

URINARY TRACT INFECTIONS AND ACUTE PYELONEPHRITIS AS SERIOUS CONCERNS IN PREGNANCY: CLINICAL COURSE, RISKS AND MANAGEMENT

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Abstract: Infections of the urinary tract are more common during pregnancy due to physiological and immunological changes. This review aims to highlight the importance of prevention and early detection of asymptomatic bacterial urinary infection, their appropriate treatment hence prevention of further serious issues during pregnancy. Asymptomatic bacterial infections if not treated properly can progress to upper parts of the urinary system and the kidney resulting in symptomatic infections of the urinary system and pyelonephritis. Severe and potentially life threatening complications can arise from these conditions.

Education and health promotion of primary care in view of the risk factors thus screening for asymptomatic bacterial infection can evidently improve the prenatal care and pregnancy outcomes, therefore declining the prevalence of the urinary tract infections, including kidney infections as well. Multidisciplinary approach and keeping up an adequate treatment of the urinary tract infections thus early detection of impaired kidney function is essential for successful treatment outcome as well as avoidance of the complications during pregnancy.

Keywords: acute pyelonephritis, urinary tract infections, pregnancy

1. INTRODUCTION

Urinary tract infections (UTIs) are common during pregnancy of which asymptomatic bacteriuria (ASB) and cystitis are the two most common diseases. Consequently these infections can progress to other serious kidney diseases such as acute pyelonephritis (APN) which can cause severe complications counting sepsis, acute kidney failure, kidney scarring, renal abscess as well if they are not treated properly (Belyayeva& Jeong, 2022; Peces et al. 2009).

Pregnancy-related physiological and immunological changes enhance chances of developing urinary tract infections and acute pyelonephritis. Pregnancy influences kidneys physiology and the physiology of the urinary tract therefore up to 80% of woman experience fluid retention and hydronephrosis. Physiologic hydronephrosis and retention of the urine system for the period of pregnancy are caused by ureter dilatation, slow peristalsis and smooth muscle relaxation triggered by elevated progesterone levels, compression of the enlarged uterus on the ureters and dilatation of the renal calyceal. Glomerular filtration rate (GFR) rises by around 50%, leading to a physiologic decrease in serum creatinine, increased glycosuria, proteinuria and alkalization of urine that supports the growth of bacteria. Most significant hemodynamic changes that occur during pregnancy are higher blood volume, decreased systemic vascular resistance and increased cardiac output as well (Wing 2001; Cheung& Lafayette2013; Rindfleisch et al. 2020).

2. PREGNANCY ASSOCIATED INFECTIONS OF THE URINARY TRACT AND RISK FACTORS

Given that pregnancy is associated with physiological changes there is a higher risk for bacterial infections of the urine and urinary tract. Bacterial development in the urine causes infection which is referred to as asymptomatic bacteriuria (ASB). Moreover bacterial infiltration of the tissues of the urinary tract induces inflammatory symptomatic response such as symptomatic acute cystitis or acute pyelonephritis. Asymptomatic bacteriuria is significantly associated with history of infections of the urinary tract, nephrolithiasis and nulliparity (Balachandran et al. 2022). The incidence of asymptomatic urinary infections during pregnancy does not increase in pregnant women, but pregnancy related physiological changes of the urinary tract increase the risk for infections thus untreated asymptomatic cases become symptomatic infections like cystitis and pyelonephritis (Saleh et al. 2015; Dawkins et al. 2012).

The prevalence of asymptomatic bacteriuria varies, thus a study reports for prevalence of 5, 7% cases of ASB and the same study shows a prevalence of significant bacteriuria of 9.9%. Cystitis and pyelonephritis have been revealed in 3.6 and 0.6% of the cases (Tchente Nguefack.et al.2019).

