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ARS Medica Tomitana - 2021; 4(27): pag. 193 - 204
doi: 10.2478/arsm-2021-0037

URINARY TRACT INFECTIONS SPECTRUM DURING PREGNANCY: ETIOPATHOGENESIS AND OUTCOME

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ABSTRACT

Background :The occurence of urinary tract infections (UTIs) in the course of a normal pregnancy should always be early diagnosed and treated, even asymptomatic as it could evolve to threatening pathological conditions, like sepsis with acute kidney injury, or preeclampsia. The aim of study was to establish a cartographic projection of the risk factors and etiopathogenesis of urinary tract infections diagnosed during pregnancy, with the purpose to control their severity and evaluate the therapeutic strategies used to reduce maternal and fetal risks. Material and methods: The study included 175 patients, pregnant women, diagnosed with UTIs hospitalized in the Nephrology Clinic and Obstetrics-Gynecology Clinic of the Emergency Clinical County Hospital of Constanta, in an interval of time of 4 years, between 2017-2021. Results: Out of the 247 patients recruited in our study, the distribution according to the trimester of pregnancy, there were : 72 pregnant women in the first trimester (41.14%), 35 in the second trimester (20.0%) and 68 in the third trimester (38.86%). The frequency of pregnant women who had other favorising conditions and detectable risk factors was 70.29%. The clinical manifestations of UTIs in our study group were distributed as follows : 36 (20.57%) asymptomatic bacteriuria, 56 (32.0%) acute cystitis, 44 (25.14%) recurrent lower urinary tract infections, and 39 (22.29%) acute pyelonephritis. There is an association ($p < 0.001$) between the type of clinical form of UTIs and a certain trimester of pregnancy, for example the highest frequency of acute pyelonephritis (AP) was noticed in the third trimester of pregnancy (71.8%, 28/39). Out of 39 pregnant women with AP, 71.8% (28) had associated ureterohydronephrosis (UHN). E. Coli was present in 41.71% of pregnant women., followed by Klebsiella pneumoniae, Enterococcus faecalis and, less frequently, Staphylococcus aureus and Proteus mirabilis. The most frequently used antibiotics in pregnancy were: 2nd and 3rd generations of cephalosporins (42.29%), followed by ampicillin (34.29%); less used were amoxicillin with clavulanic acid (10.29%), quinolones (6.29%) and nitrofurantoin (6.86%). Most of the pregnant women (94.28%, 165/175) had remission of fever within 24-48 h of using appropriate antibiotic therapy. The recurrence rate was 22.28 %, (39/175). Conclusion All clinical forms of UTIs could be present during pregnancy, but the most common are lower urinary tract infections and the most involved germ is E. Coli. UHN is a factor that influences the occurence of UTIs, being the most common favorising condition.

Keywords: pregnancy, urinary tract infections, ureterohydronephrosis

Introduction:

Despite numerous studies carried out over the time, the occurrence of urinary tract infections (UTIs) in pregnant women represents a real clinical and therapeutic challenge, both for nephrologists and gynecologists. Urinary tract infections (UTIs) in pregnant women are classified into 2 different categories: asymptomatic bacteriuria and symptomatic infections. About 80% of pregnant women associate urinary stasis, leading to deterioration of physiological anti-reflux mechanism, favouring bacterial growth and upward spread of infection. Biochemical urinary changes which are specific to pregnancy can also be added at these predisposing factors (1). UTIs are considered complicated infection during pregnancy, with particularities in approaching to clinical diagnosis and appropriate therapy, in order to reduce the risk of progression to acute

pyelonephritis and sometimes preeclampsia, and fetal consequences, like preterm birth and intrauterine growth restriction (2).

Aim of study was to make an epidemiological profile of UTIs, regarding their clinical manifestations, risk factors and specific aetiology, on a group of patients hospitalized in Constanta County Emergency Clinical Hospital in a well-established period of time. Association of clinical forms with the trimester of pregnancy and maternal hydronephrosis was followed, in order to guide physicians in their decision of adequate management and possibly prediction of a successful pregnancy.

Material and methods

We used a prospective and descriptive plan, aiming to analyse simultaneously several predominant features of urinary tract infection in pregnancy. Data were collected from blood and urine samples, as well as data obtained by ultrasonography, performed on 175 patients who were hospitalized between 01.05.2017-01.05.2021 in the Nephrology Clinic and Obstetrics-Gynecology Clinics of the Emergency Clinical County Hospital of Constanta. Some women needed reassessments during the same hospitalization, due to their evolution burdened with complications. All informations were carefully retrieved and recorded in the database, which included demographic (pregnancy age, patient age, personal pathological history), and clinical-biological and imaging data (ultrasonography), positive diagnosis, therapeutical measures, and maternal and fetal complications and outcomes.

Inclusion criteria

- Pregnant patients with specific symptoms of urinary tract infections at any level (asymptomatic bacteriuria, acute cystitis, recurrent urinary tract infections, acute pyelonephritis);
- Age over 16 years.

