LABORATORY ASPECTS OF ASYMPTOMATIC BACTERIURIA IN PREGNANCY

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Abstract. A total of 1,661 pregnant women aged between 13 and 45 years were screened for bacteriuria by urine culture. Of the 1,661 culture results, 615 (37%) yielded no growth; 728 (43.8%) yielded no significant growth (presence of $<10^5$ organisms/ml urine of one or more types of bacteria); 286 (17.2%) yielded mixed growth (presence of $>10^5$ organisms/ml urine of more than one type of bacteria) and only 32 (1.9%) showed significant growth (presence of $>10^5$ organisms/ml urine of a single bacterium). Urine microscopy was also conducted. Two hundred and twenty-four (13.5%) specimens had > 10 white blood cells/ml urine, of which 66 had > 100 white blood cells; 13 were from the significant growth group. Three hundred and seventy-four (22.5%) specimens showed the presence of bacteria, 42 (2.5%) had red blood cells, 370 (22.3%) had epithelial cells, 58 (3.5%) had crystals, and 14 (0.8%) had yeasts. The most common bacterium isolated was *Escherichia coli* (12; 40%); the others included group B Streptococcus (5; 15%), *Klebsiella* spp (5; 15%), Diphtheroids (2), and *Candida albicans* (2). Fifty-two percent of tested strains were sensitive to ampicillin; 24 of 28 strains (85.7%) were sensitive to ciprofloxacin; all 7 strains tested were sensitive to nitrofurantoin and all 20 strains tested were sensitive to cotrimoxazole; 14/20 (70%) and 16/17 (94.1%) were sensitive to cephalexin and cefuroxime respectively. This study shows that asymptomatic bacteriuria does occur in pregnant women, albeit at a very low rate in an urban setting like Cheras. Urine microscopy is not specific and only serves as a guide to bacteriuria. The commonest causative organisms are those from the gastrointestinal tract and vagina. The antibiogram showed that cefuroxime and cephalexin are likely to be effective in treating bacteriuria : ampicillin must be reserved for Gram-negative organisms. For Gram-positive organisms, of which Group B Streptococcus is important, ampicillin is still effective *in vitro*. Nitrofurantion and cotrimoxazole have excellent activity *in vitro* and should be considered for therapy. 17.2% of the urine culture yielded mixed growth: likely to indicate that contamination of urine specimens still happens despite the strict instructions given to patients about the collection of a midstream urine specimen. Proper collection, appropriate transport, and the early processing of urine specimens remain essential.

INTRODUCTION

Asymptomatic bacteriuria (ABU) is now a recognized entity in the spectrum of urinary tract infections (UTIs). Asymptomatic bacteriuria is defined as a significant bacterial count (> 10^5 organisms or colony forming units present per milliter) in the urine of a person without symptoms (Kass, 1960). Asymptomatic bacteriuria may precede symptomatic urinary tract infection and is commonly associated with individuals who have predisposing factors, such as the elderly, pregnant women, children with subtle anatomical defects of the urinary tract, patients with chronic diseases like diabetes mellitus, those who have urinary catheters, and patients who are admitted to hospital for lengthly periods.

Asymptomatic bacteriuria is more prevalent in women than in men and its occurrence during pregnancy raises the issue of routine urine

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screening. Although data are limited, it is generally accepted that asymptomatic bacteriuria is detrimental to pregnancy (Kaitz, 1961). Asymptomatic bacteriuria in pregnancy may lead to pyelonephritis and acts as an impetus for recurrent urinary tract infections (Kiningham, 1993); it has also been associated with preterm delivery and low birth weight babies (Mittendorf *et al*, 1992). Screening for asymptomatic bacteriuria, by urine culture, has already been recommended in some countries for all pregnant women, but not for the other groups mentioned above (Nicolle, 1994). In Malaysia, there is no consensus regarding specific screening during the antenatal period, although routine basic urine examination may be performed. There is a lack of local data about the incidence and prevalence of urinary tract infection in the general population; data about the antenatal group are equally scarce, which makes it difficult to recommend routine screening by urine culture.

A pilot study to address the issue was conducted in the antenatal clinic of the Department of Obstetrics and Gynecology, Hospital Universiti Kebangsaan Malaysia (HUKM) and supported by the Department of Medical Microbiology and Immunology, HUKM.

