INFECTIONS OF THE URINARY SYSTEM AT PREGNANCY
ИНФЕКЦІЇ СЕЧОВОЇ СИСТЕМИ ПРИ ВАГІТНОСТІ

Methodical instructions for students and interns
Методичні вказівки для студентів та інтернів

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INTRODUCTION

For the last decades the traditional perception of etiology and pathogenesis of infections of the urinary system (IUS) has considerably changed. Among factors which stipulate the development of IUS, the biological characteristics of microorganisms which colonize urinary tract are especially important. Urinary pathogenic features of some microorganisms explain the origin of infection in the normal urinary system. On the other hand, the non-urinary pathogenic cultures of bacteria cause inflammation in the presence of innate anomalies or due to the decline of protective forces of the organism, specifically at pregnancy.

The gram-negative flora (in about 80% patients) prevails among IUS pathogens. According to the data by different authors the second place is taken by Proteus mirabilis – 14–16%, Enterococci – 21% and Klebsiella pneumoniae – 12–15%. In case of uncomplicated IUS, E.coli, Proteus mirabilis, Klebsiella pneumoniae, S.saprophiticus, S.epidermidis prevail. In case of complicated IUS, E.coli, Klebsiella spp., Proteus spp., Pseudomonas spp., Serratia spp., Enterococcus spp, Staphilicoccus spp., Candida are prevalent.

During women’s pregnancy the spectrum of IUS agents is similar to pathogen flora at non-pregnancy. The majority of causally-meaningful IUS agents have fecal origin. Up to 75–80% cases of pyelonephritis are caused by Escherichia coli, the percentage of intestinal bacillus not exceeding 40–60% among the nosocomial pathogens. Klebsiella pneumoniae, Klebsiella oxytoca, Serratia spp., Citrobacter spp., Enterobacter spp. and Proteus spp. are found most frequently among other fermentative gram-negative aerobic bacteria. Staphylococcus and streptococcus infections make 5–20% according to the world data. The increase in yeast-like fungus occurrence is possible at pregnancy. At the same time Pseudomonas aeruginosa and other non-fermentative gram-negative aerobic bacilli are not so frequent in comparison with the data in the group of non-pregnant female patients after surgery on urogenital tract. Among other microorganisms entercoccus is found, particularly in the hospitalized female patients (up to 23%).

The results of the research show that the regional structure of causally-meaningful IUS agents in pregnant is characterized by the variety of aerobic bacteria. To a great extent these data go along with findings across the world. Among uropathogens the most common is the family of enterobacteria (58%), including colon bacillus which is inoculated approximately in the half of cases (47%). The whole number of gram-positive aerobic cocci is increased, mostly due to enterococci (12%). The change of microflora is likely linked to the protracted course of therapy for patients with current pregnancy under hospital conditions.

Undoubtedly, the urogenital infection is a ponderable factor in the development of women renal pathology, and the frequency of this condition during the reproductive age is well known. Less than 50% women with the chronic pyelonephritis have anamnesis which indicates that infection is indeed the cause of disease. The defects of development of kidneys and urinary tract (6–18% women), stones in kidneys and ureters (approximately 6%), vesicoureteral reflux at cystitis, inflammatory diseases of female reproductive organs, sexual activity, contraceptives intake, metabolic disorders, neurogenic urinary bladder and other are the high-risk factors of pyelonephritis.
The risk of urinary infection is higher in women with polycystic kidneys, sponge kidney, interstitial nephritis and other renal diseases. It is considered that the acute pyelonephritis in pregnancy is almost always aggravated by the latent chronic pyelonephritis. The urodynamics disorders caused by pregnancy (dilatation of the internal cavity system of kidneys) are instrumental in the origin of gestational pyelonephritis. We offer basic research methods recommended to be conducted in all pregnant with the inflammatory renal diseases; the additional methods should be applied based on special indications. The frequency of diagnostic tests is determined individually (Table 1).

Table 1

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<td>• biochemical test of urine (day’s excretion of albumins, oxalates, urates, cystine,</td>
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<td>calcium salts; indexes of cytomembranes instability – ethanolamin, peroxides,</td>
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<td>1) blood test for presence of P-albumins, middle size molecules;</td>
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<td>4) testing of immune status (level of secretive ALP, state of phagocytosis) in</td>
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1. GESTATIONAL PYELONEPHRITIS

This inflammatory process can be observed both during pregnancy/parturition and after delivery, i.e. within the whole gestational period. Therefore, it is expedient to refer to the inflammatory process in kidneys and renal pelves as gestational pyelonephritis. The frequency of gestational pyelonephritis is between 3–10%. Pyelonephritis develops most frequently during pregnancy (48%), rarer after parturition (35%). Pyelonephritis is observed in 17% of parturient. The origin and development of gestational pyelonephritis is conditioned by two basic factors: urodynamics disorders of upper urinary tract and presence of infectious nidus in the organism.

The most frequent complications of pyelonephritis are late gestosis, miscarriage and intrauterine fetal infection. Acute renal insufficiency, septicemia and bacterial shock are also serious complications.

Gestational pyelonephritis is diagnosed more frequently during first pregnancy. This fact can be explained by the lack of adaptation mechanisms to the changes (immunological, hormonal, etc.) women are subjected to during gestational process. It is considered that pyelonephritis develops in many women in their childhood, the disease usually proceeding latently up to the beginning of so-called ‘critical moments’: menstrual function, sexual life, pregnancy, i.e. the periods when hormonal mismatches are highly expressed.

The pregnant with pyelonephritis are attributed to the high risk group. Pyelonephritis in pregnancy is diagnosed more frequently within 12–15th week, 24–29th week, 32–34th week, 39–40th week, as well as during post-natal period on 2nd–5th day or 10–12th day. Pyelonephritis in pregnant can develop first time or aggravate if a woman had the disease prior to pregnancy. Pregnant diagnosed with pyelonephritis should be hospitalized every time the disease aggravates, at appearance of symptoms of late gestosis, and worsening of fetus state (hypoxia or hypotrophy).

