[Downloaded free from http://www.sjkdt.org on Monday, September 28, 2015, IP: 186.42.102.68]

Saudi J Kidney Dis Transpl 2014;25(1):85-90
© 2014 Saudi Center for Organ Transplantation

Saudi Journal of Kidney Diseases and Transplantation

Original Article

Urinary Tract Infections in Pregnancy: Evaluation of Diagnostic Framework

Tukur Ado Jido

Department of Obstetrics and Gynecology, Bayero University, Aminu Kano Teaching Hospital, Kano State, Nigeria

ABSTRACT. This study was performed with the objective to examine the diagnostic framework for urinary tract infection (UTI) in pregnancy and physician response to the clinical diagnosis and to correlate responses to the results of urine culture and sensitivity. Over a 6-month period, 81 consecutive patients attending the labor ward admission of a district general hospital with the diagnosis of UTI during pregnancy were analyzed. Relevant information on symptom complex, result of dipstick urinalysis and culture and sensitivity were recorded. Data were analyzed using descriptive statistics. Of the 78 patients analyzed, 79% had increased urinary frequency, 73.1% had suprapubic pains and 53.1% had dysuria. All the patients had urinalysis with dipsticks, 41 (52.6%) were positive for nitrites and 64 (82.1%) were positive for leukocyte esterase. All 78 patients had urine culture and sensitivity, 21 (26.8%) of who were positive, and coliforms were the most commonly isolated pathogens. The sensitivity for nitrite was 80.9%, specificity 57.9% and positive predictive value 41.4%. The corresponding figures for leukocyte esterase were sensitivity 100%, specificity 24.6% and positive predictive value 32.8%. Sixty-six (84.6%) patients had treatment started on the basis of the clinical diagnosis, mostly with co-amoxyclavullinic acid or amoxicillin alone. A high resistance rate to these empirically chosen antibiotics was seen in the sensitivity pattern of isolated pathogens. Current clinical diagnostic algorithms for the diagnosis of UTI when applied in the context of pregnancy have low specificity and positive predictive values; yet, empirical antibiotics are frequently employed on this basis. These are often not in keeping with the sensitivity pattern of isolated organisms. There is need for a continuing research for more specific bedside tests.

Introduction

Asymptomatic bacteriuria complicates 2–13% of pregnancies and, if not treated, may lead to adverse maternal and fetal outcomes, which include symptomatic urinary tract infections (UTI).[1] The prevalence of symptomatic urine infection during pregnancy is less common; about 1–2% of all pregnancies.[1] Diagnosis of UTI is an independent predictor of antibiotic prescription in pregnancy among patients in primary care.[2] There are national and international guidelines on the treatment of UTI du-

Correspondence to:

Dr. Tukur Ado Jido,
Department of Obstetrics and Gynecology,
Aminu Kano Teaching Hospital,
Kano State, Nigeria
E-mail: tukurjido@yahoo.com

[Downloaded free from http://www.sjkdt.org on Monday, September 28, 2015, IP: 186.42.102.68]

ring pregnancy, but these are however widely ignored in clinical practice.[3] The result is widespread antibiotic use in relation to this diagnosis. While most of the drugs have been shown to be safe to the fetus in terms of teratogenicity, other adverse outcomes such as small for gestational age remain a concern.[4] Furthermore, indiscriminate use of antibiotics portends the risk of resistance and has definite cost implications.

There is abound evidence that UTI causes adverse maternal and fetal outcomes.[3] The rates of intrauterine growth retardation (IUGR), pre-term delivery, cesarean section and pre-eclampsia have all been shown to be higher in patients treated for UTIs. The consequences of untreated infections are even worse and could lead to pyelonephritis, chronic renal insufficiency, IUGR, pre-term delivery and still birth with considerable morbidity and mortality.[5] This underlines the significance of appropriate diagnosis and treatment of these infections, especially in pregnant women.