In a secondary analysis of a prospective multicenter cohort study among 4918 low- risk pregnant women Werter et al. (2021) reports for two risk indicators that disclosed statistically significant association with urinary infections, therefore a history of repeated infections triples the risk for the development of urinary tract infections. Furthermore asymptomatic bacteriuria around 20 weeks of gestational age doubles the risk of urinary infection in pregnant women. In the same study the incidence of UTI was reported to be 9.4 % women. Dube et al. (2022) disclose a prevalence of UTI of 17.9 % among 682 pregnant women based on clinical symptoms and pus cells in urine microscopy. Diabetes, previous history of UTI and having a history of recurrent UTI, low level of education and

anemia are considered the most common risk factors. Women who have had 4 or 5 pregnancies and those with low salaries are disposed of having bacteriuria. Other risk factors which are related to increased rates of pregnancy associated UTIs are age, non-Caucasian ethnicity, smoking, and presence of asymptomatic bacteriuria (ASB), history of UTI, undernutrition and primiparity are revealed as risk factors as well (Balachandran et al. 2022; Tchente Nguefack et al. 2012, Werter et al. 2021; Dube et al. 2022; Lee et al. 2020). Tchente Nguefack et al.(2019) didn't find any statistical significant influence of age, marital status, HIV status, obesity, gestational age, parity and low monthly income on bacteriuria. Similarly, age hasn't been significantly associated with the risk of UTI in a study by Balachandran et al. (2022), moreover authors have estimated that there was no significant correlation between age or BMI and the risk of UTI as well. If not treated properly asymptomatic and symptomatic bacterial infections of the urinary tract in pregnant women may possibly progress to the renal parenchyma therefore leading to more serious condition such as acute pyelonephritis (Dawkins et al., 2012).

3. ACUTE PYELONEPHRITIS IN PREGNANCY

Female are more susceptible to acute pyelonephritis attributable to gender associated physiological differences such as hormonal imbalance and shorter length of the urethras in addition to spreading of the infection from the bladder to the kidneys namely ascending urinary tract infection. Acute pyelonephritis can be uncomplicated or complicated therefore pregnancy and many other diseases are associated with complicated acute pyelonephritis (Belyayeva &Jeong, 2022).

Higher incidence of acute pyelonephritis during pregnancy has been related with younger age furthermore a previous history of APN one year from pregnancy is considered as predictor of APN during pregnancy. Acute pyelonephritis among pregnant women occurs mostly in the last two trimesters of pregnancy and is mostly associated with younger age, lower education, black or Hispanic ethnicity, smoking during pregnancy, late prenatal care and nulliparity. Furthermore it can be exacerbated by comorbidities like immunocompromised states as well as the sickle cell gene (Dawkins et al. 2012; Ko et al.2020; Zannata et al 2017) . Also it is considered that pregestational diabetes in pregnancy increases the risk for acute pyelonephritis for 1.7 fold (95% CI, 1.3e2.1) as well. Consequently acute pyelonephritis during pregnancy increases the risk of chorioamnionitis, primary cesarean delivery and also significantly increases the risk of anemia, septicemia, acute renal failure and respiratory distress (Smaill&Vasquez2007; Wing et al. 2014).

Diagnostic criteria of pyelonephritis have been defined as abnormal, positive, urine culture test results (> 100.000 bacterial growth with high number of colony forming units (CFUs), and one of the clinical symptoms such as fever (> 37.8°C), costovertebral angle pain, flank pain or vomiting. Costovertebral angle tenderness may be present bilaterally, but mostly appears unilaterally over the affected kidney. In a study by Saleh et al. (2015) CVA tenderness appears in all cases, thus tenderness on the right side appears in 40 (66.7%) cases and bilateral tenderness revealed 16 (26.7%) cases. Pyuria has been present in all patients on laboratory tests. According to Dawkins et al. (2012) loin pain is one the commonest complaints on admission as well as abdominal pain which have been mostly present on the right side. Pyuria has been detected in urinalysis of 81.4% cases. Pyelonephritis in pregnancy mostly appears on the right side because of the pressure that uterus develops on the right ureter. The right ureter, due to its course, is most exposed to compression inducing stasis of the urine and furthermore pyelonephritis which occurs mostly in the right kidney. Studies report varying rates of urinary tract infections and acute pyelonephritis during pregnancy (Table1).