In the group of patients with gestational pyelonephritis a degree of risk depends on the disease duration and expressiveness of kidneys damage. Three degrees of risk are specified as:

- 1st degree of risk – uncomplicated pyelonephritis which develops during pregnancy;
- 2nd degree of risk – chronic pyelonephritis which existed prior to pregnancy;
- 3rd degree of risk – pyelonephritis with hypertension or azotemia; pyelonephritis of single kidney.

The infectious agents of gestational pyelonephritis are mainly (65%) microorganisms of enterobacteria group (intestinal bacillus, Klebsiella, Proteus) and enterococcus (23%). Intestinal bacillus is found more frequently in the urine of pregnant, while enterococcus is usually the most common pathogen in pyelonephritis development after delivery. Staphylococcus, Bacillus aeruginosa and other pathogens are not very common. At the first aggravation of pyelonephritis usually one agent is found in the urine, at protracted process there may be several pathogens. In some patients microflora of uterus cavity and urine is identical. Data by some authors confirm that microorganisms cultures which are inoculated from urine of patients with
gestational pyelonephritis appear resistant to wide number of antibiotics: streptomycin, tetracycline, laevomycetin and others. At the same time many microbial cultures remain sensitive to aminoglicosides: gentamicin, kanamycin and monomycin.

The primary nidus of infection, from where it spreads into kidneys, may be any festering-inflammatory process in the organism of woman. First of all, these are inflammatory processes in the genitals and urinary system organs, and also carious teeth, furuncles, etc. The ways of infection spreading into kidneys are different: haematogenic, urinogenic and others. Infecting takes place mainly by haematogenic way. Possibility of infectious agent passing into kidneys via lymphatic vessels is improbable, as in absence of inflammatory process in kidneys lymph flows out from kidneys rather than to kidneys direction. The retrograde current of lymph takes place only at lymphadenitis, i.e. in presence of inflammation. Urinogenic, ascending way of infection spreading into kidneys is possible only in presence of vesicoureteral reflux. This pathology, as a result of calyces vault damage, is instrumental in the passing of the infected urine directly into the blood current. After this the infectious agent returns via haematogenic way into interstitial tissue of kidney resulting in inflammatory nidus development.

Inflammatory changes in kidney, originally being a nidus process, gain diffuse character with every new attack. The damage of connective tissue of kidneys by inflammatory process leads to intercellular metabolic disturbance. As any inflammation, pyelonephritis develops first as serous and then as festering process. Seizure of inflammatory process does not result in natural renewal of connective tissue in kidney, and inflammatory nidi are replaced with scar tissue in interstice.

One of the main triggers, which are instrumental in disorders of urodynamics and hemodynamics of upper urinary tract in gestational period, is a change of hormonal balance in woman organism.

Gestational pyelonephritis takes place in either acute or chronic form. At aggravation of chronic pyelonephritis, the disease is considered to be an acute inflammation.

The basic characteristics of acute pyelonephritis in pregnant and parturient are:
- sudden outbreak of disease;
- temperature (39–40°C);
- pain in the lumbar region;
- common indisposition;
- headache;
- chills which are substituted for heavy sweat;
- adynamia;
- pain in whole body;
- intoxication.

The increase of pain in the lumbar area is explained by spreading of inflammatory process to the renal capsule and surrounding renal tissue. The pain is localized mainly along the ureter, urination is compromised, and the patient stays in a forced position on the side with bended lower extremities. Pasternatsky’s symptom is positive. Edema is not characteristic for this disease, diuresis is sufficient, arterial pressure
is normal. Leucocytes, erythrocytes, different cylinders and cells of epithelium are determined in urine sediment. Presence of cylinders indicates the damage of kidneys parenchyma. Nechyporenko’s test of urine reveals normal ratio of leucocytes and erythrocytes as 2:1 (4,000 leucocytes and 2,000 erythrocytes in 1 ml of urine which is a norm for pregnant).

Acute pyelonephritis in pregnant and parturient proceeds as a serious common infectious disease with the expressed intoxication of organism and presence of characteristic local symptoms, the latter is being less expressed in the parturient than in the pregnant. The general symptoms of serious infectious process prevail at the beginning of the disease while local symptoms may be absent completely or be expressed slightly. During the first days of illness chills are quite common, accompanied by the high body temperature, severe headache, dull ache in the whole body, as well as nausea, sometimes vomiting, with subsequent abundant perspiration and temperature decrease, sometimes to the normal indexes. Breathing and pulse is increased, tongue is dry. In intervals between chills patients are usually languid and adynamic.

In the process of disease development the local symptoms join gradually to the general ones. Local **symptomatology of gestational pyelonephritis** includes pain in lumbar region on the side of the damage, with the irradiation of pain into upper part of stomach, inguinal region, labia majora, and thighs. Sometimes pain is felt along the ureter. The increase of pain may indicate the spreading of inflammatory process into the renal capsule and surrounding renal tissue. The increase of hectic body temperature in patients at certain time intervals may be connected with the development of multiple festering nidi in kidney. In several days from the disease onset the pain is usually localized in the region of the damaged kidney. The pain increases at night, especially when patient is on her back or side opposite to affected kidney. Quite often pain appears or increases while patient breathes deeply or coughs.

At bimanual palpation on the affected side, tension of stomach muscles is felt with expressed painfulness: on the back side at the level of crossing of lower edge of XII rib with long lumbar muscles, and on the front, accordingly, in upper «urinary points» which are located at three transversal fingers to the left and to the right of navel. At some patients scoliosis towards the damaged kidney is present. Paster-natsky’s symptom is not always positive. Signs of peritoneal process are possible if festering process is localized on the front surface of kidney. During pregnancy similar localization of abscess may lead to the suspicion for acute cholecystitis or appendicitis. Differential diagnostics in such cases is quite difficult, as pathological changes in urine can be absent at the disease onset.

**The clinical picture of gestational pyelonephritis** in different periods of pregnancy has typical characteristics. They are conditioned by the degree of disorder of urine passage out of upper urinary tract. During first trimester of pregnancy the strong pain, similar to kidney colic, in the lumbar region irradiated into lower parts of stomach and external genitalia is noted. During second and third trimesters the pain is usually non-intensive. Only careful examination by doctor who focuses patient’s attention on the presence of pain in the lumbar region, in combination with
palpation and anamnesis allows suspecting a pathological process in kidney. It is explained by the fact that even considerably compromised passage of urine out of upper urinary tract does not cause noticeable increase of internal pressure in pelves, as pregnancy is accompanied by considerable dilatation of upper urinary tract. If in the second and third trimesters of pregnancy women with suspected pyelonephritis develop kidney colic, nephrolithiasis should be suspected.

