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Antibiotic susceptibility of bacterial strains causing asymptomatic bacteriuria in pregnancy:a cross–sectional study in harare, Zimbabwe

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Abstract

Background and objective: Effective treatment of asymptomatic bacteriuria in pregnancy requires susceptible drugs. The aim of this study was to determine antibiotic susceptibility pattern among isolated bacterial species among pregnant women with asymptomatic bacteriuria.

Materials and methods: This study was conducted at 4 selected primary health care facilities in Harare, including pregnant women registering for antenatal care at gestation between 6 and 22 weeks and without urinary tract infection symptoms. Asymptomatic bacteriuria was diagnosed by culture test of all midstream urine samples following screening by Griess nitrate test. Susceptibility test was done for all positive 24 hour old culture using the disk diffusion test. The minimum inhibitory concentration was measured and categorized as susceptible, resistant and intermediate.

Results: Tested antibiotics included gentamycin (88.2%), ceftriaxone (70.6%), nitrofurantoin (76.5%), ciprofloxacin (82.4%), ampicillin (67.6%) and norfloxacin (61.8%). Prevalence of asymptomatic bacteriuria was 14.2% (95% CI, 10.28% to 19.22%). Coagulase negative staphylococcus was the most popular (29.4%) bacteria followed by *Escherichia coli* (23.5%). Gentamycin (83.3%), ciprofloxacin (75%) and ceftriaxone (70.8) overally had the highest sensitivity. Nitrofurantoin was overally least sensitive (19.2%) but highly resistant (80.8%).

Conclusion: Drug resistance was noted to be common among bacteria responsible for asymptomatic bacteriuria in pregnancy. Susceptibility test is a recommended test to guide treatment during pregnancy.

Keywords: Asymptomatic bacteriuria, Pregnancy, Effective treatment, Antibiotic, Susceptibility test, Resistance, Susceptible, Minimum inhibitory concentration

Abbreviations

ASB, Asymptomatic Bacteriuria; UTI, Urinary Tract Infection; UTIs, Urinary Tract Infections; MIC, Minimum Inhibitory Concentration