The gold standard for diagnosis of UTI is isolation and quantification of pathogens in the presence of symptoms and obtaining the antibiotic sensitivity pattern to allow for specific treatment. Clearly, this approach will require considerable effort but will potentially reduce inappropriate antibiotic prescription and thus limit the development of resistance.[6] It however will delay important antibiotic treatment and has a huge cost implication. The current default practice is to commence empirical treatment on clinical ground and arrange for culture at the same time. UTI is the second most common cause of empirical antibiotic treatment in primary and secondary care.[7]

Clinical diagnosis of UTIs mainly based on history has only a sensitivity of 50–80%.[8] Initiating treatment on this basis produces high false positives and risks high rates of resistance.[6] Varying strategies to improve the sensitivity and specificity of the clinical diagnosis employ a number of bedside tests and clinical algorithms. The most common algorithm proposed by McIsaac[9] uses discomfort or burning sensation at micturition, positive leukocyte esterase and detection of nitrites. Any two satisfy the diagnostic criterion. The sensitivity of this algorithm is 80%, with a specificity of 54%. Microscopy and quantification of colony-forming units add insignificant probability of detection to this model.[9] However, it is pertinent to note that the specificity is low; thus, it could not reduce the rates of false positives and potential for resistance. An alternative point-based system that gives arbitrary weight to these criteria (nitrite = 2, leukocytes = 1.5, hematuria = 1, dysuria = 1 and nocturia = 0.5) improve the specificity to 74% with sensitivity of 76%.[10] Our clinical practice is limited by the fact that almost all these algorithms are modeled on non-pregnant women. Indeed, development of new models in pregnant women is limited by ethical concerns.

The current study evaluates the diagnostic framework for UTI in pregnant women attending a single center and physicians response to the clinical diagnosis and correlate the responses to the results of urinary culture and sensitivity.

Materials and Methods

A prospective analysis was performed on 81 consecutive patients attending the labor ward admission of Royal Alexandra Hospital, Paisley, UK, between 1 May to 31 October 2006. The basis for diagnosis was assessed by evaluating the patients' presenting symptoms and result of urinalysis. Request for a diagnostic test and/or commencement of treatment were performed by the attending physicians. In cases in whom treatment was started, the chosen antibiotic regimen were matched with the result of culture and sensitivity as well as the patient response.

Urinalysis was carried out using multistix to test for leukocyte esterase, nitrite and red blood cells (RBC). All cultures were using standard CLED agar and MacConkey culture media. The data were analyzed using descriptive statistics. Sensitivity, specificity and positive predictive values were computed where appropriate.

Results

A total of 81 patients had UTIs diagnosed over

[Downloaded free from http://www.sjkdt.org on Monday, September 28, 2015, IP: 186.42.102.68]

the period of the study. Three patients who had no urinary culture to confirm the diagnosis were excluded from subsequent analysis. Table 1 shows the presenting symptoms. Sixty-four (82%) patients had increased urinary frequency, 57 (73.1%) had supra-pubic pain and 43 (55.1%) had dysuria. Other symptoms were hematuria in 11 (14.1%) patients, loin pain in 9% and offensive odor of urine in 5.1%. Six patients (7.7%) described non-specific symptoms of feeling unwell. The patients were grouped on the basis of the initial diagnosis. Group one had symptoms, leukocytes esterase, RBC and nitrite, consisting of 41 patients (52.6%). Group two had symptoms, RBC and leukocyte esterase (23 patients, 29.5%). Group three had symptoms plus RBC and ketonuria, consisting of seven (9%) patients. Four and three patients each had symptoms and ketonuria and symptoms and RBC, respectively.

Treatment was initiated in 66 (84.6%) patients pending the result of culture and sensitivity. Table 2 shows the antibiotics used. Amoxicillin clavulanate was used in 31 patients (47.0%), amoxicillin in 13 (19.7%), co-trimoxazole in seven (10.6%) and nitrofurantoin in 6%. Of the 78 patients who had urine culture, only 21 (26.9%) had positive cultures and 73.1% were sterile. Coliforms were the most frequently isolated pathogens in 16 (76.2%) patients, followed by enterococci and *Staphylococcus aureus* in two (9.4%) cases each. One patient had Klebsiella spp. The sensitivity pattern showed that the isolated organisms were sensitive to fluoroquinalones in 17 (80.9%) cases, co-trimoxazole in 13 (61.9%), amoxicillin in 12 (57.1%), amoxicillin clavulanate in ten (47.6%) and nitrofurantoin in 11 (52.4%) cases.

Correlating culture result by clinical groups shows that 81% of the positive cultures were in Group one patients compared with 19% from Group two. Other clinical groups had negative cultures.