Laboratory methods of testing are important in the diagnostics of pyelonephritis. In blood of patients with gestational pyelonephritis, leukocytosis higher than $11.3 \times 10^3$, change of leukocytal formula to the left due to increase of stabnuclear neutrophils, and hypochromic anaemia (haemoglobin below 100 g/L) are defined. It should be noted that anaemia takes place until the elimination of acute inflammatory process in kidneys.

Changes of urine composition and correct urine sampling are important for diagnostics. It is necessary to collect middle portion of urine after thorough toilet of external genitalia. Catheterization of urinary bladder in pregnant is not recommended without specific indications.

If pathological elements are identified in urine, the analysis should be repeated in two portions - the first and the second. The presence of leukocyturia only in the first portion of urine indicates the localization of inflammatory process in the urethra or the genitals. The increased amount of leucocytes in both portions of urine is a sign of inflammatory process in the urinary bladder or in the upper urinary tract. In such cases additional tests are required for identification of inflammatory process localization, possibly by sampling of urine from kidneys with catheter. Nechyporenko’s test has got advantages among the existing methods of quantitative analysis of urine sediment in pregnant and parturient. Recent years research shows that a presence of so-called active leucocytes in urine at qualitative analysis is not pathognomonic for pyelonephritis in general and to gestational pyelonephritis in particular. «Active leucocytes» are identified in the urine at festering-inflammatory processes of urinary tract, including inflammatory renal diseases. The amount of such leucocytes indicates only the activity of inflammatory process: the greater «activity» of leucocytes is the more acute inflammation takes place. Thus, the identification of «active leucocytes» in urine sediment, Sternheimer-Malbin cells, does not justify the diagnosis of pyelonephritis. In doubtful cases separate sampling of urine from ureters by their low catheterization (no more than 10 cm) should be conducted. The presence of the increased amount of leucocytes (Nechyporenko’s method) in the urine sample indicates pyelonephritis, and correlation of «active and non-active leucocytes» specifies its activity. Bacteriological test of urine is also required. It is known that bacteriuria is not equivalent to pyelonephritis and it may cease without causing inflammatory changes in kidneys. However, bacteriuria should not be treated as harmless phenomenon, especially if it is confirmed at repeated urine inoculation, when the amount of bacteria in 1 ml of urine equals or exceeds $10^5$ of microbial cells. Apart from quantitative determination of bacteriuria, identification of infectious agents and determination of their sensitivity to different antibiotics is required. It should be noted that presently bacteriuria does not always precede leukocyturia. It
can be partly explained by the fact that pregnant quite often take different antibiotics and other antimicrobial preparations without prescription.

At the suspicion of gestational pyelonephritis it is important to identify the degree of disorder of urine passing from upper urinary tract. During pregnancy the most acceptable method of diagnostics is chromocystoscopy, and at post-natal period is excretory urography.

Patients with pyelonephritis must be under careful supervision of obstetrician-gynecologist at maternity ward and urologist for the identification of early signs of pyelonephritis aggravation and late gestosis of pregnant. Both of these diseases should be treated in the hospital, because they may be complicated with bacterial shock, azotemia, eclampsia, etc.

The opinion regarding expedience of pregnancy termination with the purpose of liquidation of festering nidus in kidneys has to be critically assessed and revised. Festering-inflammatory process in kidneys even after pregnancy termination will progress and will require the application of the same complex of medical treatment as during pregnancy. That is why pregnancy should be maintained and treatment limited to rational therapy of pyelonephritis.

Bacteriuria is an important symptom at pyelonephritis. Zimnitsky’s analysis of urine shows that relative density is decreased and correlation of day and night diuresis is compromised with the latter being increased. These indicate the decline of renal concentration function. Leukocytosis, increase of stabnuclear neutrophils, decrease of haemoglobin are observed in hemogram of pregnant with pyelonephritis. In biochemical blood tests total amount of protein and protein fractions change due to the decrease of albumins.

During pregnancy pyelonephritis may aggravate sometimes by two or three times. But woman should be hospitalized every time aggravation takes place. The patients with 1st and 2nd degree of risk may be allowed to sustain pregnancy under permanent dynamic supervision by physician and nephrologist. For patients with 3rd degree of risk, pregnancy is contraindicated.

**Differential diagnostics** of pyelonephritis should be performed at acute appendicitis, acute cholecystisis, kidney and hepatic colic, and common infectious diseases. Differential diagnosis is difficult at nephropathy and hypertensive disease. Expressed proteinuria and changes of eye bottom (angioretinopathy, neuroretinopathy, hemorrhage and swollen retinas) indicate gestosis which considerably worsens the state of patients.

Pregnancy and labour in women with pyelonephritis have some specific characteristics. It is known that acute pyelonephritis which manifests for the first time during pregnancy does not substantially influence pregnancy development. At the same time quite often miscarriages occur in women with chronic pyelonephritis, and terminating of pregnancy takes place in middle terms (16–24 weeks).

Delivery at pregnant with acute pyelonephritis proceeds spontaneously. At chronic pyelonephritis, due to the development of late gestosis of pregnant, artificial delivery (15.9%) is frequently conducted. Thus, in large number of parturient (10.3%) the labour is induced medically.
The efficiency of treatment of patients with acute pyelonephritis depends mainly on timely restoring of the impaired outflow of urine. That is why catheterization of ureters is necessary, as all other treatment procedures (changes of body position, application of plant diuretic and antiseptic preparations) do not allow achieving required result. Active antibacterial therapy must precede the catheterization of ureters.

While treating acute pyelonephritis at pregnant it is necessary to remember that each aggravation and therapy negatively influence the development of fetus. That is why it is recommended to simultaneously control intrauterine state of fetus, and also conduct the prophylaxis of its hypoxia and hypotrophy. The effective therapy includes vitamins and also preparations which are instrumental in the improvement of uteroplacental blood circulation and normalization of microcirculation processes in kidneys.

