

Asymptomatic Bacteriuria in Pregnancy: Can Automated Urinalysis Be Helpful for Detection?

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Abstract

Objective: To assess whether or not automated urinalysis is helpful for detection of asymptomatic bacteriuria and urinary tract infections in pregnant patients. Accuracy is evaluated by using urine culture as a gold standard.

Materials and Methods: Midstream first void urine samples obtained from 102 pregnant women were tested using automated urinalysis to detect nitrite, total bacteria and leukocyte counts. Urine cultures were performed using blood agar and eosin methylen blue agar, and more than 100,000 colony forming units per ml indicated urinary tract infection or asymptomatic bacteriuria. Each result was compared with urine culture. Validity of the automated urinalysis was investigated, using sensitivity, specificity, positive and negative predictive values for each parameter and in combination.

Results: Nitrite positivity was found to be the most accurate (96%) variable for detection of UTI and AB, and showed excellent correlation with the urine culture ($r=0.8$, $p<0.001$). The combined use of three parameters reduced the sensitivity (33%) but increased specificity (100%), accuracy (92%) rates and positive and negative predictive values (100% and 92%, respectively). Total visible cost was €211.14 for automated urine analysis and €448.38 for urine culture for the 102 patients. However, when the cost of under/over treatment according to results of automated urine analysis is taken into account, its cost exceeds that of urine culture.

Discussion: Based on its high specificity and positive predictive value, patients with positive nitrite in automated urine analysis can be treated empirically until results of urine culture obtained. However, negative results for nitrite do not exclude asymptomatic bacteriuria and urinary tract infections, and urine culture is still needed for definite diagnosis. Although, it provides useful information, a routine use of automated urinalysis for screening of bacteriuria proved neither valid nor cost-effective in pregnant patients.

Keywords: asymptomatic bacteriuria, urinary tract infections, pregnancy

Özet

Gebelikteki Aseptomatik Bakteriüri Tanısında Otomatik İdrar Analizi Yararlı Olabilir mi?

Amaç: Gebe hastalardaki aseptomatik bakteriüri ve idrar yolu enfeksiyonları tanısında otomatik idrar analizinin yararlı olup olmadığını, altın standart idrar kültürü ile karşılaştırarak araştırmak.

Materyal ve Metot: Ardışık 102 gebe hastanın ilk işeme orta idrarları, hem idrar tetkiki hem de kültür için alındı. İdrar kültürü için kanlı agar ve eozin metilen mavisi agar kullanıldı. Mililitrede $>100\ 000$ koloni yapan birim aseptomatik bakteriüri veya idrar yolu enfeksiyonu için anlamlı kabul edildi. Otomatik idrar analizi ile nitrit varlığı, toplam bakteri ve lökosit sayılarına bakılarak, sonuçlar idrar kültürü ile karşılaştırıldı. Otomatik idrar analizinin geçerliliği, bakılan her bir ölçüt için ayrı ayrı ve birleşik olarak duyarlılık, seçicilik, pozitif ve negatif öngörü değerleri kullanılarak değerlendirildi.

Sonuçlar: Nitrit pozitifliği, aseptomatik bakteriüri ve idrar yolu enfeksiyonu tanısında doğruluğu en yüksek (%96) değişken idi ve idrar kültürü sonucuyla mükemmel korelasyon gösterdi ($r=0.8$, $p<0.001$). Her üç değişkenin birlikte kullanılması duyarlılığı (%33) azaltmakla birlikte, seçicilik (%100) ve doğruluk (%92) oranlarını ve pozitif ve negatif öngörü değerlerini (sırasıyla, %100 ve % 92) artırmaktaydı. Toplam maliyet 102 hasta için otomatik idrar analizinde 211.14 €, idrar kültüründe ise 448.38 € idi. Ancak, otomatik idrar analizi sonuçlarına göre gereksiz tedavi alacak veya tedavi almayacak hastalar da hesaba katılırsa otomatik idrar analizinin maliyeti idrar kültüründen fazla olmaktadır.

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Tartışma: Yüksek seçicilik ve pozitif öngörü değeri nedeniyle otomatik idrar analizinde nitrit saptanan hastalar, idrar kültür sonucu bekleninceye kadar ampirik olarak tedavi edilebilir. Ancak, negatif nitrit sonucu asemptomatik bakteriüri ve idrar yolu enfeksiyonlarını dışlamayacağı için bu hastalara kültür yapılmalıdır. Otomatik idrar analizi yararlı bilgiler sağlamakla birlikte, gebelikteki asemptomatik bakteriüri taramasında tek başına rutin olarak kullanılması geçerli ve maliyet-etkin bir yöntem olarak görülmemektedir.