Exclusion criteria

- Pregnant women whose medical records did not contain the required determinations for the database;
- Patients with lumbar pain with vertebral origin.

The necessary information for the clinical and epidemiological study was recorded according to the request from the patient's standard file entitled "Study sheet of the particularities of urinary tract infections in pregnant women". Due to its size the specific questionnaire could not be included in this article, but only the final results of collecting data. A clinical-biological evaluation and imaging was carried out, which consisted in the collection of blood and urine samples of general analyzes performed on pregnant women. The data were obtained using the medical documents of the patients and the medical IT system owned by SCJU Constanta in order to achieve the objectives in the present study.

Statistical analysis.

The required information for the clinical and epidemiological analysis was recorded and statistically processed in Microsoft Excel database, in order to create an optimal structure and obtain the necessary graphs. The results of the study were analyzed with the IBM SPSS Statistics 23 program with use of descriptive statistics, graphs and non-parametric statistical tests. The significance level was $\alpha = 0,05$.

Results

General characteristics of UTIs

Distribution of UTIs according to the trimester of pregnancy

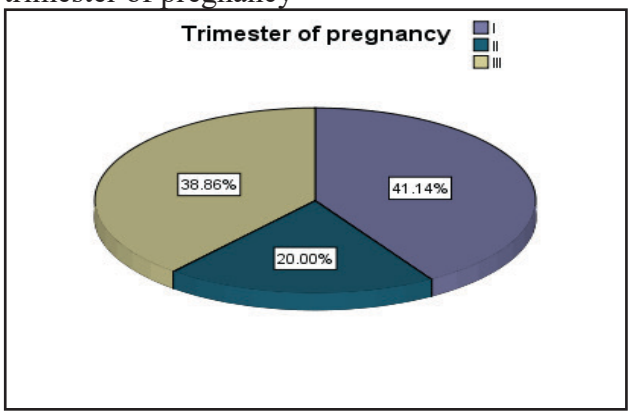


Figura 1. Pie Chart distribution of pregnant women with UTIs according to the trimester of pregnancy

From the total of 247 patients included in this study, 175 (70.85%) had at least one episode of UTISwith different clinical forms. Their distribution by trimester of pregnancy was as

follows: 72 pregnant women in the first trimester (41.14%), 35 in the second trimester (20.0%) and 68 in the third trimester (38.86%) (Figure 1).

Risk factors associated with UTIs

From the total number of 175 patients, 123 (70.29%) of pregnant women had favorable conditions and detectable risk factors such as ureterohydronephrosis (UHN), kidney stones, polycystic kidney disease, simple kidney cysts, chronic pyelonephritis and diabetes. The frequency of risk factors are represented in Figure 2 and Table 1.

Table 1. Risk factors associated with UTIs in the study group

Risk factor	Frequency	%
Hydronephrosis (UHN)	92	52.57%
Kidney stones	67	38.29%
Polycystic kidney disease	6	3.43%
Simple kidney cysts	19	10.86%
Chronic pyelonephritis	4	2.29%
Diabetes mellitus	2	1.14%

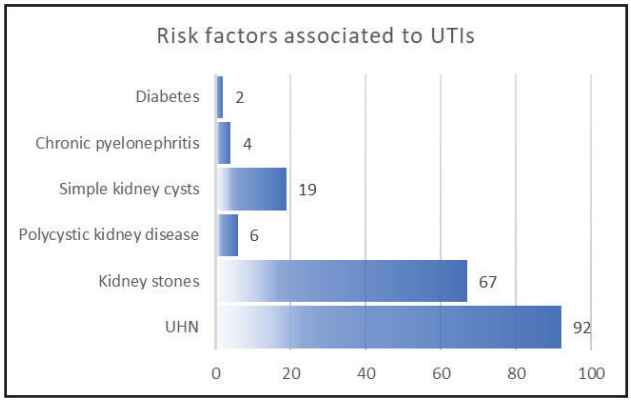


Figure 2. Bar Chart distribution of pregnant women depending on associated risk factors

Clinical manifestations of UTIs

The clinical manifestations of UTIs in our study group were distributed as follows : 36 (20.57%) had asymptomatic bacteriuria, 56 (32.0%) acute cystitis, 44 (25.14%) recurrent lower urinary tract infections, and 39 (22.29%) acute pyelonephritis (Figure 3).