**Treatment of gestational pyelonephritis.** The prophylaxis of gestational pyelonephritis is directed on recognizing of early signs of disease and prevention of its aggravation. During all pregnancy term dynamic supervision is required including urine testing (cytological and bacteriological) no less than once a fortnight, early identification of urodynamics disorders, and timely prescription of necessary therapy.

During pregnancy the treatment of pyelonephritis should be conducted taking into account the term (trimester), and in the postnatal period checking the possibility of medicinal preparations transferal into mother’s milk. In addition, the choice of antibacterial preparations doses should be made based on the information about total functional ability of kidneys. This should be assessed by the index of relative density of urine. At density of 1.018–1.020 it is possible to prescribe ordinary doses of antibiotics, at hyposthenuria doses of preparations must be reduced in 2–4 times in order to avoid accumulation and side effects. Treating pyelonephritis in pregnancy must be strictly individual taking into account tolerance to preparation, presence of allergic reactions in anamnesis, duration of kidney inflammatory disease and degree of complication.

Like any inflammation, gestational pyelonephritis causes considerable intoxication of organism. First of all, hypoproteinemia develops. That is why in complex therapy of pyelonephritis it is crucial to substitute protein deficit by transfusion of albumins and dry blood plasma. With the purpose of detoxication of such patients, intravenous drop administration of low molecular solutions (400 ml of hemodez, 200–300 ml of reopolyglukin) is prescribed. The indicated preparations have ability to improve toxins removal via kidneys, unblock reticuloendothelial system, and directly bind toxins. By liquidating erythrocytes stasis, which usually takes place during intoxication, these preparations reduce hypoxia of organs and tissues, improving renal function and increasing diuresis. Additionally, they are instrumental in passing of extracellular fluid to vascular channels which, in turn, leads to the increase of circulating blood volume and improvement of hemodynamics.

Antibiotics therapy of pregnant with acute pyelonephritis should be conducted in the hospital and begin with parenteral administration of preparations.

The recommended schemes:

**Scheme 1:** Amoxycillin/clavunulate: 1.2 g 3–4 times per day;
**Scheme 2:** Cefuroxime: 0.75–1.5 g 3 times per day or
Ceftriaxon: 1–2 g once per day;

**Alternative scheme:** Aztreonam: 1 g 3 times per day.

Duration of therapy should be no less than 14 days (5 days of parenteral administration of preparations, then per os). In the case of absence of clinical improvement during 48–72 hours from the therapy beginning the clarification of diagnosis is required with the purpose to exclude the possibility of urinary tract obstruction (catheterization of ureters or operative treatment of urolithiasis may be needed). The relapses of acute pyelonephritis at pregnant occur quite often (in 10–30%). That is why a prophylaxis should be the application of either suppressive therapy or testing of urine culture every 2 weeks until delivery time.

For treatment of gestational pyelonephritis foreign specialists recommend the followings schemes:

**Scheme 1:** Cefradin: 1 g intravenously for 3–5 days or
500 mg pill for 9-11 days;

**Scheme 2:** Cefuroxim: 750 mg intravenously for 3–5 days or
500 mg pill for 9–11 days;

**Scheme 3:** Cefalexin: 1 g intravenously for 3–5 days or
500 mg pill for 9–11 days.

Ampicillin is not recommended due to high resistance of the infectious agents cultures of urinary tract.

In the acute stage of disease the amount of liquid at the restored outflow of urine from the upper urinary tract may be increased up to 2.5–3 L per day (including transfusion therapy). During pyelonephritis aggravation and remission it is useful to drink fresh cranberry fruit drink, which contains a lot of benzoic acid sodium. Under the action of glycine enzyme in the liver this element turns into hippuric acid, which performs bactericidal function in kidney tissues.

In pregnant and parturient the signs of recovery from pyelonephritis include disappearance of clinical symptoms of disease, changes of laboratory indexes tested three times, absence of bacteriuria within 5–7 days after discontinue of antibacterial treatment. The longer pregnancy term is, the more important is the role of mechanical factor in the development of urinary tract obstruction. In connection with this, position therapy is applied, and if needed drainage of kidney is performed with special ureteral stent catheter. Infusive, spasmylytic, desensitizing, symptomatic therapy, and surgery are applied when based on the indications. Acute and aggravated pyelonephritis is not an indication to pregnancy termination, if the disease is not neglected and there is no terminal chronic renal failure or arterial hypertension.

### 2. CHRONIC PYELONEPHRITIS

During gestational process this disease is quite frequent phenomenon. However, it is necessary to note the tendency to over diagnose this disease. Minimal single changes of urine (insignificant leukocyturia) and unclear clinical picture cannot be indications for chronic pyelonephritis without further inquiry. Chronic pyelonephritis
is characterized by hypostenuria tested by Zimnitzky’s method in urine, which is observed in 56% of patients.

During pregnancy and in post-natal period chronic pyelonephritis often is a consequence of pyelonephritis which woman had in childhood. For a long time this disease proceeds latently, while gestational process triggers it. The symptomatology of chronic gestational pyelonephritis, as well as chronic pyelonephritis in non-pregnant women is various. It is explained by the degree of spreading of inflammatory process and presence of concomitant renal diseases (nephrolithiasis). Additionally, symptomatology depends on the characteristics of chronic pyelonephritis which may be accompanied by more or less frequent clinical aggravation or begin with acute attack. In any case, at every aggravation a woman should be hospitalized. In some cases the disease develops as a chronic process from the onset.

Anamnesis is an important factor for chronic pyelonephritis identification in pregnancy and after delivery. Carefully collected anamnesis indicates previously endured cystitis in 46–68% of patients with chronic pyelonephritis. The most frequent signs of chronic pyelonephritis is leukocyturia, pain in the lumbar region, high degree of bacteriuria, proteinuria, anaemia, which are identified with excretory urography. Chromocystoscopy reveals less frequent functional disorders. It is considered that diagnostics of chronic pyelonephritis should be based on at least 3–4 relevant clinical, laboratory, roentgenologic, and radioisotope indicators or periodically repeated disease aggravation.

