ACCURACY OF URINE DIPSTICK TEST IN DETECTING ASYMPTOMATIC BACTERIURIA AMONG PREGNANT WOMEN RECEIVING ANTENATAL CARE AT KENYATTA NATIONAL HOSPITAL, NAIROBI, KENYA.

Dissertation submitted as partial fulfilment of the requirements for the award of degree.

SUBMITTED BY

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REGISTRATION NUMBER: H58/75017/2014

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DECLARATION.

I declare that this dissertation is my own work done under the guidance of my supervisors. It has not been accepted for the award of a similar or any other degree or diploma at the University of Nairobi or any other educational institution.

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DEDICATION.

This book is dedicated to my husband, Dr. George Muia, for his patience, support and constant motivation throughout my training period.

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I thank the Almighty God for His mercies, grace and the good health, He endowed upon me throughout this academic journey.

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ABBREVIATIONS AND ACRONYMS

ACOG – American College of Obstetricians and Gynaecologists

ANC – Ante-Natal Care

ASB - Asymptomatic Bacteriuria

CFU – Colony Forming Units

HIV – Human Immunodeficiency Virus

FGR – Foetal Growth Restriction

KNH – Kenyatta National Hospital

LBWI – Low Birth Weight Infants

LE – Leucocyte Esterase

LR - Likelihood Ratio

NPV – Negative Predictive Value

PPROM – Preterm Premature Rupture of Membranes

PPV – Positive Predictive Value

PTD – Preterm Delivery

RCT – Randomized Control Trial

UoN – University of Nairobi

UTI – Urinary Tract Infections

WHO – World Health Organization

OPERATIONAL DEFINITIONS.

Urine dipstick test - Is a screening test that involves use of strips of different pads impregnated with chemicals. This chemicals are able to react with substances present in urine producing a characteristic colour. The reagents are able to test if proteins, glucose, ketones, haemoglobin, bilirubin, urobilinogen, acetone, nitrite and leucocytes are present in urine. Interpretation of the results is done by comparing the pad colours against a colour scale provided by the manufacturer. The strips are either qualitative (determine if the sample is positive or negative) or semi-quantitative (provide both a qualitative result and estimate the quantitative result), in that the intensity of the colour reactions are almost equal to the concentration of the substance being tested for in the urine sample.

Leucocyte esterase (LE) and nitrite tests are infection related markers. In the absence of infections, there are usually no detectable nitrites or LE in urine. The leucocyte esterase test is an indirect test for bacteriuria as it detects LE released from degraded white blood cells (WBCs) depicting the presence of WBCs in urine. LE catalyses the hydrolysis of an ester of indolecarboxylic acid. The indoxyl released combines with a diazonium salt producing a violet dye. The nitrite test is based on the conversion of dietary derived nitrate in urine to nitrite by certain bacteria present in the urine. This is the Greiss reaction where sulfanilic acid and alpha naphthylamine, undergoes a diazotization reaction with nitrites to form a pink dye.

Urine culture test - is a quantitative diagnostic method and the gold standard test for detecting bacteriuria. The sample of urine is incubated on mac-Conkey and Cysteine Lactose Electrolyte Deficient (CLED) at 35-37 degrees Celsius for 24 to 48 hours. Identification of bacterial isolates is done using a combination of morphological and biochemical characteristics. The quantity of bacteria present in the urine sample is derived from the number of colonies.

Asymptomatic bacteriuria (ASB) - refers to the presence of live bacteria in the urine of an individual who has no symptoms of urinary tract infection (UTI). Significant bacteriuria as determined by urine culture, refers to the presence of bacteria in significant numbers of $\geq 10^5$ colony-forming units (CFU) of a single bacterial species per millilitre of urine within the urinary tract.

Accuracy – refers to test ability to correctly differentiate between those with the condition and those without. It is determined by the sensitivity, specificity, predictive values and likelihood ratios.

Sensitivity - refers to the test's ability to correctly detect those who have the condition, signifying the proportion of true positives that are correctly identified by the test.

Specificity - relates to the test's ability to correctly detect those without the condition signifying the proportion of the true negatives correctly identified by the test.

Negative predictive value – probability that someone with a negative test result has no disease signifying the ability of the test to correctly predict the absence of disease.

Positive predictive value – probability that someone with a positive test result has the disease signifying the ability of the test to correctly predict the presence of disease.

Positive likelihood ratio - defined as how much more likely is it that a patient who tests positive has the disease compared with one who tests negative. Helps in assessing the value of performing a diagnostic test allowing the clinician to better interpret the results of the test by predicting the likelihood of a true positive result even before the test is done (pre-test probability).

Negative likelihood ratio – refers to the likelihood that a person who tests negative does not have the disease compared to those who test positive.

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1.0 ABSTRACT.

Background: When not detected and treated asymptomatic bacteriuria (ASB) in pregnancy is associated with development of symptomatic urinary tract infections, preterm deliveries, low birth weight infants, intrauterine growth restriction, preterm premature rupture of membranes and pre-eclampsia. Routine screening of pregnant women is necessary to avert the adverse outcomes, unlike in the general population where the disease is considered benign. The quantitative urine culture, the "gold standard" test for detection of ASB, is time consuming, expensive, requires special equipment and trained personnel hence not routinely available, especially in low resource settings. Although the dipstick test is readily available, cheaper, easier to perform and interpret, its accuracy and role in detecting ASB in pregnancy in this setting has not been evaluated.

Methodology: This was a cross sectional study conducted among pregnant women without symptoms of urinary tract infection, who were receiving routine antenatal care at Kenyatta National Hospital, in Nairobi Kenya. Clean catch, mid-stream, voided urine specimens from 132 eligible participants were subjected to concurrent dipstick and bacteriologic culture. Markers of ASB in urine dipstick (presence of either or both leucocyte esterase (LE) and nitrites) were compared with culture. Accuracy of urine dipstick, as measured from the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio(PLR) and negative likelihood ratio(NLR) in detecting ASB was estimated using culture as the "gold standard " test.

Results: Out of 320 women screened, 132(41%) were found eligible. Prevalence of ASB was 6.9%. The sensitivity, specificity, PPV and NPV was 66.7%, 74.4%, 16.2% and 96.8% for LE; 44.4%, 97.5%, 57.1% and 95.9% for nitrite; 22.2%, 100%, 100% and 94.5% for either LE or nitrite; and 88.9%, 71.9%, 19% and 98.9% for both LE and nitrite respectively. The

PLR and NLR for LE was 2.61 and 0.45 whereas that of nitrite was 17.76 and 0.37 respectively.