Table 1 Summary of studies reporting prevalence of UTIs, acute pyelonephritis and Escherihia Coli

Authors	Type of study	n	age	UTI (ASB/Cyst itis)	APN	E coli%
Balachandran et al.,2022	Retrospective cohort study	878	30.5/31.8	549 cases	1.45%	30.9
Dube et al.,2022	Prospective observational study	682	29.67+/-3.58	17.9%		27
Ko et al.,2020	Population based retrospective study	367.950	31+/-4	5.4%	0.7%	
Tchente Nguefack et al.,2019	Cross sectional study	354	28.18+/-4.4	5.7%ASB 3.6% cyst.	0.6%	48.6
Saleh et al.,2015	Prospective multicenter cohort study	60	23+/-4.88	70%ASB	all	78.6
Werter et al.,2021	Prospective multicenter cohort study (secondary analysis)	4819	31.2	9.4%		
Zanatta et al.,2017	Cross-sectional observational study	10291			1.97%	76.6
McGready et al.,2010	Clinical study	203	26+/-7	1 case	20.2% of fever cases	87.5

According to McGready et al. (2010) pregnant refugee and migrant women reveal similar rate and causes of pyelonephritis compared to developed countries, so the incidence of pyelonephritis in febrile pregnant women has been reported to be 1.1% (53/4,819), moreover premature were 8.3% (3/36) of babies and 14.3% (5/35) of with low birth weight (LBW). Pyelonephritis has been diagnosed in 20.2% (41/203) of fever cases in pregnancy. Studies estimated high possibility for preterm birth and low birth weight in women with acute pyelonephritis. Accordingly 10% of woman with acute pyelonephritis have delivered prematurely, between 33-36 weeks of gestational age, compared to 7.9% without APN (Wing et al.2014). Dawkins et al. (2012) reports for pyelonephritis in 0.7% of deliveries thus twelve subjects (17.6%) delivered prematurely and 10 babies (14.7%) have been borne with low birth weight. According to Zannata et al.(2017) relatively low incidence of low birth weight (6.7%) was revealed and on the other hand the same study reports higher risk for pre-term delivery (< 32 weeks) (3.3%) in cases who experienced pyelonephritis for the period of pregnancy related with merely 1.2% of cases without previous urinary tract infection. No notably relationship between low birth weights and urinary infections during pregnancy has been detected in the study by Balachandran et al. (2022) however women with urinary infection revealed have higher possibility for pre-term deliveries. Laboratory analyzes, considering the association with the incidence of acute pyelonephritis in pregnant women, revealed that the degree of proteinuria considerably influences the risk of APN during pregnancy. Therefore increased levels of protein in the urine raise the risk of acute pyelonephritis in pregnant women. Fasting blood sugar >100 mg/dL significantly associate with increased rates of APN in pregnant women thus remarkably, nearly twice increases the risk for infection (Ko et al., 2020).