Introduction

Asymptomatic bacteriuria (ASB), a type of urinary tract infection (UTI), is one of common infections in pregnancy requiring antibiotic treatment. ASB is defined as growth of more than 100 000 colony forming units per millilitre (cfu/ml) in culture of midstream urine obtained from an individual without signs and symptoms of asymptomatic bacteriuria.[1,2] ASB prevalence generally ranges from 2% to 10%.[3] Anatomic and physiological changes occurring during pregnancy increase the risk of ASB.[4] When ASB is untreated in pregnancy it often progresses later in pregnancy to pyelonephritis, an acute (UTI).[5] Pyelonephritis is symptomatic bacteriuria associated with several pregnancy complications and adverse birth outcomes including pre– eclampsia, preterm birth, low birth weight and neonatal death.[6,7] Up to 40% of pregnant women develop a symptomatic UTI later in pregnancy if ASB is undetected and untreated.[3,8,5] Screening and treatment of ASB during pregnancy is an important intervention to be implemented at primary care level.[9] Treatment of ASB in pregnancy using effective antibacterial treatment decreases risk of acute urinary tract infection from 40% to 1 to 4%.[3–10] All complications of ASB during pregnancy are reduced by antibiotic therapy.[9] Several international and national guidelines recommend screening and treatment of ASB to reduce risk of pyelonephritis.[6] Several antibiotics are available for selection for treatment of ASB in pregnancy including, amoxil, ampicillin, cephasporin, nitrofurantoin, trimethoprim and sulfamethoxazole.[2] Treatment of ASB with antibiotics in pregnancy aims to clear the infection, which is only possible if the isolated bacterium is susceptible to it.[6] Selection of antibiotic to treat ASB need to be based on antibiotic susceptibility results.[9] Susceptibility test informs on effectiveness of antibiotics against infectious organisms and degree of bacterial resistance pattern.[11]. The test results help to guide clinicians on appropriate selection of effective antibiotics for pathogenic strain and to prevent prescribing and administration of resistant and ineffective antibiotics.[11,12] Results of the test are often categorized as susceptible, resistant or intermediate depending on size of minimum inhibition concentration (MIC).[11] Susceptible result implies that growth of the bacterial strain is likely though not guaranteed to be inhibited by usual concentrations of an antibiotic for the site of infection where the MIC is small and or equal to diameter than the susceptible breakpoint.[12] Bacteria strain is said to be resistant when the usually achievable concentrations of antibiotic will not inhibit growth of the isolate and treatment is highly likely to fail with MIC higher or equal than resistant breakpoint.[11] Intermediate category means response rate may be lower than for susceptible isolates and that there is uncertainty on antibiotic treatment effect and possibly increasing dose may help to prevent ineffectiveness of drug, where MIC is between resistant and susceptible.[12] Empirical treatment, a common practice, is only useful and effective for some pathogens with no history of resistance.[12] There is presently alarmingly increasing reports internationally about bacterial resistance among strains responsible for UTIs including ASB.[10–13] Antibiotic resistance was known in the world since 2000 and is currently believed to cause a delay in proper treatment, resulting in prenatal mortality and morbidity.[1] Knowledge of local sensitive and resistant pattern of uro–pathogens is therefore required for efficacy and prevention of resistant rates. Accurate susceptibility results will also help nurses and doctors with a guide on determination of empirical therapies before sensitivity results are out and even in settings where culture is unavailable. Empirical approach, which could be promoting development of multidrug resistant bacterial strains. These will be difficult to clear and a result in treatment failure, prolonged hospital admissions and increased costs of care and treatment and infant or maternal deaths.[14] In Zimbabwe ASB screening and treatment in pregnancy is not well understood. Screening of the disease during antenatal care is unavailable. Urine culture and susceptibility test is not routinely done possibly due to its high cost. Empirical treatment of UTIs is popularly practiced in primary health care centres possibly due to unavailability of culture test in these settings in Zimbabwe. Wide use of this approach could be promoting development of multidrug resistant bacterial strains resulting in ineffective antibiotic treatment. Knowledge of antibiotic susceptibility patterns is therefore required to guide treatment choice on empirical therapies for UTIS, including ASB in pregnancy in the country. The aim of this study was to determine antibiotic susceptibility pattern among isolated bacterial species responsible for ASB in pregnancy. The study was conducted to determine sensitivity of organisms to antibiotics. It was also done to determine which antibiotics would inhibit growth of bacterial strains responsible for ASB in pregnancy.

Materials and methods

A descriptive cross sectional study was conducted at 4 primary care centres in Harare. Four Pregnant women were recruited for 18 weeks which extended from 23 March to 27 June 2017. Simple random sampling method was used to recruit participants. Sample size for this study was calculated using Dobson's formula; n = (Zα+ Zβ)2[P1 (1–P1) + P2 (1–P2)] (P1 – P2)2