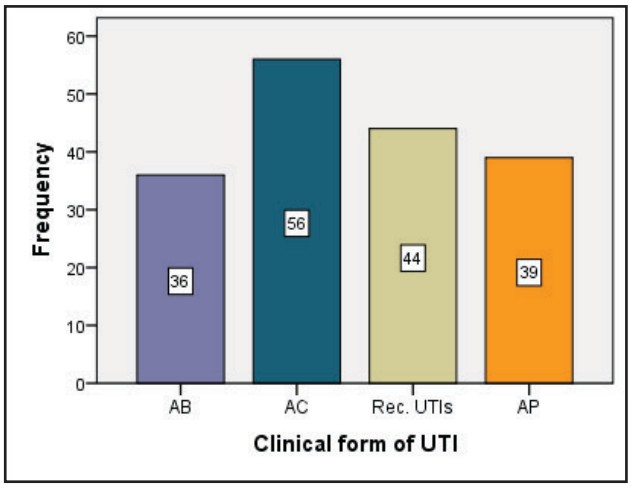


Figure 3. Clinical manifestations of UTIs in the study group

Association between clinical forms of UTIs and the trimester of pregnancy

The clinical forms of UTIs in pregnant women from the studied group could be distributed, depending on the trimester of pregnancy, as follows:

Asymptomatic bacteriuria (AB): 16 (44,4%) cases in the first trimester, 6 (16,7%) cases in the second trimester and 14 (38.9%) cases in the third trimester from the total of 36 pregnant women with AB;

Acute cystitis (AC): 43 (76.9%) cases in the first trimester, 7 (12.5%) cases in the second trimester and 6 (10.7%) cases in the third trimester from the total of 56 pregnant women with AC;

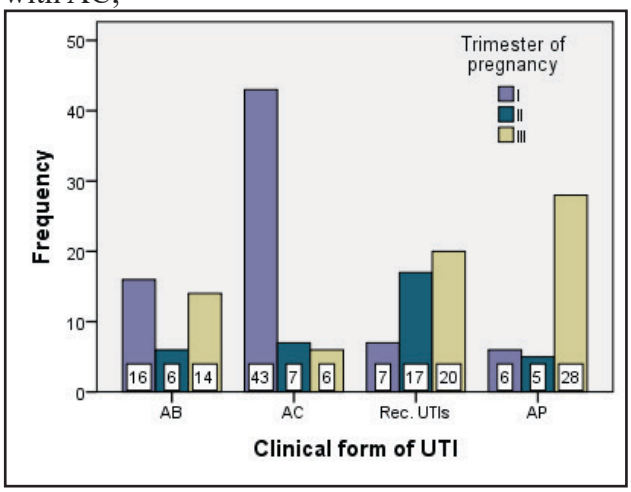


Figure 4. Distribution of clinical forms of UTIs depending on trimester of pregnancy in the study group

Recurrent lower UTIs (Rec. UTIs): 7 (15.9%) cases in the first trimester, 17 (38.9%)

cases in the second trimester and 20 (45.5%) cases in the third trimester from the total of 44 pregnant women with recurrent lower UTIs,

Acute pyelonephritis (AP): 6 (15.4%) cases in the first trimester, 5 (12.8%) cases in the second trimester and 28 (71.8%) cases in the third trimester, from the total of 39 pregnant women with AP (Figure 4).

The results showed an association between clinical forms of UTIs and trimester of pregnancy: $\chi 2calc = 63.70$, $df = 6$, $p < 0.001 < \alpha = 0.05$ (CHI-squared Test for association).

Table 2 Association between clinical forms of UTIs and the trimester of pregnancy

Clinical form of UTIs	Trimester of pregnancy			Total
	I	II	III	
AB (no. Pregnant women) % trimester of pregnancy	16 22,2%	6 17,1%	14 20,6%	36 20,6%
AC (no. Pregnant women) % trimester of pregnancy	43 59,7%	7 20,0%	6 8,8%	56 32,0%
Rec. UTIs (no. Pregnant women) % trimester of pregnancy	7 9,7%	17 48,9%	20 29,4%	44 25,1%
PA (no. Pregnant women) % trimester of pregnancy	6 8,3%	5 14,3%	28 41,2%	39 23,3%
Total	72 100%	35 100%	68 100%	175 100%

According to the results presented in Table II, we state the following:

The proportion of patients with AC in the first trimester , 59.7% (43) from the total of 72, is significantly different from the proportion of patients with AC in the second trimester, 20.0% (7) from the total of 35 ($p<0.001$), while the proportion of patients with AC in the second trimester, 20.0% (7) from the total of 35 is not significantly different from the proportion of patients with AC in the third trimester, 8.8% (6) from the total of 68 ($p> 0.05$).

The proportion of patients with recurrent lower UTIs in the first trimester, 9.7% (7) from the total of 72 is significantly different from the proportion of patients with recurrent lower UTIs in the second trimester, 48.6% (17) from the total of 35 ($p<0.001$), respectively the proportion of the patients with recurrent lower UTIs in the second trimester 48.6% (17) from the total of 35 is significantly different from the proportion of patients with recurrent lower UTIs in the third trimester , 29.4% (20) from the total of 68 ($p=0.0257 < 0.05$).

The proportion of patients with AP in the first trimester, 8.3% (6) from the total of 72 is not significantly different from the proportion of the patients with AP in the second trimester 14.3% (5) from the total of 35 ($p=0.535 > 0.05$) respectively the proportion of the patients with AP in the second trimester 14.3% (5) from the total of 35 IS significantly different from the proportion of patients with AP in the third trimester 41.2% (28) from the total of 68 ($p=0.01 < 0.05$).