Fourteen (17.3%) of the patients had further clinical encounters, in which UTI was suspected in the index pregnancy. The diagnosis was confirmed by culture in only six (7.4%) patients; three of these patients had initial positive culture results with a recurrent infection rate of 3.7%. The second episode of UTI in all three patients was also caused by coliforms.

Table 1. Clinical symptoms.

Symptom	Number (%)
Urinary frequency	64 (82.0)
Suprapubic pain	57 (73.1)
Dysuria	43 (55.1)
Hematuria	11 (14.1)
Loin pain	7 (9.0)
Feeling unwell	6 (7.7)
Offensive smell of urine	4 (5.1)

Table 2. Antibiotics used at the initial consultation.

Antibiotic	Number (%)
Co-amoxyclavullinic acid	31 (47.0)
Amoxicillin	13 (19.7)
Cefalexin	9 (13.6)
Trimethoprim	7 (10.6)
Nitrofurantoin	4 (6.1)
Erythromycin	2 (3.0)

Of the 66 patients who received treatment, only 18 (27.3%) had positive cultures. Three (3.8%) patients in the study had formal follow-up with urine culture following treatment of confirmed UTI, and they did not have another episode of urinary infection in the index pregnancy.

Only patients in clinical Groups one and two had positive urine cultures, meaning that in the presence of symptoms the presence of nitrite has a sensitivity of 80.9%, specificity of 57.9% and positive predictive value of 41.4%. The presence of leukocytes had a sensitivity of 100%, specificity of 24.6% and positive predictive value of 32.8%. On the other hand, the negative predictive value of nitrites and leukocyte esterase are 89.2% and 100%, respectively.

Discussion

Mechanical and hormonal changes occurring during pregnancy increase the frequency with which UTI is seen in pregnant women over their non-pregnant counterparts. In addition to the known complications of UTI, its occurrence in pregnancy poses the risk of miscarriage, pre-term labor, IUGR, small for gestational age child and still birth. Pyelonephritis

[Downloaded free from http://www.sjkdt.org on Monday, September 28, 2015, IP: 186.42.102.68]

Table 3. Outcome of responses by clinical group.

Clincal group (n = 78)	Number (%)	Treated at 1st visit (n = 66)	Positive urine culture
1	41 (52.6)	41 (62.1%)	17 (81.0%)
2	23 (29.5)	19 (28.8%)	4 (19.0%)
3	7 (9.0)	4 (6.1%)	0
4	4 (5.1)	2 (3.0)	0
5	3 (3.8)	0 (0%)	0
Total	78 (100)	66 (100)	21 (100)

may lead to septicemia and renal insufficiency, with considerable maternal and perinatal morbidity and mortality. Therefore, the importance of appropriate diagnosis and treatment of this common pregnancy disorder cannot be overemphasized.

The standard criterion for the diagnosis of UTI in women with and without pregnancy has remained as the culture of urine and antibiotic sensitivity of isolated pathogen. This needs 48 h, necessitating high rates of empirical antimicrobial therapy. In this study, 84.6% of the patients had antibiotics started pending the outcome of culture and sensitivity test (Table 3). Simultaneous empirical antibiotic therapy and culture of urine is normative of current clinical practice. The criteria for diagnosis, use of diagnostic tests, interpretation of signs and symptoms and initiation of antibiotic treatment have been shown to vary considerably in the UK.[11] Little et al tested various models of therapy in primary care among patients with UTI outside pregnancy.[10] Delayed antibiotic approach for 48 h at the patient's discretion was associated with 4.8 days of moderately severe symptoms compared with 3.5 days in the group immediately treated with antibiotics. The immediate use of antibiotics and simultaneous culture was associated with increased short-term cost over one month. In pregnancy, the implication of delayed treatment to pregnancy-specific complications is not documented but may include miscarriage, pre-term labor or premature rupture of membranes (PROM).