Majority of women (86.8%) experience attacks of pyelonephritis within the second trimester of pregnancy (22–28th weeks), which is explained by considerable increase of glucocorticoids amount in the blood during this period. On the background of existing disorders of upper urinary tract urodynamics, glucocorticoids, on the one hand, are instrumental in the origin of so-called primary pyelonephritis, and on the other hand, can be biologically conditioned «prednisolone test» for the identifying of latent chronic pyelonephritis.

This disease is characterized by dull pain in lumbar region (which increases at motion and physical activity), headache, rapid development of fatigue, and general weakness. However, in most cases women have no complaints. Pasternatsky’s symptom is quite often positive. Hypochromic anaemia is determined in 16% of women. Urine tests reveal moderate proteinuria (less than 1 g/L or 1%), leukocyturia and microscopic hematuria. High blood pressure in the majority of patients is a consequence of chronic pyelonephritis. It should be taken into account that patients with mainly minor or medium chronic pyelonephritis are treated in the obstetric ward. These women have no azotemia and no signs of hypertension. Hypertensive syndrome is observed in such patients less often than in non-pregnant women treated in nephrological wards. At chronic pyelonephritis hypertension is often high, progressive and worsens considerably in 15–20% cases. Presumably, women with such heavy forms of disease either do not conceive, or pregnancy is terminated early.

At the final stage of chronic pyelonephritis, when shrinking of kidney takes place, the urinary syndrome is expressed insignificantly; clinical picture is characterized by hypertension and chronic renal insufficiency.
Diagnostics of chronic pyelonephritis in pregnant may be difficult. It is connected with the fact that during pregnancy it is not possible to apply the whole range of diagnostic methods. In particular, the roentgenologic methods cannot be used. That is why clinical, laboratory and endoscopic methods are instrumental in the diagnostics of pyelonephritis.

Treatment of chronic pyelonephritis is similar to treatment of gestational pyelonephritis.

3. ASYMPTOMATIC BACTERIURIA

The condition when many virulent microorganisms are detected in women’s urine without any clinical symptoms of urinary tracts infection is called asymptomatic bacteriuria. According to the data by different authors such cases are identified in 4.5–10% of pregnant. Asymptomatic bacteriuria is diagnosed in cases when 100,000 or more bacteria are detected in 1 ml of urine taken by a catheter. Intestinal bacillus, Klebsiella, enterobacteria, and Proteus is the most frequent infection.

Pregnant with asymptomatic bacteriuria should be carefully examined for identification of latent disease of the urinary system.

The clinical manifestation of urinary system infection and, first of all, symptomatology of acute pyelonephritis develop in 40% of pregnant with non-treated asymptomatic bacteriuria during the period of gestation. This substantially worsens maternal and perinatal prognosis. In the case of successful treatment of asymptomatic bacteriuria in pregnancy the frequency of pyelonephritis reduces substantially and the prognosis is more favourable both for mother and fetus.

The roentgenologic signs of chronic pyelonephritis often appear in pregnant with bacteriuria (8–33%), especially in cases with insignificant response to treatment. Higher rates of abortions and stillborns are found in pregnant with bacteriuria, and treatment of disease does not substantially influence this dependence. Neonatal death and stillborn rates increase in 2–3 times.

Apart from increasing possibility of pyelonephritis, bacteriuria in pregnancy is a risk factor for development of other unfavorable effects for mother and fetus. There are no scientific proofs that bacteriuria results in the development of anaemia, hypertension, preeclampsia, chronic diseases of kidneys, amnionitis and endometritis. However, higher rates of innate anomalies of urinary tract, nephrolithiasis, and dilatation of ureter are noted in women with bacteriuria. Moreover, the pregnant with asymptomatic bacteriuria show higher rates of spontaneous abortions, premature births, intrauterine delay of fetus growth and perinatal death.

The majority of pregnant with bacteriuria can be detected in the early terms of pregnancy at the first visit to the doctor, and only in 1% of women bacteriuria develops in later terms.

Treatment of bacteriuria in the early terms of pregnancy prevents development of 70–80% cases of pyelonephritis, and 5–10% of miscarriages. All pregnant with bacteriuria are subject to treatment. Single dose of preparation is not effective for treatment of asymptomatic bacteriuria at pregnancy. No preparation has advantages, and preparation for treatment is chosen empirically.
Bacteriuria treatment begins with a 3-day course of antibacterial therapy with subsequent monthly tests of urine culture as a control of possible disease relapse. At the repeated occurrence of bacteriuria (16–33%), supporting therapy is prescribed prior to the end of pregnancy and 2 weeks after delivery: a single intake of preparation in the evening after meal. It is recommended to prescribe supporting treatment based on the sensitivity of urine microorganisms to antibiotics.

Antibacterial therapy of infection in lower urinary tract in pregnant (asymptomatic bacteriuria and acute cystitis) is administered perorally in ambulatory conditions.

**Scheme 1:** Amoxycillin/clavulinate: 375 mg 3 times per day or 625 mg 2 times per day for 3 days;

**Scheme 2:** Cefuroxime acetyl: 250–500 mg 2 times per day for 3 days or Cefitiben: 400 mg once per day for 3 days;

**Scheme 3:** Fosfomycin trometamol: 3 g as a single dose;

**Alternative scheme:** Nitrofurantoin: 100 mg 4 times per day for 3 days.

In case of no effect from two successive courses of etiotropic antibacterial treatment, suppressive therapy is prescribed up to delivery + 2 weeks after labour. Any complicated forms of urinary tract infection, first of all obstructive uropathy, should be eliminated.

**Suppressive therapy:**
- Fosfomycin trometamol: 3 g every 10 days;
- Nitrofurantoin: 50–100 mg once per day.

For treatment of asymptomatic bacteriuria, European specialists recommend nitrofurantoin (100 mg/day for 7–10 days), sulfisoxazol (500 mg/day for 7–10 days) and cefradin (500 mg/day for 7–10 days), cefalexin (500 mg/day for 7–10 days).

For treatment of asymptomatic bacteriuria and uncomplicated cystitis in pregnancy, the following preparations can be used as "first line" defense: amoxicillin, nitrofurantoin, cefalexin, amoxicillin/clavulan acid, or trimetoprim/ sulfametoksazol. Their application is shown below:

**Amoxicillin:**
- 200 mg as a single dose;
- 500 mg – 3 times per day – 7 days (SoluTab form: 750 mg 2 times per day);
- 500 mg – 3 times per day – 3 days.