The clinical forms of UTIs in pregnant women from the studied group had the following distribution according to the presence of UHN:

AB: 14 (38.9%) cases with UHN, respectively 22 (61.1%) without UHN from the total of 36 with AB;

AC: 13 (23.2%) cases with UHN, 43 (76.8%) cases without UHN from the total of 56 with AC;

Recurrent lower UTIs: 37 (84.1%) cases with UHN, 7 (15.9%) cases without UHN from the total of 44 with recurrent lower UTIs;

AP: 28 (71.8%) cases with UHN, 11 (28.2%) cases without UHN from the total of 39 with AP. (Figure 5).

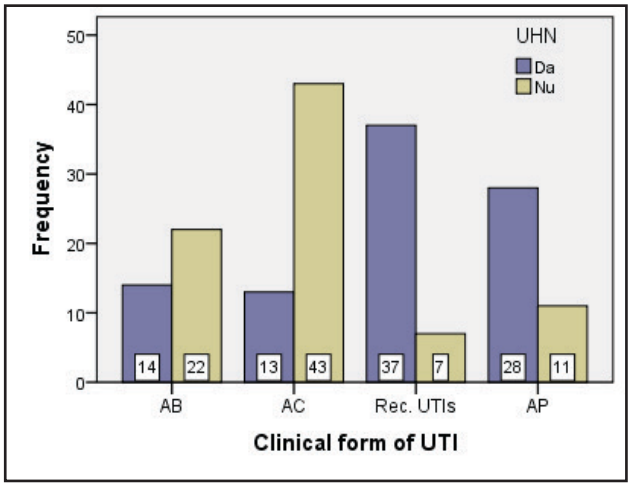


Figure 5. Distribution of clinical form of UTIs association with UHN

The results showed an association between UTIs and UHN: $\chi 2calc = 45.37$, $df = 3$, $p < 0.001 < \alpha = 0.05$ (CHI-squared Test for association).

In accordance with the results from the table III, we state the following:

The proportion of patients with AB who associated UHN, 15.2% (14) from the total of 92 does not differ significantly from the proportion of patients with AB who did not associate UHN, 26.5% (22) from the total of 83 ($p = 0.097 > 0.05$).

The proportion of patients with AC associated with UHN, 14.1% (13) from the total of 92 differs significantly from the proportion of patients with AC who did not associate UHN, 51.8% (43) from the total of 83 ($p < 0.001$).

The proportion of patients with recurrent lower UTIs who associated UHN, 40.2% (37) from the total of 92 differs significantly from the proportion of patients with recurrent lower UTIs who did not associate UHN, 8.4% (7) from the total of 83 ($p < 0.001$).

The proportion of patients diagnosed with AP who associated UHN, 30.4% (28) from the total of 92 differs significantly from the proportion of patients with AP who did not associate UHN, 13.3% (11) from the total of 83 ($p = 0.011 < 0.05$).

Tabel III. Association between clinical form of UTIs and UHN

Clinical forms of UTIs	UHN		Total	p
	yes	no		
AB (no. of patients) % from UHN	14 15,2%	22 26,5%	36 20,6%	> 0.05
AC (no. of patients) % from UHN	13 14,1%	43 51,8%	56 32,0%	< 0.001
Rec. UTIs(no.of patients) % from UHN	37 40,2%	7 8,4%	44 25,1%	< 0.001
AP (no. of patients) % from UHN	28 30,4%	11 13,3%	39 22,3%	< 0.05
Total (no. of patients) % from UHN	92 100%	83 100%	175 100%	

Etiology of UTIs in the study group

Regarding the etiology, the germs involved in the study group UTIs had the following distribution: Escherichia Coli -73 (41.71%), Klebsiella pneumoniae -32 (18.29%), Enterococcus faecalis -22 (12.57%), Proteus mirabilis -12 (6.86%), Staphylococcus aureus -6 (3.43%) and unidentified germs (sterile urine culture) but with symptomatic UTIs- 30 (17.14%) (Figure 6).

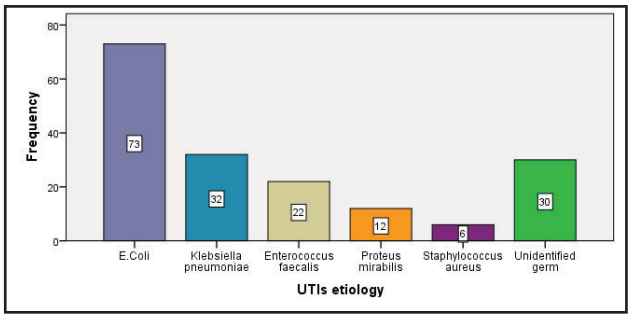


Figure 6. Etiology distribution in UTIs during pregnancy

Treatment of UTIs in pregnant women from our study group

The therapy administrated for UTIs in our study group included : antibiotic, adjuvant and symptomatic therapy, selected from a range of safe drugs during pregnancy. Antibiotic therapy used included : Ampicillin (60 patients - 34.29%), Amoxicilline + Clavulanic Acid (18 cases -10.29%), Cephalosporins (74 cases-42.29%), Quinolones (11 cases-6.29 %) and Nitrofurantoin (12 cases-6.86%) (Figure 7).