as was calculated for the main study from which data for this study was obtained. Considering an attrition of 25% the minimum sample size required was 19. Pregnant women registering and visiting sites with gestation between 6 and 22 weeks declaring no urinary tract infection symptoms, no clinical presentation of any infection and willing to participate were included in this study. Excluded were women who presented with urinary tract infection symptoms, those who were unwell and who were unwilling to participate. Once recruited participants were required to submit their signed consent for a communication of their voluntary participation and another consent for permission to transport their urine to the laboratory. Mid– stream urine samples were collected in a surgically clean labelled specimen bottles. Hands were cleaned with alcohol enriched sanitizers to reduce risk of contamination of urine samples. Perineal area cleaning was also discouraged. All urine samples were screened for ASB using the Griess nitrite test, a nitrite detecting test, which assumes that almost all bacterial species causing ASB have nitrate reductase which converts nitrate in a sample to nitrite. Two Griess reagents, sulphanilamide and N– 1– naphthylethylenediamine dehydroxide, were singly added to the samples after 5 minutes. A positive result was identified by change of colour from clear to purple but a negative sample remained clear. All Griess positive samples were stored in a cooler box with ice packs and transported to a laboratory in the Medical Microbiology Department of the University of Zimbabwe. As soon as the samples arrived at the laboratory, a medical microbiologist performed culture test to confirm diagnosis, identify causative bacteria, quantify the bacterial colony, and antibiotic susceptibility. Uncentrifuged samples were streaked on Blood and Cystine Lactose Electrolyte Deficient (CLED) agar and incubated for 24 hours at 37°C. The growth was then quantified for identification of significant ASB. Bacterial growth of more than 10^3 cfu/ml was considered significant for ASB. A growth 10^3 cfu/ml bacterium was considered contaminated. If no growth occurred the sample was confirmed negative for ASB. The disk diffusion test was used for the susceptibility test. The 24 hours old culture which had one significant bacterial growth was suspended in Tryptone water whose density was matched against 0.5 McFarland standard set for adequate bacteria. The isolates were inoculated on Mueller–Hinton plate using the lawn technique. Antibiotics impregnated discs were placed on the Mueller– Hinton plate. These plates were then incubated at a temperature of 35°C for 18. The diameter of the zone of inhibition was then measured to the nearest millimeter, recorded and compared with the standards in guidelines available in the laboratory for a specific antibiotic and organism. The results were interpreted quantitatively using the minimum inhibitory concentration (MIC) and results were categorized as susceptible, resistant and intermediate according to interpretive tables available.Isolated bacteria were tested for susceptibility to a variety of antibiotics. The antibiotics were selected by the laboratory scientist from a list of the recommended drugs primarily considering site of infection, causative agent and drug availability. The antibiotics that were frequently available in the laboratory included ciprofloxacin, nitrofurantoin norfloxacin, ceftriaxone, gentamycin, and ampicillin. Least available drugs were meropenem, chloramphenicol, erythromycin, clindamycin, cefoxitin, ceftaxidine, carbenicillin, and nalidixic acid. Ethical approval for conduction of this study was provided by Medical Research Council of Zimbabwe for the main study from which the objective of this study was derived. Confidentiality and anonymity was assured as no name but a serial number was attached to data obtained. No any form of penalty was given to anyone who neither declined nor withdrew her participation. Data was entered on a SPSS version 20 spread sheet and was analyzed using the version and STATA version 13. Frequencies, percentages, standard deviation and power of 0.05 were used on analysis. This publication was prepared from data available from an ongoing randomized controlled trial registered with ClinicalTrials.gov, number NCT03274960.

Results

A total of 240 pregnant women participated in this study, with an average of 17weeks and 3 days. Minimum age of participants was 15, maximum 41 and mean at 25.8 (SD 6.3). All participants (100%) attended primary education with majority (80%)) ending at secondary level. Majority (70.8%, n= 170) of the participants were unemployed with only 15 (6.1%) employed. Majority of participants (89 (37.1%) were nulliparous and 45 (18.8%) had above 3 previous pregnancies. Out of 50 (20.8%) participants that had positive result from the Griess nitrite test, 34 (14.2%) were confirmed positive by culture test. Samples had above 100 000 bacterial colony per millilitre and had above 1000 bacterial colony per millilitre. Prevalence for ASB in this study was 14.2% (95% CI, 10.28% to 19.22%). Ten bacterial species were identified in this study popularly including Coagulase negative staphylococcus (CoNS*)* (29.4%) and *Escherichia coli (E. coli)* (23.5%). The other isolated strains were Staphylococcus aureus, Salmonella, Klebsiella, Providencia, Streptococcus viridans and Shigella species. Table 1 below shows frequency of susceptibility tests for selected antibiotics. The frequently tested drugs included gentamycin (88.2%, 30 out 34), followed by ciprofloxacin (82.4%, 28 out of 34) and nitrofurantoin (76.5%, 24 out of 34). The other popularly tested were ceftriaxone, ampicillin, nitrofurantoin, norfloxacin,). Among the least tested antibiotics were clindamycin (4 out of 34), nalidixic acid (2 out of 34), ceftaxidine (2 out of 34) and meropenem (3 out of 34). Erythromycin was the least available (1 out of 34 tested) antibiotic. All isolated bacteria had sensitive results of varying levels for the selected antibiotics for the test. Overally highest susceptibility levels were yielded for gentamycin (83.3%), ciprofloxacin (75%) and ceftriaxone (70.8). The strains were least susceptible to nitrofurantoin (19.2%) and ampicillin (39.1%) as shown on Table 1.