PATIENTS AND METHODS

From January to December 2000, all women who were registered at the antenatal clinic for the first time were enroled into the study. Women were randomly allocated to one of two arms: women in the first arm were screened for ABU by microscopy and culture of a midstream urine sample and automated urinalysis; women in the second arm were screened by automated urinalysis alone. This paper deals only with women in the first arm of the study. Urine specimens were processed and cultured in the clinical microbiology laboratory following the guidelines of the National Committee for Clinical Laboratory Standards. Women with a positive culture were told to return to the clinic and provide a second midstream urine specimen; these patients were selectively offered treatment based on antibiotic sensitivity testing. The panel of antibiotic discs for sensitivity testing were determined by the type of organisms (either Gram-positive or Gram-negative organisms) isolated. Approval for the study was obtained from the UKM Research Ethics Committee.

RESULTS

A total of 1,661 pregnant women (999 Malays; 538 Chinese; 100 Indians; 8 Sikhs; 16 of other races) were screened for bacteriuria by the urine culture method. Their ages ranged from 13 to 45 years. Of the 1,661 urine culture results, 615 (37%) had no growth; 728 (43.8%) yielded no significant growth (presence of $<10^5$ organisms/ml urine of one or more types of bacterium); 286 (17.2%) yielded mixed growth (presence of $>10^5$ organisms/ml urine of more than one type of bacterium) and only 32 (1.9%) showed significant growth (presence of $>10^5$ organisms/ml urine of a single type of bacterium).

The urine samples were examined by microscopy for bacteria, red blood cells, white blood cells, and other elements, *eg* casts and crystals. A total of 224 (13.5%) specimens had

Table 1
Bacteria isolated.

Bacteria isolated	Number of cases (%)
Escherichia coli	12 (40)
Group B streptococcus	5 (15)
Klebsiella spp	5 (15)
Diptheroids	2 (6)
Candida albicans	2 (6)
Staphylococcus aureus	1 (3)
Staphylococcus epidermidis	1 (3)
Providencia rettgeri	1 (3)
Streptococcus viridans	1 (3)
Acinetobacter spp	1 (3)
Candida spp	1 (3)
Total number	32

Table 2
Antibiotic-sensitive strains : by organisms and antibiotic.

	AMP	CIP	GN	NIT	VAN	TET	ERY	PEN	CLO	COT	CEP	CEF
Escherichia coli	6/11	10/11	11/11							11/11	6/11	10/11
Klebsiella spp	0/5	4/5	4/5							5/5	5/5	4/4
Providencia	0/1	0/1	1/1							1/1	1/1	1/1
Acinetobacter	0/1	1/1	1/1							1/1	0/1	1/1
Group B streptococcus	5/5	4/5	5/5	5/5	4/5	1/5						
Staphylococcus epidermidis		1/1	1/1	1/1					1/1	1/1	1/1	
Staphylococcus aureus	1/1	1/1	1/1							1/1	1/1	
Streptococcus viridans	1/1	1/1		1/1	1/1	1/1						
Diphtheroids		2/2	2/2		2/2	2/2	2/2	1/2				
(All)	13/25	24/28	26/27	7/7	7/8	4/8	2/2	1/2	1/1	20/20	14/20	16/17

AMP = ampicillin; CIP = ciprofloxacin; GN = gentamicin; NIT = nitrofurantoin;
VAN = vancomycin; TET = tetracycline; ERY = erythromycin; PEN = penicillin;
CLO = cloxacillin; COT = cotrimoxazole; CEP = cephalexin; CEF = cefuroxime

> 10 white blood cells/ml urine, of which 66 had > 100 white blood cells and 13 were from the significant growth group. Three hundred and seventy-four (22.5%) specimens showed the presence of bacteria; 42 (2.5%) had red blood cells, 370 (22.3%) had epithelial cells; 58 (3.5%) had crystals; and 14 (0.8%) showed yeasts.

The most common bacterium isolated was *Escherichia coli* (12; 40%); the other organisms were group B Streptococcus (5; 15%), *Klebsiella* spp (5; 15%), Diphtheroids (2), *Candida albicans* (2), *Staphylococcus aureus* (1), *Staphylococcus epidermidis* (1), *Providencia* spp (1), *Streptococcus viridans* (1) *Acinetobacter* spp (1) and *Candida* spp (1).