**Nitrofurantoin:**
- 3 g as a single dose;
- 100 mg – 1 time in the evening – 10 days;
- 100 mg – 4 times per day – 7 days;
- 50–100 mg – 2–4 times per day – 7 days;
- 100 mg – 2–4 times per day – 3 days.

**Cefalexin:**
- 200 mg as a single dose;
- 250–500 mg – 4 times per day – 3–7 days.
Fosfomycin:
2 g as a single dose

Amoxicillin/clavulan acid:
3 g as a single dose;
500 mg – 2 times per day – 3 days.

Trimetoprim/ sulfametoksazol:
1,920 mg – 3 days;
1,920 mg as a single dose.

Single dose of antibacterial preparations can be used for treatment of asymptomatic bacteriuria in pregnancy, however, in case of inefficient therapy or relapses, more protracted treatment is prescribed (7–10-day or 3-day courses). Efficiency of 3-day therapy (evaluated by bacteriuria elimination) and tolerance to it (characterized by frequency of maternal and fetal toxic effects) is similar to 7–10-day treatment.

4. UROLITHIASIS AND PREGNANCY

Urolithiasis at pregnancy is a separate issue with quite contradictory speculations on this matter. Nephroureterolithiasis and its consequences is a serious obstacle to pregnancy retention.

Some doctors support the idea that pregnancy is instrumental in kidney stones formation and creates favourable conditions for quick growth of concretions. It is related to the high concentration of oxalates in urine, endocrine disorders, disturbances of urodynamics and inflammatory processes in urogenital organs. Indeed, above mentioned factors take specific part in etiology of urolithiasis, however, they are not the only reasons of stones formation.

It is considered that stones formation during pregnancy is conditioned by the changes of water-salt exchange, disturbances of urodynamics and secondary infection. Pregnancy is instrumental not in stones formation, but rather in clinical manifestation of disease which proceeded latently prior to that. Urolithiasis is encountered in 5.9% pregnant. Many women, ignoring dangers, aim to maintain pregnancy. It is especially difficult to make a decision regarding sustaining of the first pregnancy, although quite often is it no less important and responsible situation at subsequent pregnancies. A few decades ago the majority of obstetricians strongly objected to maintenance of pregnancy at this condition, although many examples of favourable outcome were known.

A basic leitmotif is focused on different anatomic and functional changes in kidneys and upper urinary tracts at nephrolithiasis. Morphological changes depend on duration of disease, presence of infection, obstruction of urinary tracts and some other reasons. Kidney and ureter stones favour the development of inflammatory process in kidney tissue. Nidi inflammatory reactions and diffuse excrescences of connective tissue take place at nephrolithiasis in combination with pyelonephritis.
approximately in 80–85% patients. The most considerable disorders of kidneys function are observed at bilateral nephroureterolithiasis and damage of single kidney.

Unfortunately, the mechanism of kidney stone formation is not yet clear to this day, but undoubtedly, it is a polyetiological disease. At the same time there is no convincing evidence that pregnancy can cause urolithiasis. Some researchers’ ideas about such possibility appeared in connection with the fact that in 10–15% cases nephrolithiasis shows no symptoms and manifests first time during pregnancy. In this case the destructive changes of parenchyma may take place leading to complete death of kidney.

For example, coral-like stones in kidneys are the most serious form of urolithiasis, often with few symptoms and it is recognized only at acute disorder of kidneys function or complete destruction of kidney tissue.

**Symptomatology.** The changes of urodynamics and hypertrophy of ureters are instrumental in advancement of stone that is why urolithiasis gets worse during pregnancy. Quite often the disease is first diagnosed at pregnancy.

Urolithiasis manifests by the classic triad of symptoms: pain, hematuria, stones passing. At the same time the clinical picture can be various. Kidney stones cause characteristic pain in the lumbar region. This type of pain is similar to one at gynecological diseases. Ureterolithiasis manifests mostly by kidney colic. Kidney colic is the frequent symptom of kidneys and upper urinary tract diseases which are accompanied by urodynamics disorder. However, without organic causation it is observed comparatively rarely.

Under typical conditions kidney colic is recognized easily enough. Tension of muscles of lumbar region, positive Pasternatsky’s symptom, palpation of enlarged painful tense kidney, as well as the results of vaginal testing with stone identification in the lower compartment of ureter, allow preliminary conclusion regarding the nature of disease. A diagnosis becomes more reliable when hematuria (micro- or macroscopic) and pyuria are present. However, in 30% pregnant women kidney colic is atypical resembling a clinical picture of acute stomach. In such cases it is quite difficult to diagnose differentially kidney colic and acute diseases of intraperitoneal organs.

The presence of dyspepsia, rebound tenderness (Blumberg sign), increase of body temperature, blood leukocytosis with the change of formula to the left, especially under the unchanged urine (complete impassability of one ureter), absence of dysuria are the sources for diagnostic and tactical errors. In many cases chromocystoscopy helps to avoid such mistakes.

**Diagnostics.** Diagnostics of urolithiasis in pregnancy is difficult. Roentgenologic (X-ray) research is unacceptable in the first half of pregnancy, and undesirable in the second half. That is why it is important to recognize the disease prior to pregnancy. It is acceptable to use radioisotope renography, chromocystoscopy, catheterization of ureters or renal pelves and ultrasonography.

The modern tests allow determination of concretions in the urinary system, but it does not mean ignoring information of anamnesis, keeping in mind the possibility of spontaneous stone passing or stone removal by surgery. In case of relapse such pregnant complain on pain in a lumbar region, disorders of urination and periodic concretions passing.
It is important to provide objective examination such as palpation of kidneys and ureters. During vaginal examination it is easy to feel a stone located in the distal compartment of ureter. Catheterization of ureter is of great help; this is performed not only for diagnostic but also for treatment purpose.

A wide and short urethra in women allows performing cystoscopy painlessly. However, the specialist has to be extra careful not only during introduction of cystoscope in pregnant, as specified earlier, but also in interpretation of observed changes. The extended and sanguineous vessels in the bottom region of the bladder and swollen mouths of ureters often simulate the concretion passing. Additional tests are required to avoid erroneous conclusions.