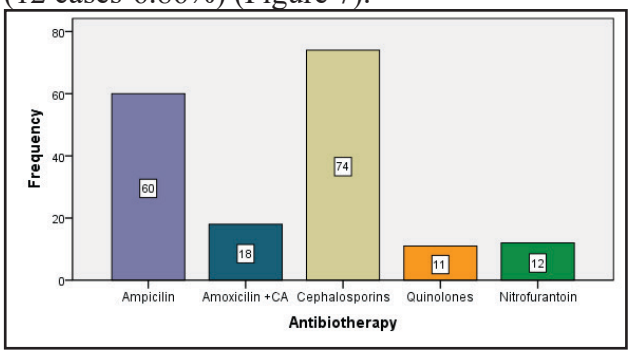


Figure 7. Antibiotics used in UTIs of pregnant women from studied group

Adjuvant therapy has been used in 141 patients (80.57% women), and was represented by supplements with D-mannose and cranberry extract which has demonstrated their efficacy in decreasing the recurrence of UTIs.

From the total of 175 pregnant women with UTIs, there were 10 patients (5.71%) who had an unfavorable evolution, so they required the association of carbapenems (Meropenem). The recurrence rate of UTIs was 22.28% (39 of 175 pregnant women).

The duration of antibiotherapy was correlated with the clinical form, as follows:

AB: oral antibiotherapy 5 days (26 cases) and 7 days (10 cases)

AC: oral antibiotherapy 5 days (36 cases)

and 7 days (20 cases)

AP: intravenous antibiotherapy 14 days (32 cases) or 21 days (7 cases)

Rec. UTIs: oral antibiotherapy 7 days (17 cases) or 10 days (27 cases).

Evolution of UTIs in the study group

Among the 175 patients included in our study, 165 (94.28%) of pregnant women had a favorable clinical evolution with the remission of symptoms; in these situations the therapy was carried out respecting the spectrum of sensitivity, in accordance with the result of antibiogram. The cases whose evolution was not favorable (with the persistance of fever and urinary symptoms) were those in which empirical antibiotic therapy was initially recommended, being considered lower UTIs (Cephalosporin) without prior performance of a urine culture with antibiogram. Due to unfavorable evolution, the cases represented by 10 pregnant women with APN (5.71%) required a switch in therapy to i.v. amoxillicin+clavulanic acid, respectively meropenem. The oral administration of antibiotic therapy was preferred in the treatment of AB, AC and recurrent lower UTIs, but in the case of AP the administration was always parenteral, at least until 48 hours after fever disappearance. Apart from the cases of APN, in which the cephalosporin was changed to meropenem, the other cases received monotherapy with ampicilin, amoxicilin+clavulanic acid, cephalosporins, quinolones or nitrofurantoin. All pregnant women had their urine culteres repeated 7-10 days after the use of antibiotic. The recurrence rate was 22.28% (39 from the total of 175 pregnant women).

Complications of UTIS during pregnancy

Complications in our studied group were detected in 10 pregnant women with upper urinary tract infections (5,71%), especially in those with acute pyelonephritis.

Maternal complications were represented by acute kidney injury (AKI) in 7 cases, one of which ended with death of the pregnant woman due to septic shock, and 3 cases with exacerbation of chronic kidney disease, the basic renal pathology being chronic pyelonephritis (1 case with CKD progressing irreversibly from stage G2 to G3b) and diabetes mellitus. All of the 3 cases evolved to urosepsis, 2 of which ended in death. The rest of the pregnant women with AKI had ureteral lithiasis (3 cases), the clinical form involved being acute pyelonephritis.

Fetal complications accounted for 6.85% (12 cases) of the total number of cases included in the study. Regarding the association between complications and the clinical form of UTI, from the 39 pregnant women with acute pyelonephritis, prematurity was present at 20.5% (8/39 cases) and intrauterine growth restriction at 10.2% (4/39 cases).

Mortality in the study group with UTIs was 1.71% (3 cases) by toxic-septic shock and disseminated intratravascular coagulation.

Discussion

The most obvious physiological change during pregnancy is represented by the increase in the glomerular filtration rate starting with 10-12th week of pregnancy, which can be associated with hormonal changes that produce the relaxation of the smooth muscles leading to the dilation of the urinary tract and urinary stasis increasing the vesicoureteral reflux. All these changes are predisposing factors for urinary tract infections (UTIs), commonly seen during pregnancy.