Anahtar sözcükler: asemptomatik bakteriüri, idrar yolu enfeksiyonu, gebelik

Introduction

Urinary tract infections (UTI) occur more frequently in women as compared to men. Approximately 15% of women will have urinary tract infections at some time during their life. During pregnancy the incidence of asymptomatic bacteriuria (AB) and symptomatic UTI may be as high as 8% with potentially devastating results for both the mother and the baby (1,2). Nearly 1-2% of women may develop acute pyelonephritis secondary to bacteriuria during pregnancy that can be attributable to ureteral dilatation, urinary stasis on vesico-ureteral reflux, and glucosuria leading to bacterial growth. The risk of premature labor and low birth weight infants is also increased in patients with asymptomatic bacteriuria (3). On the other hand, inappropriate empirical antibiotic therapy increases the cost and the bacterial resistance. Therefore an easily performed, fast, non-invasive and cost-effective test that will accurately allow early diagnosis of asymptomatic bacteriuria during prenatal visits, is highly desired.

Although, urine culture is the definitive standard for the screening of asymptomatic bacteriuria, it is time consuming and expensive. Automated urine analysis is a widely available, rapid and relatively inexpensive test that is performed as part of the routine screening of pregnant patients for kidney or urinary tract disorders, and other medical conditions. The aim of this study was to evaluate the accuracy and cost-effectiveness of computerized urine analysis compared to standard urine culture.

Materials and Methods

Study population

Between May 2005 and September 2005, 102 consecutive pregnant patients undergoing routine obstetrical examination in the Obstetrics and Gynecology Clinic of Denizli State Hospital were prospectively investigated for the presence of bacteriuria. The age of the patients ranged from 17 to 40 years (mean \pm SD, 26 \pm 5 years), and all women had singleton pregnancies between 7 weeks and 39 weeks' (mean \pm SD, 20.5 \pm 9.1 weeks) gestation. All subjects were informed on the aim of the study and gave consent. Patients with active vaginal bleeding or those currently on antibiotic therapy were excluded from the study.

Urinalysis

Midstream first void urine samples were obtained at the same time for both urine analysis and urine culture during routine prenatal visits. Urine analysis was performed with fully automated urine analyzer (TOA Medical Electronics,

Kobe, Japan). Urine cultures were performed immediately within 5 to 10 minutes of sampling. Blood agar and eosin methylene blue dye were used for cultures. More than 10⁵ colony forming units per milliliter indicated urinary tract infection or asymptomatic bacteriuria. Disc diffusion technique was used for antibiotic sensitivity test in accordance with National Committee for Clinical Laboratory Standards (NCCLS) criteria (4). According to standard references in our laboratory, the leukocyte count above 10/ml, the bacteria count above 1200/ml and positive nitrite were considered abnormal.

Leukocyte count, bacterial count, PH and nitrite positivity were evaluated and compared to urine culture results separately. Sensitivity, specificity, positive and negative predictive values and accuracy were calculated for each parameter.

Costs

Only direct costs were considered. Indirect costs such as loss of earnings were not analyzed. Cost data were actual costs extracted from the database of our hospital, during the fiscal year 2005, and expressed in Euro (1€=2 Turkish Liras). Cost-effectiveness of automated urine analysis was compared to that of urine culture.

Statistical analysis

The statistical analyses were performed using commercially available software (SPSS, 11.0, Chicago, IL, USA). Continuous variables were expressed as mean \pm standart deviation (SD). The Mann-Whitney U test was used to investigate the differences of the leukocyte and bacteria count in urine between patients with and without positive urine culture. The χ^2 test was used to analyze differences between patients with and without positive urine culture in terms of nitrite positivity, elevated leukocyte and bacteria counts. Spearman's rank correlation coefficients were applied to assess the correlation between the culture positivity and leucocyte and bacterial counts in the urine. A *p* value equal to or less than 0.05 was considered statistically different.

Results

Urine culture was positive in 12 (11.8%) patients out of 102. *E. coli* was isolated in 11 of the 12 patients and *Proteus mirabilis* in one patient. We performed urine culture for all patients, and waited for the culture results to start treatment in the asymptomatic patients. For each individual, €2.07 and €3.39 were spent for urine analysis and urine culture, respectively. Performing urine culture for all the study population cost €345.78. Treating patients with asymptomatic bacteriuria cost around €6.15 (Fosfomycin-Monurool granül®)

Table 1. The relationship between positivity of the urine culture and the elevated counts of bacteria and white blood cells and nitrite-positivity

		Elevated bacteria count		Elevated WBC count		Nitrite		Total
		Positive	Negative	Positive	Negative	Positive	Negative	
Culture	Positive	9	3	8	4	8	4	12
	Negative	35	55	44	46	0	90	90
Total		44 (43)	58 (57)	62 (61)	50 (49)	8 (8)	94 (92)	102

WBC: white blood cell count.
Numbers in parentheses are percentages.