Chromocystoscopy is of great value for diagnostics of urolithiasis. During this procedure the indigo carmine either does not secret from the damaged kidney or passes out in a languid stream with the weak colouration.

It is known that at nephroureterolithiasis the nitrogen-electrolyte secretive and concentative functions of kidneys are affected, with negative consequences both for the organism of expectant mother and future child.

For the evaluation of kidney function the complex of tests is applied, which includes determination of urea or remaining nitrogen and creatinine, electrolytes in blood serum, concentration tests and isotopic renography. At one-sided uncomplicated nephroureterolithiasis the amount of remaining nitrogen in blood in most cases remains within the normal limits or slightly increases. However, this index always increases at bilateral kidney damage or single kidney disease. At nephroureterolithiasis similar dynamics is observed in changes of renal concentration function, which is affected to greater extent than nitrogen secretive function.

The examination of pregnant is concluded with application of Roentgenologic methods. The image of the urinary system is taken followed by excretory urography which is one the most effective methods. Detection of concretions sometimes is very difficult especially in the second half of pregnancy, due to shadows of bone skeleton of fetus. In addition, in 5–8% cases X-ray-negative stones are not detected on the image. Because of this, excretory urography substantially complements the examination. It allows identification of kidneys size, location, function, and also whether the shadows are of concretion nature. Retrograde ureteral pyelography is used when it is necessary to confirm the diagnosis.

It is possible to get complete picture of the functional state of kidneys and upper urinary tracts, applying the complex of modern methods such as laboratory, Roentgenological and radiological tests. At one-sided lithiasis the total function of kidneys, as a rule, is not compromised, as opposite kidney compensates the insufficient function of the impaired one. Radioisotope renography substantially complements and extends information about the functional condition of each kidney. The minimal radial exposure allows to apply this method but under strict indications.

Anamnestic data, dull pain in lumbar region, concretions passing help to confirm the diagnosis of urolithiasis. Instrumental testing methods include ultrasonography and chromocystoscopy. Urine sediment contains large number of erythrocytes with or without leucocytes, and large amount of oxalate crystals.
Thus, each of the above mentioned tests should be conducted with careful consideration of individual cases, minding the expectant mother.

The pain attacks at urolithiasis provoke the threat of abortion and premature births. There is a possibility of more threatening complications development such as premature abruption of normally located placenta. Development of pyelonephritis results in infection of fetus and hypoxia. Labour is conducted via natural birth canal. In the post-natal period the condition of patients improves considerably. In pregnant with frequent attacks and with no response to the treatment, pre-term birth is considered at late terms of pregnancy. The disease outcome is favourable for a fetus.

**Treatment.** With the purpose to cease the kidney colic attack the following medicines are applied: 1.0 ml intramuscularly of 2% promedol solution, 2.0 ml intramuscularly of 50% analgin solution, 5 ml baralgin, 2.0 ml of 2.5% galidor solution, 2% papaverine solution, 2 ml of 2% noshpa solution, 1% dimedrol solution, 2 ml of 2–2.5% pipolphen. Twenty drops of cystenal, 0.05 of avisan 3 times per day. In case of medical therapy ineffectiveness the catheterization of ureter is necessary. In most cases the catheter favours urine outflow from the blocked kidney and creates conditions for normalization of lymph and blood circulation in kidney tissue. Kidney colic is often ceased by spontaneous concretions passing.

However, it is not always possible to achieve the positive effect by ureter catheterization and antibiotics treatment. In these cases the urine flow is maintained by pyelo- or nephrostomy. This prevents the development of festerering process in kidney.

Thus, first of all, it is necessary to identify and eliminate the cause of kidney colic, rather than to terminate pregnancy. At the same time one should bear in mind that kidney colic attacks may cause the involuntary pregnancy termination or premature birth.

Clinical experience of many researchers shows that urolithiasis does not substantially affect the development of pregnancy and fetus condition. Pregnancy can develop normally at single infection-free stone in renal pelves and calyces. Thus, careful approach is required, as pregnancy and labour complicate the outcome of illness in a number of cases. That is why a dynamic control of the state of the urogenital system is needed.

Nephroureterolithiasis, when accompanied by acute pyelonephritis, complicates the pregnancy and often is a reason of involuntary abortion or premature births. In order to reduce pain and cease an inflammatory process in kidney the catheterization of ureter is conducted, but on condition that catheter is positioned higher than concretion. As a rule, the catheter provides the complete urine outflow from the blocked kidney and in combination with antibiotics treatment creates conditions for normalization of lymph and blood circulation in kidney tissue. However, this method does not work in all cases. The stone often tightly obturates the ureter making catheterization impossible.

Instrumental procedures, directed to the stone removal with a loop, are dangerous and almost never used at expectant mothers. It is advisable to avoid surgical interventions for nephro- and ureterolithiasis treatment during pregnancy.
In the dynamics of pregnancy it is recommended to conduct kidneys ultrasonography for determination of concretions presence and location as well as possibility of change in their position.

These are exemplary recommendations on prophylaxis and treatment of urolithiasis in pregnancy, however, one should bear in mind that conservative methods of treatment in pregnancy (medicinal, physical therapy and resorts) have very selective application, as they require long time and considerable water loading:

- Plenty of drink (more than 2.5 L/day) for intensive urine outflow.
- A diet depends on character of mineral exchange disorder. At uroacidic diathesis, when urates are extracted with urine and form stones in urinary tracts, a diet poor in purines is prescribed. Purine bases are present in large numbers in fried meat, brains and meat broth. A diet must be milk and vegetable, which makes urine alkaline, thus, reducing acidosis. Milk diet compensates lack in animal albumins, and plant diet contains vitamins and acids, which are transformed into carbonates in the organism, making urine alkaline. The diet should not include beans, nuts, sorrel, cacao, chocolate and black tea. Pregnant should have boiled fish or fat-free meat once in 2–3 days. Vegetable soups, vegetables, fruit, dairy products are not limited. Such diet is fully consistent with dietary requirements in pregnancy. Alkalization of urine up to pH 6.5–7 is achieved by taking basic solutions, for example, 20 ml of Shol’s solution (430 ml of 1 mekv NaHCO3) inside 2–3 times per day.