In the present study, the highest frequency of UTIs was observed in the first (41.41%) and third trimester (38.86%) of pregnancy, this had a direct connection with risk factors specific to pregnancy (hormonal changes, ureterohydronephrosis and urinary stasis), as well as the associated underlying pathology (associated comorbidities and favorising conditions). Their particularities were reviewed in the present study, 70.29% of the 175 pregnant women associated conditions and associated comorbidities such as kidney stones, kidney cysts, diabetes and chronic kidney diseases (chronic pyelonephritis).

In the study group, the most common risk factor encountered during pregnancy, after urinary stasis (52.57%), was kidney stones (38.29%). There is a bilateral relationship between UTIs and nephrolithiasis, as stones can influence the development of urinary infections, they can also be seen to cause the appearance of struvite stones. Kidney stones can create a favorable environment for bacteria leading to UTIs (3,4). Data from the literature suggests

that the most common composition of stones in pregnancy is calcium phosphate, in contrast to non-pregnant women, in whom calcium oxalate predominates(5).

Depending on the frequency, the next risk factors involved in the occurrence of UTIs in pregnancy in our study group, after renal lithiasis, were represented by simple renal cysts and autosomal dominant polycystic kidney disease, with a frequency of 13.91% of pregnant women (19 cases - renal cysts simple, 6 cases - autosomal dominant polycystic kidney disease (ADPKD). It is estimated that 30-50% of cases of ADPKD will be complicated with urinary tract infection during pregnancy, intracystic infection being the most common complication of polycystic kidney disease, which can cause perinephric abscess and bacteremia (6,7). Intracystic infection in pregnant woman should be considered in the presence of acute lumbar pain and fever, which can be the result of an ascending infection, propagated along the urinary tract to the renal parenchyma (8) or even hematogenous infection, in the absence pyuria (9)

In addition, diabetes mellitus may be an important risk factor for urinary tract infections (10,11) our study included only one pregnant woman with diabetes. The prevalence of urinary tract infections in non-pregnant women is 3–10%, while in pregnant women it can reach 27% (12,13). In addition to specific changes of pregnancy, the predisposition to diabetes is due to suppression of the immune system and the presence of factors such as glycosuria and bacterial adhesion to the urothelium (14).

Urinary tract infection during pregnancy takes multiple clinical forms, starting from asymptomatic bacteriuria to acute pyelonephritis or recurrent infections. In the study group, the most common cases were acute cystitis (32.0% - 56 pregnant women), followed by recurrent lower urinary tract infections (25.14% - 44 pregnant women), acute pyelonephritis (22.29% - 39 pregnant women) and asymptomatic bacteriuria (20.57%- 36 pregnant women).

The distribution of pregnant women with recurrent lower UTIs depending on trimester of pregnancy reached the highest values in the 2nd and third 3rd trimester (38.9%, 17/44; respectively 45.5%, 20/44). Analyzing a possible association of recurrent lower UTIs with the trimester of pregnancy, it can be concluded that the proportion of the 3 groups were significantly different ($p > 0.05$) with the dominance of the proportion in the 2nd trimester (48.9%, 17/35) compared to the first and the 3rd trimester (9.7%, 7/72 and 29.4%, 20/68 respectively). AP had the highest frequency in the third trimester of pregnancy (71.8%, 28/39. Analysing a possible association between the occurence of acute pyelonephritis and the trimester of pregnancy, it was shown that the proportion of those in the third trimester is the highest (41.2%, 28/68), being significantly different ($p = 0.01 < 0.05$) from those in second trimester (14.3%, 5/35). The proportion of pregnant women with acute pyelonephritis between the first two trimesters were not significantly different (8.3%, 6/72, respectively 14.3 5/35; $p = 0.535 > 0.05$).

Thus, in the present study, it can be observed that the most severe clinical forms of UTIs (AP and recurrent lower UTI) have a predisposition to develop in the second part of pregnancy, the proportion being significantly different from those in the first part of pregnancy. This phenomenon is explained in the literature data by the peak of urinary stasis and accentuated immunological changes during this period of pregnancy (15). AP is more common in the end of pregnancy and is usually the consequence of an undiagnosed and inadequately treated asymptomatic bacteriuria The incidence of AP reaches 2% of all pregnancies (compared to 1% of the general population) (16). Analyzing the association of acute cystitis with the trimester of pregnancy, the proportion of pregnant women in the first and second trimester was significantly different ($p < 0.001$), the group in the first quarter having a higher proportion than in the second trimester (59.7%, 43/72; respectively 20.0%, 7 / 35). On the other hand, the proportion of acute cystitis in the last two trimester was low, the two groups not being statistically significantly different (20.0%, 7/35, respectively 8.8%, 6/68, $p > 0.05$).

Thus, from research data of our study group, it was concluded that AC is more frequent in the first part of pregnancy, most likely due to the hormonal changes that occurred at the beginning of it (increased levels of progesterone,

estrogen), the reduction of urinary acidity, the increase glycosuria (17). Therefore, it is recommended that all pregnant women perform urinary infection screening in the first part of pregnancy for identifying early asymptomatic bacteriuria and acute cystitis, in order to treat and reduce maternal and fetal risk (18).

