indicates the risk of developing kidney pathology from birth or from an early age. Early risk of nephropathology in children is associated with infectious diseases of the mother's urinary system during pregnancy, namely: acute pyelonephritis and relapse of chronic pyelonephritis. It has been shown that the manifestation of the inflammatory process in the presence of a complicated perinatal history and congenital malformations occurs at birth or in early childhood.

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Ethic Committee: Meeting of the Department of General and Clinical Pathological Physiology named after D.O. Alpern, Kharkiv National Medical University and the Department of Microbiology, Virology and Immunology named after D.P.Grynyov, Kharkiv National Medical University (Protocol No. 22, 03/10/2024).

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: MY: conducting experimental research, analyzing and interpreting the obtained data, writing the text of the article, formulating conclusions. MM: formulation of the purpose of the work, research concept, development of a model of chronic maternal inflammatory process of the genitourinary system, final approval of the article. MM, MA: reproduction of a model of chronic maternal inflammatory process of the genitourinary system, article editing. AM, RP, OB, AC: analyzed and interpreted data. All the Co-Authors contributed to the interpretation of data and provided critical comments on the manuscript for important intellectual content. All authors have critically reviewed, approved the final draft and are responsible for the content and similarity index of the manuscript.

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