Conclusion*:* A negative urine dipstick test very likely rules out ASB in pregnancy and the need for routine culture. On the other hand, a positive dipstick test has low accuracy in detecting ASB in pregnancy and requires confirmatory testing with culture. Treatment for ASB based on positive dipstick alone would expose a large number of women to unnecessary antibiotics and their associated side effects.

Recommendation: A urine dipstick test should be done for all pregnant women as an initial screening test to exclude those without ASB. However, all dipstick positive cases should undergo confirmatory testing with culture instead of giving empirical treatment. This testing approach will ensure a high diagnostic performance, prevent unnecessary administration of antibiotics and reduce laboratory costs and workload because not all urine samples will be subjected to routine culture.

2.0 INTRODUCTION

Urinary tract infections (UTIs) form part of the commonest infections that increase disease burden in pregnancy(1). Globally, approximately 150 million people are diagnosed with UTIs yearly. This is estimated to cost over 6 billion US dollars(2). Infections of the urinary tract can be categorized as either involving upper tract (pyelonephritis) or lower (urethritis, cystitis, asymptomatic bacteriuria (ASB)). Apart from ASB, other categories of UTIs are symptomatic(3).

ASB is defined as the presence of live bacteria in the urinary tract in significant counts of $\geq 10^5$ colony forming units (CFU) of a single bacterial species per millilitre of urine in an individual with no symptoms of a urinary tract infection(1). Anatomic and physiologic changes that occur in the urinary tract during pregnancy increase the risk of the disease progression. The anatomic changes are due to the enlarging uterus that subsequently compresses on the bladder and ureters whereas the physiologic changes are due to progesterone that causes smooth muscle relaxation, leading to urine stasis (4). Unlike in pregnancy, there is no benefit in treating ASB in the general population as the disease is benign(5). ASB in pregnancy is associated with development of symptomatic UTIs, preterm deliveries (PTD), low birth weight infants (LBWI), foetal growth restrictions (FGR), preterm premature rupture of membranes (PPROM) and pre-eclampsia(6)(7) (8). Randomized control trials (RCTs) have demonstrated that antibiotic treatment significantly reduces the incidence of these adverse obstetric outcomes(9)(10).

Routine screen-and-treat policies have been incorporated in many antenatal care (ANC) guidelines as a cost-effective strategy geared towards improvement of maternal and neonatal health by early detection and treatment of UTI. For example, the American College of Obstetricians and Gynaecologists and National Institute of Clinical Excellence guidelines

recommend urine culture in early pregnancy or at the first antenatal visit if later to detect ASB (11)(12).

Accurate and quick diagnostic methods are important to inform patient management decisions. A test should be sensitive and specific enough, in order to detect all positive cases and rule out the negative ones. Quantitative urine culture being the gold standard test for detection of ASB is costly, time-consuming, requires special equipment and trained personnel. The dipstick test commonly used in low resource settings to detect bacteriuria is cheap, easy to perform, interpret the results and can be used in primary health care centres, patient bedside and office settings. In conformity with most low resource settings, the Kenyan Ministry of Health (MOH) guidelines recommend detection of ASB using a urine dipstick test at every antenatal visit (12). In the MOH protocol, pregnant women with positive urine dipstick are usually treated with antibiotics for presumptive diagnosis of ASB. However a wide variability in sensitivity and specificity of the dipstick test in detecting ASB has been reported, resulting in a lack of consensus in recommendation of the most appropriate diagnostic test for ASB in pregnancy especially in low resource settings. A meta-analysis by Shadi et al, of 13 studies reported a broad range of sensitivity (16 to 100 percent) and specificity (25 to 100 percent) for the LE whereas for the nitrite test the sensitivity range was (18 to 66 percent) and specificity (31 to 100 percent)(13). The authors who reported high sensitivities and specificities recommended the use of dipstick test for detecting ASB. Alternatively those who reported low sensitivities and specificities recommended the use of urine culture method. After assessing for methodological quality the heterogeneity was suspected to be due to involvement of variable causative organisms among different populations(13).

The aim of this study was to determine the accuracy of the urine dipstick test commonly used in low resource settings to detect ASB among pregnant women compared to the gold standard test, urine culture.

3.0 LITERATURE REVIEW.

3.1 Epidemiology

Pregnancy has not been shown to increase the prevalence of ASB, but is associated with an increased risk of progression from asymptomatic to symptomatic urinary tract infections (14). Prevalence of ASB in pregnancy varies between and within countries with most literatures quoting prevalence of 2-10%. However higher prevalence has been reported in developing countries compared to developed countries. This could be attributed to the differences in the socio-economic levels and standards of living. In Delhi, northern India it was reported as 5%(16), 4% in Gazi university hospital, Turkey(17), 4.8% in Sharjah, United Arab Emirates(18), 12.5% in Cairo, Egypt(19), 7.3% in Kumasi, Ghana(20) and 7.8% in Buea, southwest Cameroon(21). A cross-sectional study in a teaching hospital in Ilorin Nigeria reported a prevalence of ASB of as high as 40 percent (22) while Ingari et al at Kenyatta National Hospital (KNH) in 1986 found a prevalence of ASB of 9% (23). For screening of ASB to be cost effective, the prevalence in a given population should be more than 2% and the risk of progressing to pyelonephritis in untreated bacteriuric women more than 13%(24). In an era of routine screening of women for ASB, prevalence of cystitis is generally low at approximately 1 to 2 percent while pyelonephritis being the most severe form of UTI has a prevalence of 0.5 to 2 percent(25). Pyelonephritis occurs mostly during the second and third trimesters as the enlarging uterus increasingly compresses the ureters(26).

3.2 Urinary tract changes in pregnancy that increase the risk of urinary tract infections

Unlike men, women have a higher chance of getting a urinary tract infection(UTI) due to their short length of urethra and closeness of urethra to the vagina and rectum(26). Hence these infections are caused mainly by existing perineal and rectal floras that ascend and colonize the urinary tract. Once bacteria colonize the bladder, they are often eliminated by voiding or by the immune system, otherwise a UTI may result (27)

Pregnant women need special considerations because despite pregnancy being an immune-suppressive state, it involves functional, mechanical and hormonal changes that significantly cause changes in the urinary tract, hence impacting on the natural history of bacteriuria. Physiological increase in progesterone causes the smooth muscle relaxation and subsequent dilatation of the ureters, renal pelvis and calyces. Resulting urinary stasis allows time for bacteria to multiply while the dilatation enables the bacteria to easily ascent from the bladder to the kidney and hence greater risk for cystitis and pyelonephritis(4). Increase in the glomerular filtration rate and impaired resorption of glucose occurring in pregnancy lead to aminoaciduria and glucosuria that cause change in urine pH and osmolality providing an excellent medium for bacterial replication(4).