From the total of 39 pregnant women with AP, 71.8% (28) had associated UHN; and of the 44 patients with recurrent lower UTIs, 84.1% (37) pregnant women had associated UHN. Analyzing the association between the clinical form of UTIs and UHN, it shows that the proportion of pregnant women with AP and recurrent lower UTIs that have associated UHN was significantly different from those that did not have UHN ($p < 0.001$), the dominant proportion being in those that associated UHN. AC does not seem to be influenced by the presence of UHN, the proportion of the pregnant women who did not have UHN was higher than the group that presented UHN, being significantly different (51.8%, 43/83, respectively 14.1% 13/92, ($p < 0.001$).The groups with AB were not significantly different ($p > 0.05$) demonstrating that there is no association between AB and UHN.

It was concluded that there is an association between the clinical form (PNA, recurrent low UTIs) and the presence of UHN (anatomical change involving urinary stasis). The pyelo-calyceal system in pregnancy, due to UHN, will collect approximately 200-300 ml of urine responsible for urinary stasis increasing the risk of acute pyelonephritis in pregnant women by 40% compared to non-pregnant women (19). Data from the literature confirms that upper urinary tract infection in pregnancy is due to vesico-ureteral reflux and UHN specific to pregnancy, these being more obvious on the right side in the second part of pregnancy (15,17). Our data may advance the idea that UHN would influence the occurrence of recurrent lower UTI, but also of AP, these data are also found in the specialized literature data (20).

The precise detection of uropathogens in pregnancy is extremely important in order to optimize of antibiotic therapy used in the empiric treatment of urinary infections (21). There are various studies related to the most common microorganisms present in pregnancy, most of them indicating an increased frequency for E. Coli, the same increased frequency being found in non-pregnant women (22,23). In our study, E. Coli was present in 41.71% of pregnant women. Other microorganisms involved in the development of UTIs in the studied group were: Klebsiella pneumoniae, Enterococcus faecalis and, less frequently, were Staphylococcus aureus and Proteus mirabilis. Thus, Klebsiella pneumoniae was detected with an increased frequency (21.5 % of pregnancies with asymptomatic bacteriuria) (24–27). Enterococcus faecalis is a germ reported to be less frequent in pregnant women (28), but in our study it ranked third in frequency, after E. Coli and Klebsiella pneumoniae, with a frequency of 12.57% (22 patients). The lowest frequency in the study group was reached by Proteus mirabilis and Staphylococcus aureus (6.86%% and 3.43%, respectively). There were also pregnant women with UTIs in which the germ was not identified (17.14%), often due to the initiation of antibiotic therapy before collecting the urine sample.

Once the clinical form and etiopathogenesis are established (at least predictable until the urine culture results), the most appropriate therapeutic scheme should be initiated. Because of the potential risk to mother and fetus, initiating effective treatment of UTIs is an important clinical issue. It is advisable, as a first line, to assess risk factors for UTIs, given that some diagnostic imaging procedures are not advisable during pregnancy. If possible, any antibiotic use should be avoided in the first trimester because organogenesis and development of the nervous system occur during this period, and there is an increased risk of teratogenic effects.

In addition to maternal and fetal safety, during pregnancy there are physiological changes that can cause pharmacokinetic changes, with an impact on the efficiency of antibiotic therapy (29). Total water volume, blood volume, and plasma volume increase by up to 40%, thus contributing to the increased volume of distribution of antibiotics. Due to hypersecretion of progesterone during pregnancy, renal plasma flow and glomerular filtration rate will increase, leading to increased renal excretion of antibiotics.

In the case of 10 (5.71%) pregnant women with upper UTIs under antibiotic therapy, they presented severe clinical evolution requiring the

replacement of antibiotics with carbapenems, such as meropenem. According to the FDA (Food Drug Administration 2014), most antibiotics used in the study group are considered to be category B, with the exception of quinolones which are category C.

The antibiotics with the highest frequency of use in pregnant women in the study group were those from the group of cephalosporins (ceftriaxone, cefuroxime, cefixime, etc.) (42.29%), followed by ampicillin (34.29%); and less used were amoxicillin with clavulanic acid (10.29%), quinolones - in the last trimester of pregnancy (6.29%) and nitrofurantoin (6.86%). Adjuvant therapy was administered in 80.57% of cases (141 pregnant women), these being natural products that have safety studies during pregnancy (cranberry or blueberry extracts, methylene blue, D-mannose, etc.) demonstrating a decrease in the recurrence of infections (30). In the case of 10 (5.71%) pregnant women with upper UTIs under antibiotic therapy, they presented severe clinical evolution requiring the replacement of antibiotics with carbapenems, such as meropenem. According to the FDA (Food Drug Administration 2014), most antibiotics used in the study group are considered to be category B, with the exception of quinolones which are category C (31).