The Gram-negative organisms, *eg E. coli* and *Klebsiella* spp, were tested for their sensitivity to ampicillin, ciprofloxacin, gentamicin, cotrimoxazole, cephalexin and cefuroxime. Group B Streptococcus was subjected to ampicillin, ciprofloxacin, gentamicin, nitrofurantoin and vancomycin.

Of the 25 strains that were exposed to ampicillin, 13 (52%) were sensitive; of the 28 strains exposed to ciprofloxacin, 24 (85.7%) were sensitive; 7 of 8 (87.5%) strains exposed to vancomycin were sensitive; 14 of 20 (70%) were sensitive to cephalexin; 16 of 17 (94.1%) were sensitive to cefuroxime; all of the strains that were exposed to nitrofurantoin and cotrimoxazole were sensitive : 7/7 and 20/20 respectively.

DISCUSSION

Urinary tract infection (UTI) is one of the commonest infections affecting females (Barnet and Stephens, 1997); it is also a common, if not the commonest nosocomial infection (Mulholland and Bruun, 1973). UTI can occur primarily or secondarily in which it is associated with a predisposing factor. The predisposing factors are related to either the functional integrity of the urinary tract (*eg* old age, pregnancy, anatomical abnormalities, chronic and debilitating diseases) or to invasive intervention (*eg* catheterization, surgery). UTI refers to infection anywhere in the urinary tract (the urethral meatus to the kidneys) and is defined by the presence of a significant quantity of bacteria in the urine (bacteriuria) and clinical symptoms of infection. Traditionally, UTI is the finding of greater than 10^5 colony forming units (cfu) of an organism per milliter in a symptomatic patient (Pryles and Lustik, 1971). Symptoms include frequency of micturition, dysuria, pyuria, hematuria, lower abdominal and

flank discomfort or pain, and fever. Kass (1956) identified a population of individuals who presented with significant bacteriuria but without symptoms. These individuals were found to also have a propensity to develop recurrent UTI and the complications associated with UTI; the term of 'asymptomatic bacteriuria' was coined. Asymptomatic bacteriuria usually occurs in individuals with predisposing factors: this raises the issue of screening for asymptomatic bacteriuria. However, because screening may not be cost effective, it is recommended only for a selected group. UTI is the most common infectious disease to occur in pregnancy resulting in five times as many febrile episodes as viral infections (Maranchie *et al*, 1997); it also carries a much greater risk of progressing to recurrent symptomatic UTI and chronic renal disease (Kinningham, 1993). The evidence that UTI in pregnancy may lead to preterm delivery and low birth weight babies (Mitterdorf *et al*, 1992) supports screening for asymptomatic bacteruria in pregnancy (Nicolle, 1994). Studies have shown that the screening and subsequent treatment of asymptomatic bacteriuria in pregnancy are effective methods for the reduction of symptomatic UTI and preterm delivery (Mitterdorf *et al*, 1992; Gratacos *et al*, 1994). Various studies have determined the prevalence of asymptomatic bacteriuria in pregnancy (Brown *et al*, 1987; Hooton, 1990; Kinningham, 1993). The prevalence ranged from 2 to 7% of normal pregnancies. Our study showed a comparatively low prevalence (1.9%). Data about the socio-demographic status of the study population was not available and therefore, the relationship between socio-demographics and the low prevalence rate could not be considered.

One study has shown that universal urine screening for pregnant women is cost effective if the prevalence of asymptomatic bacteriuria is greater than 2% and the cost of the screening test was less than US$ 26.00 (RM65.00) (Wadland and Plante, 1989). In our study, the prevalence of asymptomatic bacteriuria was only 1.9% and may have been less considering that some of the isolates were due to contamination. In view of this, universal urine screening for pregnant women will not be cost-effective, although further studies remains warranted.