3.3 Risk factors for asymptomatic bacteriuria in pregnancy.

The major risk factor for ASB has been shown to be previous history of UTI(25). Other risk factors include; low socioeconomic status, poor genital hygiene, advanced maternal age, increasing gestational age, iron deficiency anaemia, urinary tract anomalies and urinary catheterization(25)(26)(28). Medical conditions that increase the risk of ASB include diabetes mellitus which increases the risk three fold(26), sickle cell disease(28) and human immune deficiency virus (HIV) infection(26).

3.4 Maternal and foetal complications of ASB

History of ASB dates back in 1957 when Kass et al established that significant bacteriuria can occur in the absence of urinary tract symptomatology and that early treatment of this bacteriuria in pregnancy prevented progression to pyelonephritis(26). A review of 20 studies in the 60's by Whalley et al found that symptomatic UTIs(urethritis, cystitis and pyelonephritis) occurred in 30% of patients with ASB compared with 1·8% of non bacteriuric controls leading to the establishment of many screening policies(26). Urmilla et al recently in a prospective study involving 800 women in India noted a 6 times risk of developing symptomatic UTIs in pregnant women with ASB compared to non bacteriuric ones(7).

Treatment of ASB with antibiotics in pregnancy has been shown to decrease the incidence of pyelonephritis. A Cochrane review of 14 randomized control trials involving over 2000 pregnant women with ASB, comparing antibiotic treatment with placebo or no treatment, reported that antibiotic treatment of ASB effectively reduced the risk of pyelonephritis(10). Pyelonephritis on the other hand is a risk factor for some adverse obstetric outcomes. Farkash et al 2012 in a 20 year retrospective population-based study noted that patients with pyelonephritis have a three times risk of pre-term delivery(PTD) (29). Pregnant women with pyelonephritis are also at risk of complications like anemia, septicaemia, acute pulmonary insufficiency and acute renal dysfunction compared to those without. This is due to endotoxin induced haemolysis or tissue injury(25)(30).

ASB can first progress to symptomatic UTIs or be an independent risk factor for preterm delivery(31)(32). A prospective cohort study among 800 pregnant women in India reported PTD in 20.83% bacteruric compared to 4.8% non-bacteriuric women. The association with LBWI was also significant (16.67% bacteriuric versus 6.12% in non-bacteriuric women(26). PTD results in prematurity and LBWI with high perinatal morbidity and mortality. Annually an estimated 1 million neonatal deaths globally occur due to prematurity related

complications(33). Recurrent abortions, foetal growth restrictions, preterm premature rupture of membranes and pre-eclampsia are adverse obstetric outcomes also associated with untreated ASB in pregnancy(6). This is thought to be caused by increase in pro-inflammatory cytokines such as interleukin 6, gamma interferon and tumour necrosis factor(34).

These studies underline the significance of appropriate diagnosis and treatment of ASB to avert the associated adverse obstetric outcomes.

3.5 Microbiology of asymptomatic bacteriuria

Ideally urine is sterile. Escherichia coli is the commonest pathogen implicated in ASB representing 60-70 percent of the isolates (25)(16)(18). Other gram negative bacterial species include; Klebsiella , Proteus, Enterobacter and pseudomonas while the Gram positive organisms include Streptococcus and Staphylococcus species(1). A study by Jones et al noted no difference in prevalence of bacterial virulence factors like fimbriae, adhesins and hemolysin between those who had ASB and those who had symptomatic UTIs(35). However in ASB, the bacteria were found to poorly adhere to epithelial cells or were unable to stimulate inflammatory cytokine responses due to poor immune system activation. Since the bacterial virulence factors cannot discriminate symptomatic from ASB, in most cases it is the patient characteristics i.e. their immune systems that determine whether one gets symptomatic or asymptomatic infection(35).

3.6 Antenatal screening for asymptomatic bacteriuria

Screening calls for attention to the possibility of a disease even before symptoms become apparent. Hence tests with high sensitivity are preferred. According to Wilson et al (WHO 1968) on principles of screening for diseases, the condition sought through a continuous screening process should be an important health hazard with a latent phase recognizable by simple and acceptable test(36).

In a study by Gratacos et al in Chicago, after introduction of screening programs to diagnose and treat ASB in pregnancy, there was a reduction in the annual incidence of pyelonephritis (from 1.8% to 0.6%, P < .001) (37). Cost-benefit analysis study on screening versus no screening for ASB in Alabama showed that, screening for and treatment of ASB in pregnancy was beneficial whether based on culture or dipstick compared to treating pyelonephritis with a policy of no screening(38).

There is conflicting literature as to the best time and the frequency of screening for ASB in pregnancy. The United States Preventive Services Task Force recommends that screening for ASB in pregnancy should be done via a urine culture between the 12^{th} to 16th week of gestation while ACOG recommends screening at the first prenatal visit(1). This was based on prospective studies that showed that the onset of ASB was optimum between the 9th and 17th week with 80 percent of the women with ASB identified between 12 and 16 weeks of gestation, however only 1% to 1.5% acquired bacteriuria later in the pregnancy(1). The Kenyan MOH protocol recommends screening for ASB at every ANC visit(39). Early screening and treatment of ASB before 20wks gestation is preferred as the risk of Pre-eclampsia, foetal growth restriction, low birth weight infant and pre-term delivery is lower compared to that in patients screened and treated at 32-34 weeks gestation(1).

But in order to improve the detection rate of ASB especially for those who had no bacteriuria at the initial screening, McIsaac et al in a prospective study of 1050 women in Toronto, concluded that screening for ASB in pregnancy should be done via urine culture in every trimester(40).

3.7 Diagnostic testing for asymptomatic bacteriuria

The diagnosis of ASB is based on culture of a clean-catch midstream voided urine sample with isolation of > 10^5 CFU of a single uropathogen species in an individual presenting with

no symptoms of UTI(1). However, some authors argue that two consecutive specimens are required to make a diagnosis of ASB (1). A single positive urine culture gives 80% probability of true infection while a repeat culture increases this probability to more than 95%(41).

A meta-analysis by Shadi et al, of 13 studies reported a broad range of sensitivity (16 to 100 percent) and specificity (25 to 100 percent) for the LE whereas for the nitrite test, the sensitivity range was (18 to 66 percent) and specificity (31 to 100 percent) (13). After assessing for methodological quality the heterogeneity was suspected to be due to variable prevalence of ASB and variable causative organisms as not all uropathogens are able to reduce nitrates to nitrites and that some organisms convert the nitrates to ammonia hence no nitrites available to permit detection(19). The studies that reported high sensitivities and specificities recommended the use of dipstick test for routine screening of ASB. While the studies that reported low sensitivity opted for the routine urine culture(13)(16). A 2009 WHO study of 3048 eligible pregnant women in Argentina, Philippine, Thailand, and Vietnam also concluded that dipstick testing for the diagnosis of ASB was poor and if used to identify those with or without ASB, 46% of pregnant women would be mis-diagnosed(42).