CoNS was highly sensitive gentamycin (90%), ciprofloxacin (77.8%) and norfloxacin (71.4%) but was least sensitive to ceftriaxone (25%) and nitrofurantoin (30%) as shown on Table 2. E coli was highly sensitive to ceftriaxone (83.3%) and gentamycin (71.4) but least sensitive to norfloxacin (25%) and nitrofurantoin (33.3%). Staphylococcus aureus was sensitive to all (100%) but one, nitrofurantoin (0%), among the commonly tested antimicrobials. Klebsiella *pneumonia* was 100 sensitive to ceftriaxone and 66.7% to ciprofloxacin and gentamycin. CoNS:Coagulase negative staphylococcus, *E. coli*:*Escherichia coli*, S. aureus:Staphylococcus aureus, Strep viridands:Streptococcus viridans, Freq:frequency, nt:not tested. CoNS was resistant to all frequently tested antibiotics at differing levels. The bacteria was least resistant to gentamycin (10%), ceftriaxone (12.5%) and ciprofloxacin (20%) but highly resistant to nitrofurantoin (70%) and ampicillin (60%) as shown on Table 3 below. E. coli was also resistant to all antibiotics. It was least resistant to ceftriaxone (16.7%) and ciprofloxacin (25%) but more so to norfloxacin (75%) and nitrofurantoin (50%). Staphylococcus aureus and Kle*bsiella* were 100% resistant to nitrofurantoin. CoNS:Coagulase negative staphylococcus, E. coli:Escherichia coli, S. aureus:Staphylococcus aureus, Strep viridands:Streptococcus viridans Freq:frequency, nt:not tested. Table 4 shows intermediate results. *CoNS* had several intermediate results for ceftriaxone (62.5%). *E. coli* also had intermediate result for ampicillin (14.3%) and ciprofloxacin (16.7%).

Table 1 Frequently tested antibiotics and summary of susceptibility results

Antibiotic	Sensitivity Tests Done Out of 34		Sensitive		Resistant		Intermediate	
	Frequency	%	Frequency	%	Frequency	%	Frequency	%
Gentamycin	30	88.2	25	83.3	4	13.3	1	3.3
Ciprofloxacin	28	82.4	21	75	6	21.4	1	3.6
Nitrofurantoin	26	76.5	5	19.2	21	80.8	1	0
Ceftriaxone	24	70.6	17	70.8	2	8.3	0	20.8
Ampicillin	23	67.6	9	39.1	13	56.5	5	4.3
Norfloxacin	21	61.8	13	61.9	8	38.1	1	0
Clindamycin	4	11.8	4	100	0	0	0	0
Chloramphenicol	4	11.8	3	75	0	0	0	25
Meropenem	3	8.8	2	66.7	1	33.3	1	0
Carbenicillin	3	8.8	2	66.7	1	33.3	0	0
Nalidixic acid	2	5.9	0	0	2	100	0	0
Ceftaxidine	2	5.9	0	0	2	100	0	0
Erythromycin	1	2.9	1	100	0	0	0	0