Table 2. The sensitivity, specificity, positive and negative predictive values, and accuracy for parameters of urine analysis

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Elevated bacteria count	75 (42-94)	61 (50-71)	20 (9-50)	94 (85-98)	63
Elevated WBC count	67 (34-90)	51 (40-61)	15 (6-28)	92 (80-97)	53
Nitrite positivity	67 (34-90)	100 (95-100)	100 (63-100)	96 (89-98)	96
Cumulative*	33 (9-65)	100 (95-100)	100 (39-100)	92 (84-96)	92

WBC: white blood cell count,
PPV: positive predictive value,
NPV: negative predictive value.
*Combination of elevated bacteria and white blood cell counts and nitrite positivity.
Numbers in parentheses are 95% Confidence Intervals calculated with binominal expansion.

and €8.55 (Amoxicillin-clavulanate potassium, Augmentin®) for each patient, resulting in €73.8 to €102.1 for 12 patients. When the cost of urine culture was added, the total amount was €328.98 to €448.38.

Of the 102 patients, 52 (51%) had white blood cell count above the cut off level (>10/ml), and 44 (43.1%) had bacterial count above the cut off level (>1200/ml). Nitrite was positive in 8 (7.8%) patients. When patients with positive and negative urine cultures were compared, nitrite positivity and bacterial count was significantly different between two groups ($p<0.001$, and $p=0.02$, respectively). Nitrite positivity showed excellent correlation with the positive urine culture ($r=0.8$, $p<0.001$), whereas both white blood cell (WBC) and bacterial counts showed mild correlation with urine culture results ($r=0.23$, $p=0.02$, and $r=0.22$, $p=0.03$, respectively).

Bacterial count above the normal limits predicted bacteriuria with 75% sensitivity (95% confidence interval [CI], 0.42-0.94). The most specific parameter for bacteriuria was nitrite positivity with a specificity of 100% (95% CI, 0.95-1.0); positive and negative predictive values of 100% (95% CI, 0.63-1.0) and 96% (95% CI, 0.89-0.98), respectively and an accuracy of 96% (Table 2).

If the bacterial count were taken as a reference, we would have treated 35 patients unnecessarily at a cost of €482.47 and €587.85, according to medicine chosen, including the cost of urine analysis, and we would have missed three patients.

Leukocyte count was the other parameter we took into consideration. It showed 53% accuracy and was able to

detect most patients with UTI but we would have overtreated 44 patients. Depending on the prescribed medication, it would have cost around €464.94 to €689.94 and we would have missed four patients.

Nitrite positivity was observed as the most accurate (96%) test for detection of bacteriuria. Sensitivity, specificity, positive and negative predictive values of nitrite positivity were 67% (95% CI, 0.34-0.90), 100% (95% CI, 0.95-1.00), 100% (95% CI, 0.63-1.00), and 96% (95% CI, 0.89-0.98), respectively.

The combined use of the three parameters increased the accuracy to 92%, as well as improving specificity, and the positive and negative predictive values, but lowered the sensitivity (Table 1).

Discussion

Urinary tract infection in pregnancy is a common cause of serious maternal and perinatal morbidity (5) which can be reduced with prompt diagnosis and appropriate treatment. Pregnant women with asymptomatic bacteriuria have a 20-30 fold increased risk of developing pyelonephritis compared to women without bacteriuria (6,7). Antimicrobial treatment of asymptomatic bacteriuria during pregnancy decreases the risk of subsequent pyelonephritis from 20-35% to 1-4% (7). Pregnant women with asymptomatic bacteriuria are also more likely to have premature delivery and low birth weight infants (6). Meta-analysis of cohort studies and randomized clinical trials support the conclusion that antimicrobial treatment of asymptomatic bacteriuria decreases the frequency of low-birth weight infants and preterm delivery (8). Hence, screening at least once in

early pregnancy of all gravid women for bacteriuria, and treatment, if the results are positive, is recommended. Implementation of screening programs reportedly decreased the rate of pyelonephritis from 2.1% to 0.5% in a health care center in Turkey (9).