Deville et al studied patients in different clinics and found that the sensitivity of dipstick test was highest in urology patients and children(43). The study by Demilie et al that included both symptomatic and asymptomatic pregnant women noted that the sensitivity and specificity of LE and nitrite was high in women with symptomatic UTIs compared to those with ASB .This was due to increase in percentage of significant pyuria in symptomatic UTIs compared to ASB(44). Eigbefor et al in Nigeria reported that the LE component of the dipstick test was the most reliable with the highest sensitivity and positive predictive value, and that when the nitrite and LE components were combined, the sensitivity and specificity of the LE decreased. Hence recommending antibiotic treatment as long as the LE test was

positive(3). Others concluded that, the nitrite test was more reliable compared to the LE test(16)(17). Combination of LE and nitrite tests had a high specificity range of 91 to 98.3 percent hence considered effective in excluding the presence of infections(13) while Hosam et al in Egypt found no added value after combining the two(19). In Kenya there is no published study on the accuracy of the dipstick test in detecting ASB among pregnant women, yet the MOH protocol adopted the screen and treat approach based on results of the dipstick test.

3.8 Treatment of asymptomatic bacteriuria

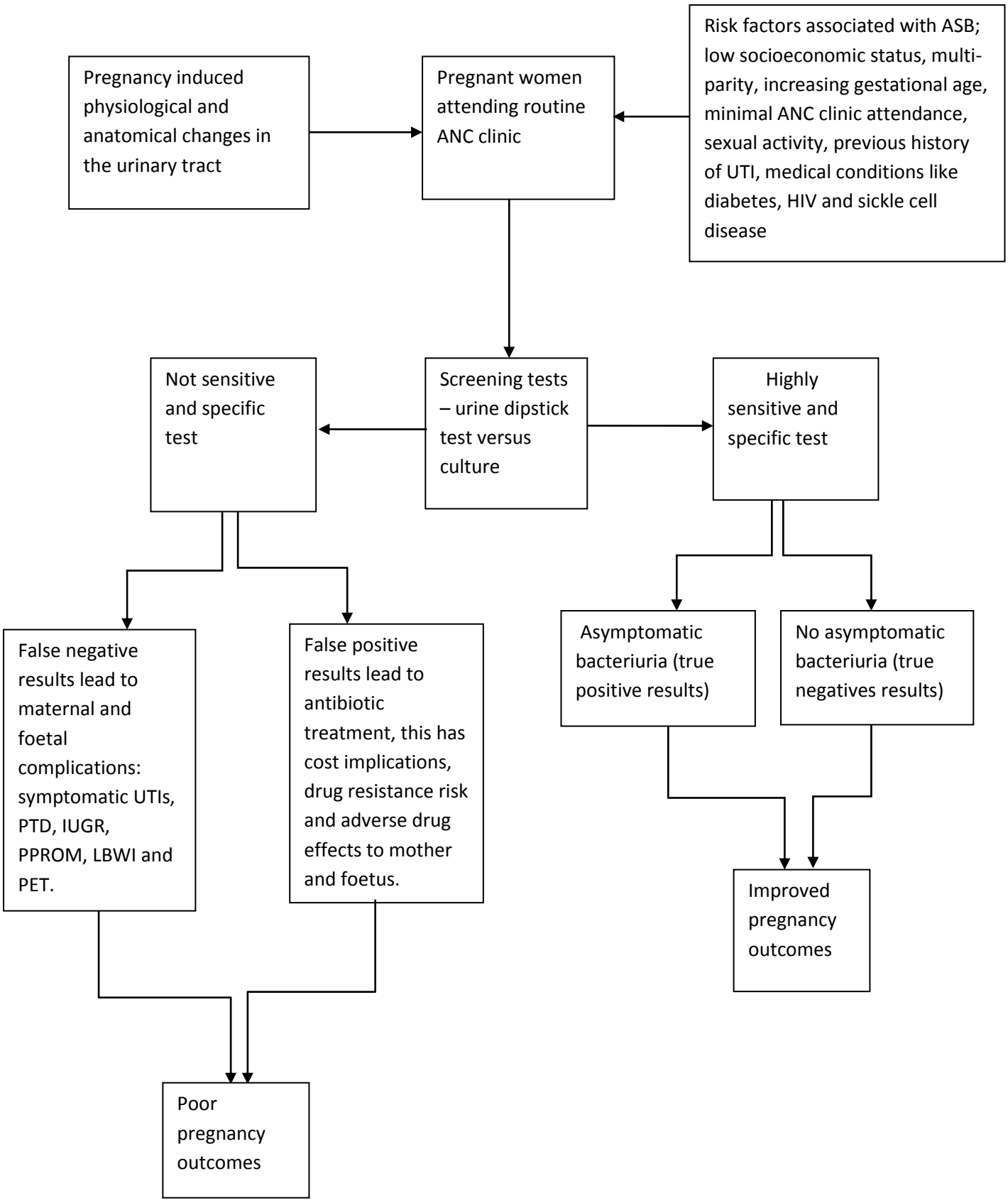
Antibiotic treatment aims to stop or slow the progression of ASB(45). Choice of antibiotics should be based on maternal and foetal safety profile, efficacy and high sensitivity rates in a given population. The susceptibility of these organisms to antibiotics can vary geographically hence culture and sensitivity testing can be used to guide antibiotic prescription patterns. With antibiotic abuse in giving empirical regimens, more resistant bacterial strains can emerge hence increasing antibiotic resistance in a locality. Andabati et al in Uganda demonstrated high resistance of uropathogens to ampicillin and gentamicin calling for a change in hospital treatment policies(46). The standard practice is to treat ASB with oral antibiotics for at least 7 days(1). Though a Cochrane review of 8 studies with over 400 women, that compared single-dose versus a four- to seven-day course of antibiotic treatment for ASB reported no difference in the cure rate or reduction in the incidence of PTD or pyelonephritis(42). In this review, the four- to seven-day course of treatment was associated with higher reports of drug adverse effects, while short duration had lower costs and increased compliance(42). Due to the associated vaginal colonization by the bacteria in pregnant women with group B streptococcal bacteriuria, an additional intrapartum antibiotic prophylaxis should be given to prevent early-onset neonatal group B streptococcal disease(47).