4. PATHOGENS ASSOCIATED WITH THE URINARY TRACT INFECTIONS

Since urinary tract pathogens which can cause asymptomatic bacteriuria (ASB), and those causing pyelonephritis are likely similar, effective treatment of asymptomatic bacteriuria with antibiotics could prevent ascending infections of the urinary tract and clinical pyelonephritis as well (Smaill & Vazquez, 2007). Microbiological analyzing of the urine with urine culture and urinalysis are the best diagnosing methods for diagnosis of the bacterial infections of the urinary tract and the most common detected bacteria that have been associated with UTI and pyelonephritis in pregnancy is *Escherichia Coli* (Rindfleisch et al., 2020). Studies report for different extent of this pathogen in urine cultures so Zannata et al. (2017) demonstrates that *Escherichia coli* has the highest occurrence in the urine samples, isolated in 76.6% of the antibiograms, following with *Klebsiella pneumoniae* and *Proteus mirabilis* as well. According to Balachandran et al. (2022) in patients with UTI dominant pathogen was Group B streptococcus followed by *Escherichia Coli*, *Enterococcus*, *Klebsiella pneumoniae*, as well as smaller groups of pathogens. Asymptomatic bacteriuria is associated with identical cultures comprising Group B streptococcus, *Escherichia Coli*, *Enterococcus* thus *Klebsiella*.

Pathogenesis of uropathogenic *Escherichia coli* (UPEC) during pregnancy is based on the possibility to closely attach, grow and increase of the bacterial load thus form biofilm in the urinary tract and kidneys. Studies suggest that the damage of protective barriers of the kidney cells caused by bacterial adhesion induces confined reaction in order to prevent and contain the spread of the infection. Moreover damage of the renal parenchymal and renal scars can occur as a consequence of an acute inflammatory reaction. Many reactive mechanisms, including the role of inflammatory cytokines, can induce serious kidneys infection, pyelonephritis, complications for the mother and the fetus thus life threatening complications including kidney failure, abscess, sepsis and shock. Infections of the urinary tract in pregnant women mostly are reinforced by pregnancy associated changes of the urinary system which are considered essential for the occurrence of urinary infections thus influence the incidence of infections caused even by less virulent bacteria (Belyayeva & Jeong, 2022; Ramos et al. 2012).

5. PREVENTION AND MANAGEMENT OF UTIS IN PREGNANCY

Infections of the urinary system are serious complaints for the period of pregnancy and perinatal period thus require a special diagnostic approach and management. Studies suggest that asymptomatic bacteriuria is an important risk factor for pyelonephritis and outlines a population at risk of pyelonephritis hence screening of ASB thus adequate treatment is recommended in every diagnosed case (Smaill & Vazquez, 2007; Matuszkiewicz-Rowińska et al. 2015). Moreover, these infections can cause additional stress and anxiety for the possible impact of the infection or the antibiotics on pregnancy and the baby (Ghouri et al.2019). Appropriate antenatal care, considering for asymptomatic bacteriuria and proper treatment are of great importance (Rindfleisch et al. 2020). Studies recommend additionally basic laboratory analyses despite urine and blood culture in order to exclude other causes (Matuszkiewicz-Rowińska et al. 2015). Ultrasound and MRI scans are considered useful for diagnostic of serious complications of pyelonephritis counting kidney abscess, hydronephrosis thus vesicoureteral reflux as well (Peces et al.2009).

Reducing of the rate of pyelonephritis by an antibiotic treatment has been related with decrease of the incidence of low birthweight and preterm birth. Asymptomatic bacteriuria can be effectively cleared with proper antibiotic treatment otherwise it is considered that the infection persists in 70% of pregnant women without treatment (Smaill & Vazquez, 2007). In the first trimester of pregnancy single-dosing of fosfomycin is considered crucial for the therapy of uncomplicated urinary infections of lower parts of the urinary system, furthermore in the second and the third trimester is recommended the use of sulfonamides and nitrofurantoin as well. Periodical urine cultures thus antibiotic treatment as a preventive measure are recommended for women with cystitis during pregnancy (Serena et al. 2020). *Escherichia coli* have been posed as the most commonly isolated pathogen of organisms cultured which is responsible for UTI and pyelonephritis. Management of acute pyelonephritis in pregnant women includes hospitalisation, intravenous hydration, antipyretics and parenteral antibiotic treatment using wide- spectrum beta-lactams. Oral antibiotic treatment can be used if fever free for 48 hours therefore widely used oral beta-lactams, or in the second trimester trimethoprim-sulfamethoxazole are administered (for no less than 10- 14 days) is recommended. Intense monitoring and antibiotic prophylaxis till the rest of pregnancy are recommended owing to pronounced relapse rate (Wing, 2001; Serena et al. 2020).