Immediate antibiotic and culture approach on the other hand is based on clinical diagnosis, can have high false-positive rates, increases cost and has potential for antimicrobial resistance. Attempts to develop and validate an alternative diagnostic test based on bacterial DNA in the urine is limited by cost and low sensitivity and specificity.[12] The sensitivity of clinical diagnosis is 50–80%, but the specificity is low. There is a plethora of evidence that the urine dipstick test improves the specificity and sensitivity for UTI diagnosis in non-pregnant women.[10,13-15] The diagnostic accuracy of leukocyte esterase and nitrites among pregnant women was the subject of other studies with varying results. Similar to what has been reported by D'Souza and D'Souza, in this study also the presence of nitrites on bedside urinalysis had a sensitivity of 80.9% and specificity of 57.9%, and can form the basis for empirical antibiotic treatment where clinically deemed appropriate, but the specificity of leukocyte esterase (24.6%) was too low and antibiotic therapy on this basis should attract careful consideration.[16] Similarly, Bachman et al in a study of asymptomatic pregnant population also found that urine dipstick for nitrite identified half the patients with asymptomatic UTI, but the correlation of leukocyte esterase with UTI was poor.[17] On the other hand, Onakoya et al found a high specificity for both nitrite 78.8% and 90.5% for leukocyte esterase. The latter authors also had an unusually high rate of UTI of 46.3% in a randomly selected population of pregnant women, mostly asymptomatic.[18] In the current study of self-selected (symptomatic) patients, the rate of positive culture was 26.9%.

In this study, none of the patients in clinical Groups three, four and five had positive cultures. The rates of positive culture in Groups one and two on the other hand were 41.5% and 21.1%, respectively. Similarly, only the presence of nitrites and leukocyte esterase on dipstick testing of urine in patients attending

[Downloaded free from http://www.sjkdt.org on Monday, September 28, 2015, IP: 186.42.102.68]

outpatient with suspected diagnosis of UTI predicted the diagnosis. In this study, nitrites predicted the diagnosis with a sensitivity of 80.9%, similar to 77% in non-pregnant primary care patients, but the specificity and positive predictive values are considerably lower at 60% and 41.5% compared with the reported 70% and 81%, respectively.[12] In this pregnant population, the sensitivity of leukocyte esterase in the urine was 100%, with 28.3% specificity and positive predictive value of 32.8%. The corresponding reported figures outside pregnancy are 65%, 69% and 54%, respectively.[12] Possible reasons for very low specificity and positive predictive values for both leukocyte esterase and nitrite include the higher rates of UTI-like symptoms of urinary frequency and abdominal discomfort in pregnant state and the ease with which attending physicians entertain the diagnosis and start treatment. Overall, the predictive ability of dipstick test in symptomatic women has sensitivity of 75%, specificity of 69%, positive predictive value of 81% and negative predictive value of 57%.[10]

This study also examined the pattern of antibiotic use pending the outcome of culture results. Sixty-six (84.6%) patients were given immediate antibiotics following clinical diagnosis and UTI was confirmed in only 21 (31.3%) patients. Similarly, co-amoxiclavullinic acid, the most frequently prescribed antibiotic at this stage (47% patients), was found to have a resistance rate of 52.4%. The resistance rate to amoxicillin prescribed in 19.7% of the patients was 47.6% and that of cephalexin was 42.9%. The high rate of antimicrobial resistance in uropathogens isolated among renal transplant patients is common and has resulted in the development of algorithms like the Essen's algorithm to optimize treatment response.[19] A similar approach in pregnancy will limit unnecessary antibiotic exposure while mitigating the serious consequences of UTI for both the mother and fetus.

Trimethoprim and nitrofurantoin were empirically prescribed to 10.6% and 6.1% of patients, respectively. Yet, their sensitivity pattern revealed more modest resistance rates of 38.1% for trimethoprim and 47.6% for nitrofurantoin. The relatively low tendency of clinicians to empirically employ these antimicrobial agents is probably rooted in their perceived adverse effects on the fetus.[4]

Quinolones had the lowest resistance rate of 19.1% were not empirically prescribed in these subjects. There is a tendency to reserve this group of antibiotics for more severe infections, and their use in pregnancy is limited by safety concerns.[20] Three (3.8%) patients were further treated for confirmed UTI due to coliforms, although they had UTI due to the same organisms earlier on. It was difficult to ascribe the diagnosis of recurrent UTI to them as there was no documentation of clearing of their initial infection by urine culture.

In this study, it is seen that the present clinical algorithms for the diagnosis of UTI in pregnancy have low specificity and positive predictive value. Yet, there is a high rate of empirical treatment on this basis and the antibiotics often used are inconsistent with the sensitivity pattern. Empirical antibiotics may be considered in the presence of nitrites, but the specificity of leukocytes is too low to justify antibiotic use except on clinical grounds.