4.0 CONCEPTUAL FRAMEWORK

4.1 Narrative

Asymptomatic bacteriuria involves growth and multiplication of micro-organisms in the urinary tract without symptoms of UTIs. Physiological and anatomical changes of the urinary tract that occur in pregnancy encourage multiplication of the pathogens and greater propensity to ascend to upper urinary tract. The risk factors associated with development of ASB include multi-parity, increasing gestation, sexual activity, low socio-economic status, previous history of UTI and inter current medical conditions like diabetes, HIV and sickle cell disease. Pregnant women should be screened for ASB during their routine ANC visits. If not detected and treated, ASB in pregnancy is associated with development of symptomatic UTIs, PTD, LBWI, FGR, PPROM and pre-eclampsia. A reliable testing method is required in order to avoid misdiagnosis. A highly sensitive and specific test will enable accurate detection of those with ASB and those without. The urine dipstick test has the LE and nitrite components, as the markers of infection in urine. With appropriate antibiotic treatment of those with ASB the maternal and neonatal morbidity and mortality associated with ASB can be averted. Testing method with low sensitivity leads to false negative results and the missed bacteriuria has the risk of worse progression causing the adverse pregnancy outcomes. Low specificity on the other hand leads to false positive results and hence unnecessary prescription of antibiotics to the patients. These antibiotics have cost implications, increases risk of drug resistance and adverse effects to both the mother and the foetus.

4.2 Diagrammatic



5.0 JUSTIFICATION

The ability to avert adverse pregnancy outcomes with antibiotic treatment, justifies the need to have all pregnant women screened for ASB. A reliable diagnostic test is crucial to avoid false positive results which lead to unnecessary prescription of antibiotics to the patients. These antibiotics have cost implications, increases risk of drug resistance and adverse effects to both the mother and the foetus. A false negative result on the other hand leads to lack of treatment hence the bacteriuria could progress to cause medical and obstetric complications.

The gold standard test for detecting ASB is urine culture, which is able to quantify the infection, give information on the microbes involved and the antibiotic sensitivity profile. But this test is expensive, takes approximately 3 days to get the results, labour intensive, requires trained personnel and appropriate laboratory equipment. Hence the need to evaluate the reliability of cheaper, easier to perform and interpret testing methods like the dipstick test commonly used in resource poor settings.

Conflicting results, with broad range of sensitivities and specificities reported with the use of the dipstick test among different populations with some authors recommending its use to detect ASB in pregnancy while others discourage its use justifies the need for a local study on the same.

The information on the diagnostic accuracy of the dipstick test will help clinicians and laboratory technologists to know the utility of the dipstick test in detecting ASB in pregnancy especially when giving empirical treatments or be able to decide which patients need further confirmatory laboratory tests. If found to be effective, this simple, rapid test will minimize the need for routine urine cultures either during the initial investigation or follow up of patients after treatment.

The study results will determine if ASB in pregnancy is being mis-diagnosed, hence contribute to the evaluation of the hospital and national policies on the diagnosis of ASB.

Data on the prevalence of ASB in our setting will give an estimate on the burden of the disease and justify the continuing routine screening in pregnancy. There is no local data on the best testing strategies for ASB.

6.0 RESEARCH QUESTION

How accurate is the urine dipstick test in detecting asymptomatic bacteriuria among pregnant women receiving antenatal care at Kenyatta National Hospital?

7.0 OBJECTIVES

7.1 Broad objective

To determine the accuracy of urine dipstick test in detecting asymptomatic bacteriuria among pregnant women receiving antenatal care at Kenyatta National Hospital.

7.2 Specific objectives

Among pregnant women receiving antenatal care at Kenyatta National Hospital;

1) To compare the prevalence of asymptomatic bacteriuria detected using dipstick test versus urine culture method.

2) To determine the sensitivity and specificity of detecting asymptomatic bacteriuria using the LE and nitrite components of the dipstick test individually and in combination compared to the gold standard test, the culture.

3) To determine the positive and negative predictive values for detecting asymptomatic bacteriuria using the leucocyte esterase and nitrite components of the dipstick test individually and in combination compared to the culture method.

4) To determine the positive and negative likelihood ratios for detecting asymptomatic bacteriuria using the leucocyte esterase and nitrite components of the dipstick test individually and in combination compared to the culture method.

8.0 STUDY METHODOLOGY

8.1 Study design

This was a cross sectional study on prevalence of ASB among pregnant women seeking ANC at KNH, Nairobi Kenya. The study was designed to compare the accuracy of detection of ASB from a clean catch midstream urine specimens subjected to dipstick test by determining the sensitivity, specificity, predictive values and likelihood ratios. Urine culture was used as the gold standard test against which the dipstick test was compared. This design would enable the evaluation of the role of urine dipstick test in identifying those with or without ASB.

8.2 Study site

This study was carried out in the ANC clinics at KNH, Kenya's national referral hospital, located in Nairobi, the capital city of Kenya, within Nairobi County. KNH is Kenya's largest referral and teaching hospital, and forms the apex of Kenya's public healthcare system. KNH has 50 wards, 24 theatres and 22 out-patient clinics an Accident and Emergency Unit and a bed capacity of 1800. The hospital runs ANC from Monday to Thursday, handling approximately 600 pregnant women per week. In this clinic, as per the MOH guideline, all pregnant women undergo urine dipstick testing to detect ASB at every antenatal visit. Diagnosis and subsequent treatment is initiated based on positive urine dipstick for LE, nitrites or both. Cultures are not routinely performed for detection of ASB in pregnancy.

KNH receives many pregnant women of varied socio-demographic and obstetric characteristic. KNH microbiology laboratory is able to conduct urine cultures and antibiotic sensitivity studies and was used to run the urine culture tests for this study.

8.3 Study population

The study participants were pregnant women at varied gestational ages, selected among those who were receiving routine ANC at KNH. Simple random sampling with a set inclusion and exclusion criteria was applied until the desired sampled size of 132 pregnant women was achieved.

8.3.1 Inclusion criteria

1) Pregnant women receiving ANC at KNH.

2) No symptoms suggestive of UTI (dysuria, frequency of micturition, urgency, hesitancy, incontinence, haematuria, nocturia, incomplete voiding, lower abdominal pain and flank pain)

3) 18 years of age or greater

4) Ability to provide informed consent.

8.3.2 Exclusion criteria

Women were excluded from the study if they had any of the following;

1) Fever irrespective of aetiology

2) History of prior antibiotic treatment in the last one month for any indication

3) Active per vaginal bleeding, discharge or drainage of liquor

8.4 Sample size estimation

The sample size was calculated using Buderer's formulae used for estimating the number of participants required to assess test performance(48).