The causative organisms usually associated with UTI in pregnancy are members of the gastrointestinal and vaginal flora. These include Gram-negative organisms, *ie Escherichia coli*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Proteus*, *Providencia* and *Morganella* spp (Elder *et al*, 1971; Maranchie *et al*, 1997). These organisms are also the major causative agents of UTI in other groups of patients; *Serratia* spp, *Pseudomonas aeruginosa*, *Acinetobacter* spp, and *Candida albicans* are often responsible for nosocomial UTIs (Mulholland and Bruun, 1973). These organisms are rarely found to be the cause of uncomplicated UTIs in pregnancy. Their isolation in our study is questionable because they could have arisen from contamination. For example, *Candida albicans* can be either normal vaginal flora or the cause of candidiasis. Were improper collection of mid-stream urine to occur, the yeast, and even numerous white blood cells would be present in the urine. The Gram-positive organisms, *ie* group B streptococci, enterococci, *Staphylococcus saprophyticus* and *Staphylococcus epidermidis*, are common causes of pregnancy-associated, community acquired, and nosocomial UTIs. Diphtheroids and *Streptococcus viridans* which are normal skin flora rarely act as pathogens and can be regarded as contaminants (Kellog *et al*, 1987). Having considered the likelihood of contamination, the prevalence of significant asymptomatic bacteriuria in pregnancy in this study was as low as 1.4% (24/1661).

The antibiotic sensitivities of the isolated organisms are helpful in determining the appropriate antibiotics. The range of antibiotics that can be used in pregnancy is rather limited because the possibility of fetal damage (Bukhari and Livsey, 2000). Ampicillin can be used selectively for Gram-negative organisms and remains the best choice for group B *Streptococcus*. Ciprofloxacin, while fairly effective across the board, is contraindicated in pregnancy.

Nitrofurantoin is very effective against Gram-positive organisms *in vitro*. Its long record

of safety in pregnancy and its bioavailability in urine make it a good choice. For the Gram-negative organisms, cephalexin remains a sound choice, provided that urine culture and an antibiogram support its use. Cefuroxime may give even better results, as it does *in vitro*. Cotrimoxazole showed impressive activity against both Gram-positive and Gram-negative organisms, however it must be used with caution in pregnancy.

From this study, the drug of choice for the empirical treatment of suspected UTI in pregnancy is cefuroxime, assuming that the Enterobacteriaceae are the predominant pathogens. Cephalexin is recommended only when an initial urine for culture and sensitivity is available and patients can readily be followed-up. If vaginal colonization with group B *Streptococcus* is diagnosed, then ampicillin or nitrofurantoin can be used empirically. In cases of GBS UTI, vaginal carriage should be investigated: positive carriage should prompt the vigilant and noted so that there is an increased monitoring of infections in both the neonate and the mother. Antibiotic treatment, notably penicillin, during labor or after membrane rupture, has been recommended for pregnant women who have a GBS UTI or who have had a baby with GBS disease, or those who are found to be GBS carriers (Hankins and Chalas, 1993). After delivery, cotrimoxazole or ciprofloxacin can be used to treat subsequent UTIs.

Regardless of the low incidence of asymptomatic bacteriuria in pregnancy, UTI should always be kept in mind because of its serious complications. Effective treatment should be instituted and closely monitored; follow-up is recommended. Ideally, the management of asymptomatic bacteriuria in pregnancy would start with first trimester screening of urine by culture. If significant bacteriuria is found, then a second specimen should be repeated within a few days: if this is positive, then antibiotic therapy should start. Depending on the results of antibiotic susceptibility testing, either cefuroxime 125-250 mg or cephalexin 250-500 mg or ampicillin 250-500 mg or nitrofurantoin 100 mg four times a day is recommended. Treatment should be for at least 10 days, followed by a repeat urine culture. Despite the clearance of bacteria after treatment, urine screening is still recommended in the third trimester to ensure that there is no recurrence. At least one further screen should be conducted postnatally. This strategy would be difficult to adopt in our circumstances because patients are often seen elsewhere in early pregnancy and are only referred to us late in the second trimester or in the third trimester; moreover, patients with uncomplicated pregnancy and delivery are referred back to their local clinic for postnatal follow-up and are not seen again in our hospital.

The use of urine microscopy as a means of screening for UTI was found to be non-specific (Pels *et al*, 1989). A diagnostic yield of less than 3% in detecting clinically significant disorders by routine microscopic examination of urine that appears to be grossly normal was reported in several studies (Bachman *et al*, 1993; Schumann and Greenberg, 1979). In this study the number of specimens yielding mixed growth, which is highly likely to be a result of contamination secondary to improper collection of a mid stream urine specimen, amounted to 17.2 %. Other studies have shown higher rates of contamination (Bartlett and Treiber, 1984). The proper collection of urine, followed by appropriate transportation and early processing is imperative.

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