References

1. Bahadi A, Kabbaj D, Elfazzazi H,et al. Urinary tract infection in pregnancy. Saudi J Kidney Dis Transpl 2010;21:342-4.
2. Santos F, Oraichi D, Barard A. Prevalence and predictors of anti infective use during pregnancy. Pharmacoepidemiol Drug Saf 2010;19: 418-27.
3. Management of urinary tract infections in adults. Scottish Intercollegiate Guidelines Network. Guideline No. 88. SIGN; 2006: 13-15.
4. Santos F, Sheehy O, Perreault S, Ferreira E, Berard A. Exposure to anti infective drugs during pregnancy and the risk of small for gestational age newborns: A case control study. BJOG 2011;118:1374-82.
5. Le J, Briggs GG, McKeon A, Bustillo G. Urinary tract infections during pregnancy. Ann Pharmacother 2004;38:1692-701.
6. Schiemann G, Kniehl E, Gebhardt K, Matejczyk M, Hummer-Pradier E. The diagnosis of urinary tract infections a systematic review. Dtsch

[Downloaded free from http://www.sjkdt.org on Monday, September 28, 2015, IP: 186.42.102.68]

Arztebl Int 2010;101(21):361-7.
7. Morgan MG, McKenzie H. Controversies in the laboratory diagnosis of community acquired urinary tract infection. Eur J Clin Microbiol Infect Dis 1993;12:491-504.
8. Bent S, Mallamothu BK, Simel DL, Fihn SD, Saint S. Does this woman have uncomplicated urinary tract infection? JAMA 2002;287:2701-10.
9. McIsaac P, Moinedin R, Ross S. Validation of decision aid to assist physicians in reducing unnecessary antibiotic drug use for acute cystitis. Arch Int Med 2007;167:2201-6.
10. Little P, Turner S, Rumsby K, et al. Dipsticks and diagnostic algorithms in urinary tract infections: Development and validation, randomised trial, economic analysis, observational cohort and qualitative study. Health Technol Assess 2009;139:iii-iv, ix-x, 1-73.
11. Nazereth I, King M. Decision making by general practitioners in diagnosis and management of women with lower urinary tract symptoms. BMJ 1993;306:1103-6.
12. Lehmann LE, Hauser S, Malinka T, et al. Rapid qualitative urinary tract infection pathogen identification by SeptiFast real time PCR. PLoS One 2011;6:e17146.
13. Little P, Turner S, Rumsby K, et al. Validating the prediction of lower urinary tract infection in primary care: Sensitivity and specificity of urinary dipsticks and clinical scores in women. Br J Gen Pract 2010;60:495-500.
14. Dos Santos JC, Weber LP, Perez LR. Evaluation of urinalysis parameters to predict urinary tract infections. Braz J Infect Dis 2007;11:479-81.
15. Lunn A, Holden S, Boswell T, Watson AR. Automated microscopy, dipstick and the diagnosis of urinary tract infection. Ach Dis Child 2010;95:193-7.
16. D'Souza Z, D'Souza D. Urinary tract infection during pregnancy- dipstick urinalysis vs culture and sensitivity. J Obstet Gynaecol 2004; 24:22-4.
17. Bachman JW, Heise RH, Naessens JM, Timmerman MG. A study of various tests to detect asymptomatic urinary tract infections in an obstetrics population. JAMA 1993;270: 1971-4.
18. Onakoya JA, Amole OO, Ogunsanya OO, Tayo O. Comparing the specificity and sensitivity of nitrate and leucocytes tests on multistick in screening for urinary tract infections amongst pregnant women at Lagos state University Teaching Hospital Ikeja Nigeria. Nig Q J Hosp Med 2008;18:61-3.
19. Becker S, Witzke O, Rubben H, Kribben A. Urinary tract infections after kidney transplantation: Essen algorithm for calculated antibiotic treatment. Urologe A 2011;50:53-6.
20. Wagenlehner FM, Schmiemann G, Hoyme U, et al. Recommendations for treatment and management of uncomplicated community acquired bacterial urinary tract infections in adult. National S3 guideline. Urology A 2011; 50:153-69.