W was the maximum clinically acceptable width of the 95% confidence interval

P was the estimate of the prevalence of ASB in pregnant women estimated at 40%

SN was the expected sensitivity of dipstick in screening bacteriuria

SP was the expected specificity of dipstick in screening bacteriuria

$Z_{\alpha/2}$ = Two tailed 95% confidence interval, for alpha = 0.05, Z = 1.96

(W, P, SN and SP are expressed as numbers between 0 and 1, rather than as percentages.

Sample size required for sensitivity N1

$$TP + FP = Z_{\alpha/2} \frac{SN(1-SN)}{W^2} = TP + FP = 1.96 \frac{0.3(1-0.3)}{0.13^2}$$

$$N1 = \frac{TP+FP}{P}$$

= 47.735/0.4 = 80

Sample size for specificity N2

$$FP + TN = Z_{\alpha/2} \frac{SP(1-SP)}{W^2} = TP + FP = 1.96 \frac{0.7(1-0.7)}{0.13^2}$$

$$N1 = \frac{TP+FP}{P(1-P)}$$

= 47.735/0.4 (1-0.4) = 120

N2 > N1, thus N (minimum required sample size) was 120 subjects

Add 10% to cater for non-response = 132

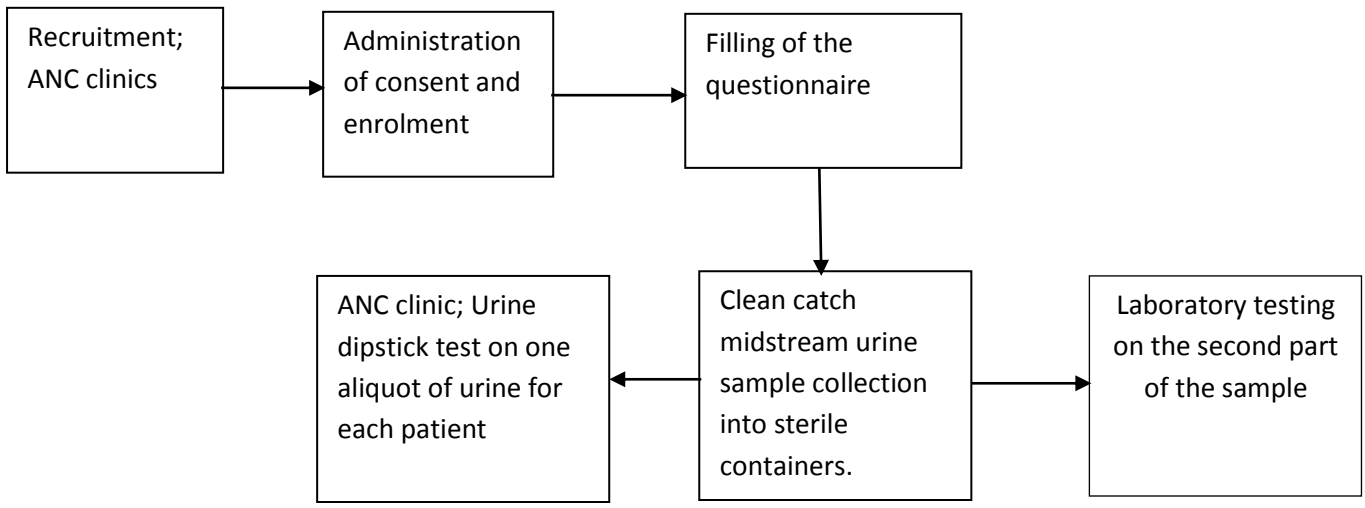
n = 132

8.5 Sampling procedure.

Consecutive simple random sampling was used to recruit eligible women into the study until the desired sample size of 132 study participants was achieved.

8.6 Study flow chart

The following was the study flow chart followed in the ANC clinic and laboratory.



8.7 Study procedure.

The research assistants comprised of nurses trained on the study details, how to fill the questionnaire in a standardized manner, recruit eligible participants, specimen collection and how to perform the dipstick test. Two laboratory technologists were also given details of the study and the culture and antimicrobial sensitivity tests that were to be done. Recruitment of study participants, filling of the questionnaire, specimen collection and dipstick testing was done in the ANC clinics. Those who met the inclusion criteria were informed about the study and written informed consents obtained. A structured questionnaire on socio-demographic and obstetric characteristics of the participant was administered by the principle researcher or trained research assistants. The participants were then given clear instructions on how to clean their hands with water and how to collect approximately 10ml of a clean-catch (spread the labia and clean the inter-labial area three times from the front going backwards each time with a separate piece of sterile gauze soaked in saline), midstream (collection of the second portion of the voided urine after discarding the initial stream) sample into labelled, sterile,

wide mouthed 50 millilitre containers covered with tight-fitting lids. A trained female nurse research assistant accompanied them during the urine sample collection. No antiseptics were used. Each participants sample was divided into two aliquots, approximately 5mililitres each in separate sterile containers for the dipstick and culture tests. The first aliquot was subjected to dipstick testing using a multiple reagent strip, one of those recommended by WHO due to high sensitivity and specificity. The dipstick test was performed by the principle investigator with the help of the trained research assistants. This first sample was tested for the presence of nitrite and LE by immersing the dipstick test strip completely in the sample of urine. The strip would then be extracted from the container and supported over the mouth of the container to drain excess urine. It was then left to stand for a while awaiting for the reactions to occur (1 minute for nitrite test and 2 minutes for the LE test). The colours that appeared were compared with those in the chromatic scale provided by the manufacturer. The nitrite component of the test was read as positive if the reagent pad turned pink, and the LE component as positive if the reagent pad matched a colour coded +,++ or +++. A positive dipstick was defined by the presence of nitrites or a reaction of greater than or equal to a trace of leukocytes. Combination of LE and nitrite test was interpreted as positive if any one or both tests were positive and as negative only when both tests were negative. The microbiologist was blinded to the results of dipstick test. The second urine sample was kept in a cool box at 4 degrees Celsius and delivered to the laboratory within one hour of collection. KNH microbiology laboratory was used to run the culture and antibiotic sensitivity tests.

Quality of the culture media was tested for sterility by incubating one of the plates overnight at 35-37 ^{o}C without specimen inoculation. Each sample was inoculated using a sterile calibrated wire loop to deliver 0.001ml in a streaking method to produce discrete colonies on Mac-Conkey and Cysteine Lactose Electrolyte Deficient (CLED) agar. Sterile loops were

used for each streak made. This was incubated aerobically at 37°C and read at 12, 24 and 48 hours. Culture plates with no visible growth were further incubated for an extra 24 hours before being discarded. The number of CFUs were multiplied by 1000 to determine the number of microorganisms per millilitre in the specimen.