- Phosphor-acidic diathesis is accompanied by alkaline reaction of urine, urine sediment containing mainly calcium salts rather than phosphorus salts. A diet should be poor in calcium salts (up to 500 mg per day) which favours turning urine alkaline reaction into acidic. The products containing lots of calcium are either contraindicated (eggs, dairy products) or limited (green vegetables, potatoes, peas, kidney beans). At phosphor-acidic diathesis, contrary to acidic diathesis, a meat meal (up to 1 g/kg per day) is recommended; fried meat, sweets, various crops, fruits (apples, grapes, pears) are also allowed. Products containing vitamin A should be part of the diet (butter, liver, carrots, decoction of sweetbrier, cod liver oil). Drink is limited, as diuresis reduces urine acidity (alkalosis develops) and the amount of protective colloids decreases which facilitates formation of phosphoric and carbonate stones. Table salt intake should not exceed 10 g per day.

- The diet recommended for patients with phosphor-acidic diathesis is not physiologically suitable for pregnant women. Pregnant require calcium and phosphorus salts which are contained in milk, vitamins-rich fresh fruits and vegetables, and also products containing mineral salts, in particular potassium salts. That is why diet recommendations at urolithiasis do not favour the development of fetus.

- At oxalic acidic diathesis the diet combines the elements of diets recommended for patients with phosphaturia and uraturia. Meals should not contain products which favour oxalates formation. That is why milk, eggs, beans, nuts, sorrel and black tea are excluded from the diet. The consumption of strong meat broths, brains, tomatoes, potatoes and cacao should be limited. The products alkalizing urine are recommended, such as apples, pears, apricots, peaches, quince, water-melons, extract of blackcurrant and sweetbrier. It is allowed to eat boiled meat and fish (2–
3 times per a week), flour and crop dishes, dairy products, any fats, cabbage, pumpkin, cucumbers and melons. Plenty of drink is useful. The diet recommended at oxalaturia is not as strict as at phosphor-acidic diathesis and is more consistent with necessities of pregnant women.

- For the improvement of urodynamics and increase in diuresis, decoctions of the field horsetail, leaves of birch, knotgrass, renal tea, sweetbrier, fresh cowberry/cranberry drink and some other are used.
- For the prophylaxis of salt sedimentation and stone formation pH urine can be changed. The recommendations are:
  - at oxalaturia: mild mineralized waters (Essentuki No 20, Naftusya);
  - at uraturia: Essentuki No 14 and 17, Smirnovskaya, Slovjanska, Borzhomi;
  - at phosphaturia: Dolomite Narzan, Arzni, Naftusya, mineral waters of Truskavets and Berezovski resorts.
- Spasmolytic preparations: papaverine, drotaverine, platifilin.
- Terlen preparations: cyctenon.
- Vitamin therapy.
- In case of infection, the therapy should be consistent with general principles of treatment of pyelonephritis.

Stones which prevent urine flow create conditions for development of festering-inflammatory processes in kidney. Such complication, regardless of term of pregnancy, indicates the necessity of urgent surgery.

If catheterization of ureters is not effective, decompression of kidneys is carried out operatively. This should be done early enough to prevent accumulation of nitric metabolism products in the organism. Clearly, indication to operative treatment in such group of patients must be stricter, as the aim is not only to remove stone but also to maintain pregnancy.

The optimal term for operative treatment is 15th–18th week of pregnancy. By this time the formation of placenta is completed and threat of involuntary abortion is minimal. If the operation is performed in much earlier terms, maintenance of pregnancy is less successful. In the last weeks of pregnancy the operative treatment should be done only in extreme cases, when there is a clear threat for patient’s life. In urgent cases operation is performed regardless of pregnancy term.

The elimination of infection is very important, as pyelonephritis complicates urolithiasis approximately in 80–85% cases. Protracted and continuous course of antibiotics and chemotherapeutic treatment is prescribed; otherwise, pyelonephritis progresses and the prognosis for both mother and fetus may be unfavourable. The terms of renal function recovery depend on timely efficient treatment of pyelonephritis and degree of functional damage.

Thus, nephrolithiasis complicated by acute inflammatory process is the definite indication for termination of pregnancy in its first half, and for kidney drainage or caesarean section in the second half. However, this should not be an irrefutable rule, and maintaining or terminating pregnancy should be considered in every case individually.
Urinary tract sanitation with antibiotics and chemotherapeutic preparations is fully justified in pregnant, as it causes no serious complications both for mother and fetus.

Above mentioned arguments allow to draw the following conclusion. The decision in favour of pregnancy sustaining should be made strictly individually at one-sided nephrolithiasis without disturbance of urine outflow and with moderately expressed chronic pyelonephritis. First of all, the elimination of infection nidi in tonsils, carious teeth and other organs should be done for the prophylaxis of aggravation of pyelonephritis. Often in such pregnant patients with the moderately expressed pyelonephritis no consequences are noted both for mother and fetus.

A condition for recurrent stone formation is not only mineral imbalance but also inflammatory process in kidney tissue. At urinary infection the relapses of stone formation are observed 3 times more frequent than without it. Medium frequency of repeated stone formation is about 40%. Usually chemical composition of recurrent stone is similar to primary stone. Efforts should be directed to suppression of pathogenic flora. At the same time the formation of stone is only an episode in many patients’ lives. After operative or instrumental removal of stone, the inflammatory process in urinary system is ceased and stable remission is achieved.

Pregnancy and labour present no danger for patients with urolithiasis at clinical convalescence, i.e., at normal composition of urine and absence of relapse of disease during 3 years.

The termination of pregnancy is indicated at complicated and late gestosis, caused by anatomic and functional damage of kidneys. The decision regarding pregnancy maintaining should be made taking into account the following issues: disease duration, concretion localization, kidneys function, degrees and acuteness of inflammatory process. As a rule, pregnancy develops normally at one-sided nephrolithiasis and satisfactory function of contralateral kidney. Bilateral nephrolithiasis is often accompanied by kidney insufficiency, which unfavorably affects the organism of pregnant, thus, maintaining of pregnancy in such patients is undesirable.
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ІНФЕКЦІЇ СЕЧОВОЇ СИСТЕМИ ПРИ ВАГІТНОСТІ

Методичні вказівки для студентів та інтернів

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