Table 2 Bacterial susceptibility results, nt meaning not tested

Bacterial Species	Antibiotics											
	Norfloxacin		Ampicillin		Nitrofurantoin		Ciprofloxacin		Gentamycin		Ceftriaxone	
	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%
E. coli	5	71.40%	3	30	7	77.8	9	90	2	25	4	40
CoNS	1	25	2	33.3	3	50	5	71.4	5	83.3	3	42.9
S. aureus	4	100	0	0	4	100	4	100	4	100	nt	nt
Shigella	1	100	0	0	1	100	1	100	nt	nt	1	100
Strep Viridans	1	100	nt	nt	1	100	1	100	1	100	nt	nt
Klebsiella	0	0	nt	nt	2	66.7	2	66.7	3	100	1	100
Providencia	0	0	nt	nt	nt	nt	1	100	nt	nt	nt	nt
Salmonella	0	0	nt	nt	1	100	1	100	1	100	1	100

Table 3 Bacterial resistant results

Bacterial Species	Antibiotics											
	Norfloxacin		Ampicillin		Nitrofurantoin		Ciprofloxacin		Gentamycin		Ceftriaxone	
	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%
E. coli	2	28.60%	7	70	2	20	1	10	1	12.5	6	60
CoNS	3	75	4	50	2	25	2	28.6	1	16.7	3	42.8
S. aureus	0	0	4	100	0	0	2	0	0	0	0	0
Shigella	0	0	1	100	0	0	0	0	nt	nt	0	0
Strep Viridans	0	0	1	100	0	0	0	0	0	0	1	100
Klebsiella	2	100	2	66.7	1	1	1	33.3	0	0	1	50
Providencia	1	100	1	100	1	1	1	100	1	100	1	1
Salmonella	0	0	nt	nt	1	1	1	100	0	0	nt	nt

Table 4 Bacterial intermediate results

Bacterial Species	Ciprofloxacin		Gentamycin		Ceftriaxone		Ampicillin		Chloramphenicol		Ceftaxidine	
	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%
E. coli	1	16.70%	0	0	0	0	1	14.3	1	100	1	100
CoNS	0	0	1	10	5	62.5	0	0	0	0	0	0