Gram negative bacterial identification was done with use of biochemical tests which included indol, urease and Simmon's citrate tests. Whereas gram positive bacteria identification was carried out using gram staining reaction, catalase and coagulase tests. Samples were classified as "sterile" if no growth was obtained, as "significant growth" if the growth of the pathogen(s) was at a count $\geq 10^5$cfu/ml of urine and as "insignificant growth" if growth of $<10^5$ CFU/mL.

The antimicrobial sensitivity testing of the isolates was performed by the disk diffusion technique. A sterile cotton swab was used to distribute the bacteria from 3-5 selected colonies evenly over the entire surface of Mueller Hinton agar. The inoculated plates were impregnated with the different antibiotic discs and incubated in aerobic atmosphere at 37 degrees Celsius for 24 hours. Diameters of the zone of inhibition around the disc were measured to the nearest millimetre using a graduated calliper and the isolates were classified as either sensitive or resistant.

8.8 Quality assurance

●Labelled, sterile wide mouth containers with tight fitting lids were used to collect the urine samples.

●A trained female nurse research assistant accompanied the study participants during the urine sample to ensure clean catch midstream urine was collected.

●Similar strips were used for all patient samples. The strips were kept at room temperature and expiry dates also checked.

●The samples for culture were kept in a cool box at 4 degrees Celsius and delivered to the laboratory within an hour of collection. Quality of the culture media was tested for sterility by incubating one of the plates overnight at 35-37 ºC without specimen inoculation.

●Standard reference strains of Staphylococcus aureus (gram positive) and Escherichia coli (gram negative) were used for quality control. Temperature of incubator was monitored daily.

8.9 Data collection

Data on socio-demographic characteristics, dipstick and culture test results were collected by use of the questionnaire with open ended questions. The section on socio-demographic characteristics was designed to capture participants socio-demographic, obstetric and relevant past medical history. History of symptoms suggestive of UTIs was sought in order to define participants' suitability for inclusion or exclusion from the study.

The dipstick test form captured results of the dipstick test based on the LE and nitrite components. While the laboratory form captured results of the culture and antimicrobial sensitivity test.

Before data collection was undertaken, the questionnaire was pretested using randomly picked pregnant women to enable appropriate amendments.

8.9.1 Data management.

A coded number, unique for each study participant was used on the questionnaire, sample bottles and on both test results. The coded numbers matched with the patient's real name. Confidentiality was maintained. Data collected was sorted, coded and entered into a computer. Data entry and editing for any errors was done throughout the study period.

8.9.2 Data analysis.

Analysis was done using SPSS® version 21. Descriptive analysis entailed use of the mean. Chi- square goodness of fit test was used to test for association between positive culture results and the socio-demographic and reproductive health characteristics. A P-value of less than 0.05 was considered statistically significant. The diagnostic value of the LE and nitrite components of the dipstick test method in terms of sensitivity, specificity, predictive values and likelihood ratios was evaluated against the culture method and presented as percentages or ratios as appropriate.

8.9.3 Calculation of sensitivity, specificity, predictive values and likelihood ratios.

Contingency table based on Altman et al formula(49)**.**

		THE TRUE RESULT		
		Have disease	**Have no disease**	**Total number**
TEST RESULT	**Test positive**	True Positive	False positive	Total test positive
	Test negative	False Negative	True negative	Total test negative
		Total disease	**Total no disease**	**Total**

- True positives = Persons who have disease and the test is positive
  - True negatives = Persons who do not have disease and the test is negative
  - False positives = Persons without disease but with positive test
  - False negatives =Person with disease but with negative test
  - The true result = urine culture result
  - Test result = Result of the urine dipstick test (nitrite and LE components)

1. Sensitivity (%)

$$\frac{\text{True positive}}{\text{True Positive + False Negative}} \times 100$$

2. Specificity (%)

$$\frac{\text{True Negative}}{\text{False Positive + True Negative}} \times 100$$

3. PPV (%)

$$\frac{\text{True Positive}}{\text{True Positive + False Positive}} \times 100$$

4. NPV(%)

$$\frac{\text{True Negative}}{\text{False Negative + True Negative}} \times 100$$

5. Positive likelihood ratio

$$\frac{\text{sensitivity}}{\text{1-specificity}}$$

6. Negative likelihood ratio

$$\frac{\text{1- Sensitivity}}{\text{specificity}}$$

7. Combined sensitivity = (sensitivity A + specificity B) – (sensitivity A × sensitivity B).

8. Combined specificity = specificity A × specificity B.

(A denotes nitrite component of the dipstick test while B denotes the LE component).

9.0 ETHICAL CONSIDERATIONS.

The study was approved by KNH/ UON Ethics and Research Committee and KNH administration (Protocol number P684/09/2016). Each of the eligible participants was given information on the purpose of the study and allowed to voluntarily give a written informed consent. Confidentiality of the participants' identity and that of all the data acquired was taken care of by use of unique coded numbers.

No extra costs or risks to the study participants. They benefited by having urine bacteriologic culture and antibiotic sensitivity testing at no cost. Failure to participate in the study did not compromise the care received by the patient from the hospital.

10.0 STUDY LIMITATIONS.

The main study limitation was inability to strictly collect the early morning urine sample or urine that had been in the bladder for at least four hours. However, this did not adversely affect the interpretation of our study findings since in routine practice, urine is collected as soon as the patients present irrespective of duration of stay or time of the day.

11.0 STUDY RESULTS.

Table 1: Socio-demographic and reproductive health characteristics of pregnant women receiving ANC at KNH.

Characteristic	Number (N=130)	Percent (%)
Age in years		
18 – 25	29	22.3
26 – 35	75	57.7
>35	26	20.0
Occupation		
Unemployed	29	22.3
Self employed	63	48.5
Formal employment	38	29.2
Marital status		
Single	19	14.6
Married	111	85.4
Highest education level		
None	1	0.8
Primary	16	11.6
Secondary	39	30.0
Tertiary	76	58.5
Parity		
0	54	41.5
1	37	28.5
2	27	20.8
≥3	12	9.2
Gestational age (weeks)		
<13	12	9.2
13 – 28	41	31.5
>28	77	59.2
History of UTI in current pregnancy based on dipstick test		
Yes	33	25.4
No	97	74.6

**UTI- Urinary Tract Infections*

11.1 Socio – demographic and reproductive health characteristics of study participants.

As shown in table 1 above, a total of 130 pregnant women without symptoms of urinary tract infection, were subjected to concurrent urine dipstick and bacteriologic culture testing for detection of ASB. Majority of the women were in the age group 26 to 35 years 75 (57.7%), with the minimum and maximum age being 18 years and 42 years respectively. The mean age was 30 years (± standard deviation of 5.5 years). Nearly two thirds were self-employed 63(48.5%), had attained tertiary level of education 76 (58.5%) and majority were married 111(85.4%).