Penicillins have a long experiences research data of maternal and fetal safety, with ampicillin and amoxicillin having the strongest safety data (31). Cephalosporins have a documented history of use in pregnancy and remain a first-line option for many infections during pregnancy, particularly in penicillin-allergic patients (32). They have low plasma concentrations in pregnant patients due to increased renal elimination, requiring, as in the case of ampicillin, an increase of doses (33). Quinolones are usually avoided during pregnancy due to the increased affinity for bone tissue and cartilage described in animals (34), although there are studies that have shown no significant risk of cartilage damage in children (35). Data in the literature are not yet enough for their routine use during pregnancy, recommending their use only in cases where there is no other alternative (36). Of the carbapenem category, meropenem and doripenem are considered to be category B according to the FDA, while imipenem is considered category C (37). In the study group, carbapenem therapy was reserved for pregnant women whose infections were resistant to initial antibiotic therapy and whose clinical and biological evolution was unfavorable. The contraindicated antibiotics during pregnancy are tetracyclines, sulfonamides, aminoglycosides, rifampicin, chloramphenicol. Antibiotics that should be avoided or prescribed with caution are gentamicin or tobramycin, which are ototoxic and can only be used in multiresistant infections with Gram-negative bacteria(38).

According to the CDC (Centers for Disease Control and Prevention) guidelines revised in 2010 and approved by ACOG (American College of Obstetricians and Gynecologists) and AAP (American Academy of Pediatrics) (39) they recommend the initiation of oral or parenteral antibiotic therapy in all asymptomatic and symptomatic pregnant women to reduce maternal and fetal risks. AB and AC have similar treatment indications in terms of duration of short-term and oral administration (5-7 days), with a tendency to be administered for a longer period in case of AC, and for AP it is recommended to initiate intravenous treatment, with long-term administration (10-14 days), ideally the treatment should be based on microbial sensitivity testing (40).

Most of the pregnant women in the studied group (94.28%, 165/175) have had remission of fever within 24-48 h of using appropriate antibiotic therapy, according to the antibiogram, data that can also be found in previous studies published in the specialized literature (41). Although hospitalization is often recommended for the AP in pregnant women, it is not always necessary, as it is indicated for women with vomiting, intense dehydration syndrome, signs of urosepsis or imminent miscarriage. The present study demonstrated a slightly lower recurrence rate (22.28 %, 39/175). In other countries, the risk of UTIs recurrence was reported to be present in approximately one third of cases (42). AP requires early initiation of aggressive treatment in order to prevent complications, and initial treatment failure is often caused by increased resistance of the involved. Microorganism. Mortality in our study

group was 1.71% (3 cases) being represented by cases with AP that did not respond to treatment, with evolution towards toxic-septic shock and disseminated intravascular coagulation (DIC).

According to data from the literature data, fetal complications associated with pyelonephritis cause prematurity and intrauterine growth retardation (43). The frequency of prematurity due to AP in the present cohort was 20.5% (8/39 cases). Sharma and Thapa (44) reported an incidence of prematurity of 7% and an incidence of intrauterine growth retardation of 14%. Studies conducted in the United States have also confirmed the association of pyelonephritis with an increased rate of prematurity, suggesting a frequency higher than 50% [68]. In the present study, the frequency of intrauterine growth retardation was 10.2% of AP cases (4/39), relatively low compared to other studies, with Sharma et al (44) reporting an incidence of 13.8%.

Maternal and neonatal complications of urinary tract infections during pregnancy can be devastating: 30% of pregnant women with untreated AB may develop acute cystitis and up to 50% AP (43). By screening and aggressively treating pregnant women with AB, a significant decrease in the incidence of AP (45) and low birth weight or prematurity can be achieved (46).

Unfortunately, the available data is often limited. The development of new recommendations requires thorough, well-planned studies that answer the still unresolved questions regarding the frequency of screening and follow-up examinations, the objectivity of prophylaxis, the safety of studies on antibiotics used during pregnancy, and the choice of optimal therapy.

Conclusions

Lower urinary tract infections associated with pregnancy are a common pathology and the most frequent conditions favoring UTIs is represented by maternal hydronephrosis and renal lithiasis. All clinical forms of UTIs could be present during pregnancy, but the most common are lower urinary tract infections and the most involved germs E. Coli. The clinical form is influenced by the trimester of pregnancy, acute pyelonephritis being more frequent in the third trimester, and acute cystitis in the first trimester. The basic treatment of UTIs is antibiotic therapy and the most used antibiotics are still ampicillin and cephalosporins. Maternal and fetal complications are frequently associated, usually with AP. All pregnant women should be tested for UTIs and urine culture can be included in the screening analyzes from the beginning of pregnancy, remaining the gold standard in the diagnosis and subsequent treatment of UTIs according to the antibiogram. A multidisciplinary team of nephrologists and gynecologists is needed to successful pregnancy, together with the direct decisional involvement of the patient and family members.

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