Discussion

Use of a reliable cost effective screening method for ASB is required especially in settings where culture test is unavailable.[15] In this study the Griess nitrite test used for screening ASB. This test is reliable and effective.[16] Urine culture though costly, remains the gold standard for diagnosing ASB because it identifies the bacteria, quantifies it and useful for sensitivity test. Diagnosis of ASB theoretically and generally considers significant level of 10^5 cfu/ml but clinically 10^3 is a significant value which marks presence of infection, including staphylococcus saprophyticus.[17,18] ASB prevalence is generally ranging between 2% and 10%.[19] In this study prevalence of ASB was 14.2% (95% CI, 10.98% to 19.22%). This prevalence was above the general range of 2% to 10% but fits in the range from 1.9% to 15% being reported.[20] The prevalence in this study was close to 13.2% found in Mangalore, Karnataka in India.[21] Higher prevalence (46.6%, 46.5%) for ASB was found in Bangalor in India, Abakaliki Nigeria and lower prevalence of 12.8% in Abuja.[22–24] Therefore ASB prevalence differs from setting to setting. E. coli is the most common isolate in ASB as it was also confirmed in a prospective study in Odisha state, India and in Abuja (56.%).[19–23] CoNS is one of isolated uropathogens.[25] In another study CoNS was second most common (16.8%) after E. coli (58.96%).[26] In this study *E. coli* was second most common (23.5%) bacteria after *CoNS* (29.4%). This was similar to findings in a study conducted in Southern Ethiopia where *CoNS* was most frequently isolated (32.6%) followed by E.coli (26.1%).[8] Similarities and differences in aetiological agents for ASB exist from setting to setting. Treatment of ASB is recommended in pregnancy due to the serious complications that are likely to occur.[27] Treatment of the disease is one main reason for antibiotic use, the main driver of bacterial resistance.[13] Meanwhile some researchers argue that ASB treatment often lead to unnecessary use of antibiotics and could be a mere waste of resources as there is no benefit found in treatment of the disease.[28] Although it is generally recommended that antibiotics be used for effective clearance of ASB during pregnancy, it is still debatable as some argue that treatment of the disease is associated with increased antibiotic resistance.[6–29] Antibiotics must therefore be given only when required and with adequate patient education on importance of compliance because failure to take antibiotic for the full period recommended also causes resistance.[30] Effective ASB treatment during pregnancy is expected to reduce risk of pyelonephritis and adverse birth outcomes including preterm birth and low birth weight.[2,5] Treatment and clearance of bacteria in the pregnant women requires that sensitive antibiotics be identified by culture sensitivity test where possible.[6–15] If ASB is not treated appropriately in pregnancy, it is associated with up to 50% risk of developing pyelonephritis later in pregnancy which is associated with adverse pregnancy outcomes.[5–15] It is, however argued that extensive use of antibiotics even to treat ASB in pregnancy could increase bacterial resistance to alarming level.[13] In this study isolated bacteria agents grew resistant to all frequently tested and available antibiotics, though at different levels. The bacteria were more susceptible to gentamycin, ceftriaxone and ciprofloxacin but resistant to nitrofurantoin and ampicillin. Nitrofurantoin is a widely recommended antibiotic for ASB treatment in pregnancy and it is associated with 80% cure rate with a 5 to 7 day course.[15–29] Suggested first line treatment include amoxil, nitrofurantoin and oral cephalosporins and gentamycin and ceftriaxone for staphylococcus and pseudomonas.[30,31] Recommended antibiotics for ASB caused by *E. coli* as stipulated in South Australian antenatal guidelines include cephalexin, nitrofurantoin, trimethoprim and amoxil + clavulanate.[29–31] Safety of antibiotic choices should always be considered in pregnancy.[32] A study in India showed that E. coli was highly sensitive to nitrofurantoin but had high resistance to ampicillin.[22] In this study E. coli was moderately resistant to Nitrofurantoin but lowly sensitive to the drug. CoNS was highly sensitive to ciprofloxacin and gentamycin but highly resistant to nitrofurantoin and ampicillin. Ciprofloxacin could be considered as the oral drug of choice even in empirical treatment. Nitrofurantoin may not be effective in treating urinary tract infection due to high resistance pattern of bacterial species. Nitrofurantoin had overally the least bacterial sensitivity result but highly resistant. In a separate study in Nigeria nitrofurantoin had an overall sensitivity of 87.5% which was higher than found in this study.[24] Possibly the extensive use of nitrofurantoin or drug compliance could contribute to its high resistance. Nalidixic acid could not inhibit bacterial growth (100% resistance) though tested on two bacterial agents only. More tests would have helped to objectively establish its effectiveness. Overally all bacterial strains were resistant to frequently prescribed antibiotics including nitrofurantoin, norfloxacin, ampicillin and cephalexin and this poses a big threat to effective treatment of ASB in pregnancy.[33] This could be an indication to susceptibility test for all urine samples, though it is difficult to implement in our setup due to unavailability of the test in most settings. Antibiotic susceptibility tests need to be frequently or routinely done to establish effective treatment and to guide drug selection for empirical approach which is popularly used in our setting. Research on antimicrobial susceptibility is needed time to time to provide an insight to susceptibility and resistant levels of antibiotics for asymptomatic bacteriuria.

Conclusion

Asymptomatic bacteriuria is a prevalent disease among pregnant women. Drug resistance was noted to be common among bacteria responsible for ASB in pregnancy. Antibiotic susceptibility tests are routinely needed to guide doctors with drug selection for effective treatment of ASB and UTIs in primary care settings in Zimbabwe. Ciprofloxacin could be considered as oral drug of choice with gentamycin and ceftriaxone injections being useful when orals are not tolerated but nitrofurantoin may not be effective for treatment of ASB in our setting.

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Conflicts of interest

The authors have no conflict of interest to declare.

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