Studies reveal that ceftriaxone is first- line of antibiotic because of low level of bacterial resistance thus is commonly used for the intravenous phase of the treatment of pyelonephritis (Zannata et al. 2017), also frequently used antibiotic are intravenous Amoxicillin-Clavulanate and Gentamycin, oral Amoxicillin-Clavulanate, oral Cefuroxime, Cotrimoxazole, Nitrofurantoin (Dawkins et al. 2012; Samaga, 2016; Mandal et al. 2017). According to McGready et al. (2010) *E. coli* shows low rate of susceptibility or highest bacterial resistance to ampicillin/amoxicillin (14%), cotrimoxazole (21%) and to amoxicillin-clavulanic acid. Antibiotics are used according to culture and sensitivity report. The antibiotics ampicillin and cephalosporin (cephalothin) disclose the

highest bacterial resistance according to Zannata et al. (2017), in 52 % and 36. 2 % of the cases, and according to Samaga (2016) ampicillin shows resistance in 89. 5 % of cases. According to Dawkins et al. (2012) the average duration of the intravenous administration of antibiotic is three days (ranging from 1-10 days) while the average duration of oral antibiotics is seven days, respectively from 1–14 days. Furthermore after completion of the antibiotic course, and repeated urine culture in seventy patients (68.6%), 43 samples (61.3%) resulted positive and 25 cases (24.0%) revealed recurring pyelonephritis. Although short term course of an antibiotic treatment for asymptomatic bacteriuria during pregnancy is considered more efficient comparing to single- dose treatment, established regimens of antibiotics should be used for the treatment of women with ASB during pregnancy prior to additional studies and until further research data become available concerning the effectiveness of different treatment courses considering the duration of the treatment regimens (Widmer et al. 2015).

Regardless of the various treatment procedures studies reveal very high cure rates and rare complications (Vazquez & Abalos, 2011), so treatment failure mostly may occur due to antimicrobial resistance or abscess, nephrolithiasis and structural diseases. In order to avoid maternal and fetal problems thus to reduce the complications correct diagnosis and adequate treatment are essential (Umeh et al. 2022). Additionally proper prenatal care and screening for asymptomatic bacteriuria between weeks 12 and 16, also later in pregnancy, are crucial in preventing pyelonephritis (Rindfleisch et al. 2020; Matuszkiewicz-Rowińska et al. 2015). Early recognition and treatment of acute pyelonephritis in pregnancy and additional serious urinary system diseases allows effective treatment thus enables avoidance of serious life threatening complications (Dawkins et al. 2012; Mishra et al. 2023). Guideline of The World Health Organization (WHO), related to woman and female adolescents receiving antenatal care, comprise recommendations from different fields counting nutrition as well as monitoring of the pregnant women and fetus, screening and therapy of asymptomatic bacteriuria and urinary infections in low-middle income countries (LMICs), as cited by Lee et al. (2020), in order to improve antenatal care and pregnancy outcome (WHO, 2016). Improved maternity and child health care can be achieved by use of disease preventive strategies in addition with screening for ASB and appropriate therapy of urinary infections. (Tchente Nguefack et al. 2019).

Infections of the urinary tract are serious concern during pregnancy and the perinatal period as they may cause health complications for both the mother and the baby. Education and health promotion in primary health care in view of the risk factors thus screening for asymptomatic bacterial infection can evidently improve the prenatal care and pregnancy outcomes, therefore decrease the prevalence of the urinary tract infections, including kidney infections as well. Multidisciplinary approach and keeping up an adequate treatment of the urinary tract infections thus early detection of impaired kidney function is essential for successful treatment outcome as well as avoidance of the complications during pregnancy.

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