Simple urine analysis, dipstick and enzymatic urine screening tests are usually preferred to urine culture for screening purposes since they are fast, cheaper and easily performed even at the first step medical centers. Automated urine analysis is a widely available, fast and relatively inexpensive test that is performed as part of the routine evaluation of pregnant patients screened for renal or urinary tract disorders. However, to date, no previous study has evaluated the clinical utility of the automated urine analysis to detect bacteriuria during pregnancy. In this study, we aimed to evaluate the accuracy and the cost-effectiveness of computerized urine analysis compared to the definitive standard urine culture.

Our results showed 33% cumulative sensitivity and 100% specificity of the automated urinalysis for detecting bacteriuria (Table 2). The published studies on enzymatic urine screening test have conflicting results (10-12). Hagay et al. (10) claimed that the uriscreen test is a reliable alternative to culture for screening pregnant patients, giving 100% sensitivity and 81% specificity in the detection of 24 (8%) women with positive urine cultures out of 313 pregnant population. However, Millar et al. (11) and Teppa et al. (12) reported that the test had an inadequate accuracy with a sensitivity of 70% and 61%, and specificity of 45% and 89%, respectively, in populations of 383 and 150 pregnant women, respectively. Wide variations in sensitivity and specificity in the previous studies probably originated from the spectrum of uropathogens isolated in different populations or different methods used for the analyses. Since the results are highly variable, the reliability of urine analysis is questionable whether or not it is automated.

Leukocyte and bacterial counts and nitrite positivity are commonly taken into consideration for evaluation of patients. Pyuria may be seen in up to 30-70% of pregnant patients with asymptomatic bacteriuria (13,14). It also accompanies other genitourinary inflammatory conditions such as vaginal infections, renal tuberculosis and interstitial nephritis (6). Therefore, pyuria has a low sensitivity in allowing the identification of bacteriuria in only half of the affected pregnant women (13). In line with the previous reports, the presence of pyuria had a sensitivity of 67% and a specificity of 51% in this study. Thus, presence of pyuria neither reliably detects presence of bacteriuria nor differentiates the symptomatic from asymptomatic urinary tract infection.

Nitrite is not found in normal urine and the gram-negative bacteria reduce dietary nitrate to nitrites. In this study, positive nitrite test seems to be highly specific (100%)

variable with high positive (100%) and negative (92%) predictive values. On the other hand, it has low sensitivity (67%) which may result from the lack of dietary nitrate or infections due to *enterococci* and *Acinetobacter spp.* that do not reduce nitrate as well as some *Pseudomonas* species that reduce nitrate to nitrogen gas (10,11). Furthermore, pathogens may not have time to reduce nitrate to nitrite when the bladder incubation time is insufficient. Therefore, a positive urinary nitrite test is highly suggestive for bacteriuria but absence of it does not necessarily eliminate the possibility of infection.

The present study was performed in only 102 pregnant patients and 12 of them had positive urine culture. Except one, *E. coli* was the isolated microorganism in all patients with positive urine culture. Usually Ampicillin has been the drug of choice, but in recent years 20% to 30% rise in *E. coli* resistance to ampicillin has been observed (15). Amoxicillin/clavulanate and cephalosporins are well tolerated and can be selected for the treatment. Usually 5-10 days of treatment is recommended for the treatment of pregnant patients (5). Fosfomycin (Monourol), a new single-dose antibiotic, may be another alternative. All of these three drugs are in group B category and can be used in pregnant women safely (15,16).

Our study did have limitations. Firstly, the study population and the patients with positive urine culture results were relatively small with an apparent predominance of *E. coli* as an isolated microorganism. Larger series of patients with a whole spectrum of uropathogens would have been more appropriate to draw strong conclusions. Secondly, the timing of screening in our cohort covered a wide range. Selective screening in the first trimester with a prospective follow up could have provided more information about the outcome of the mother and baby, and the effectiveness of the treatment regimens.

In conclusion, automated urine analysis seems to be a practical and fast test independent of performer bias for the detection of urinary tract infection and asymptomatic bacteriuria in pregnancy. Nitrite positivity appears to be the most accurate variable for detection of bacteriuria. Because of high specificity and positive predictive value, those patients with positive nitrite results can be treated empirically until culture results are obtained. Nevertheless, the absence of nitrite does not reliably exclude the possibility of infection. Thus, automated urinalysis does have misleading results precluding its general use for screening purposes in pregnancy. Although it is inexpensive compared to urine culture, it is not cost-effective when the cost originating from unnecessary treatment is considered. Urine culture remains the definitive standard technique and its use as the screening method for asymptomatic bacteriuria seems to be more reliable and cost-effective compared to computerized urine analysis.

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