Regarding the reproductive health characteristics, slightly below half 54(41.5%) were primigravidae and most were at a gestational age greater than 28 weeks (59.2%). About one quarter 33 (25.4%) of the participants had a history of having had UTI in the current pregnancy.

Table 2: Urine culture and dipstick results (leucocyte esterase and nitrite components) of pregnant women receiving ANC at KNH.

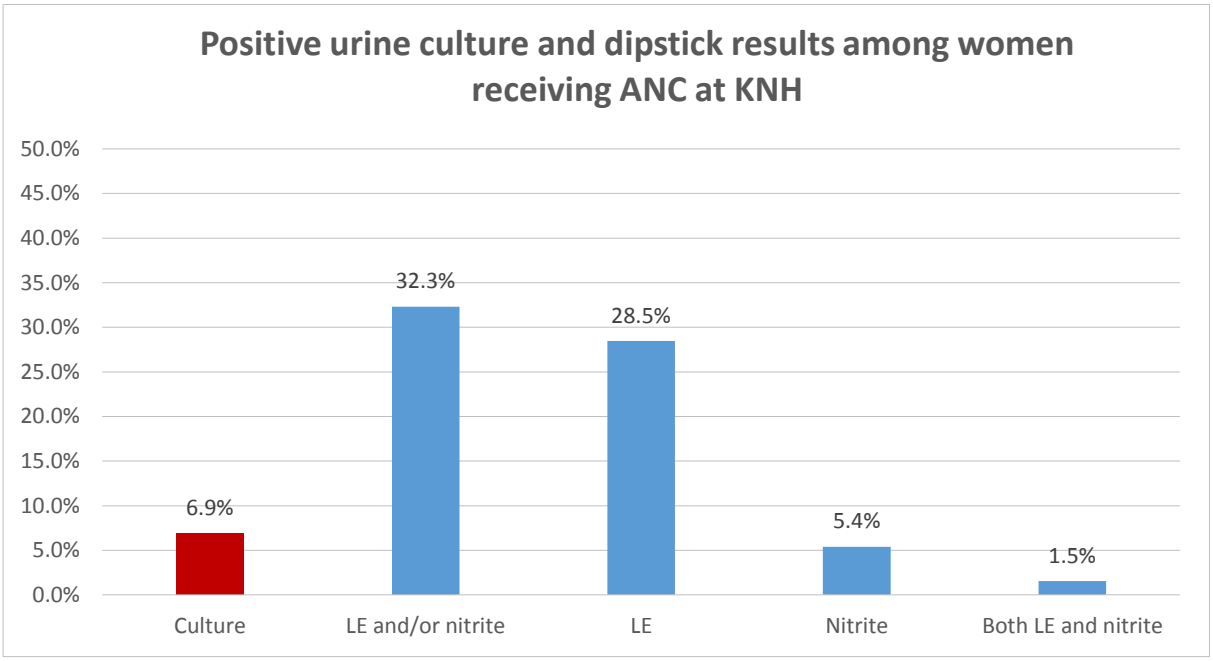
Characteristic	Number positive	Number positive n(%)	Number negative n(%)
Culture	9	9(6.9)	121(93.1)
Leucocyte esterase(LE)			
+	10		
++	14		
+++	13	37(28.5)	93(71.5)
Total leucocyte esterase	37		
Nitrite	7	7(5.4)	123(94.6)
Combined LE and nitrite			
LE and/or Nitrite			
LE (+) or Nitrite (Positive)	10		
LE (++) or Nitrite (Positive)	14	42(32.3)	88(67.7)
LE (+++) or Nitrite (Positive)	13		
LE (Negative) or Nitrite (Positive)	3		
Both LE and Nitrite positive	2		
Total LE and/or nitrite	42		
Both LE and Nitrite	2	2 (1.5)	88 (67.7)

11.2 Results of urine culture and dipstick.

The dipstick test results showed that 37(28.5%) and 7(5.4%) were positive for LE and nitrite respectively as demonstrated in table 2 above.

With the combined LE and nitrite test (any one of the two tests positive), 42(32.3%) women were positive. Only 2(1.5%) women had both positive LE and nitrite tests, while 88(67.7%) had both LE and nitrite tests negative.

Figure 1; Prevalence of asymptomatic bacteriuria on culture and positive dipstick test



LE-Leucocyte esterase

11.3 Prevalence of asymptomatic bacteriuria and that of positive dipstick test results.

The prevalence of ASB in this study was found to be 6.9%. This was based on results of the gold standard test, quantitative culture, where bacteria were isolated from 9 out of the 130 samples. On the other hand the prevalence of positive LE, nitrite test and both LE and nitrite test were 28.4%, 5.4% and 1.5% respectively as shown in figure 1 above.

Table 3: Association between socio-demographic, reproductive health characteristics and positive urine cultures of women receiving ANC at KNH.

Characteristic	Culture Positive Number (%)	Culture Negative Number (%)	P - value
Age in years			0.984
18 – 25	2 (22.2)	27 (22.3)	
26 – 35	5 (55.6)	70 (57.9)	
>35	2 (22.2)	24 (19.8)	
Occupation			0.705
Unemployed	1 (11.1)	28 (23.1)	
Self employed	5 (55.6)	58 (47.9)	
Formal employment	3 (33.3)	35 (28.9)	
Marital status			0.758
Single	1 (11.1)	18 (14.9)	
Married	8 (88.9)	103 (85.1)	
Highest education level			0.556
None	0 (0.0)	1 (0.8)	
Primary	1 (11.1)	13 (10.7)	
Secondary	4 (44.4)	35 (28.9)	
Tertiary	4 (44.4)	72 (59.5)	
Parity			0.172
0	1 (11.1)	53 (43.8)	
1	5 (55.6)	32 (26.4)	
2	2 (22.2)	25 (20.7)	
≥3	1 (11.1)	11 (9.1)	
Gestational age (weeks)			0.484
<13	1 (11.1)	11 (9.1)	
13 – 28	4 (44.4)	37 (30.6)	
>28	4 (44.4)	73 (60.3)	
History of UTI in current pregnancy based on dipstick test			0.166
Yes	4 (44.4)	29 (24.0)	
No	5 (55.6)	92 (76.0)	

**UTI – Urinary Tract Infections*

11.4 Association between socio-demographic, reproductive health characteristics and positive urine cultures.

As demonstrated in table 3 above, there were no statistically significant associations between socio-demographic, reproductive health characteristics and positive urine cultures as assessed for age in years, occupation, marital status, highest education level attained, parity, gestational age and history of UTI in the current pregnancy. However, ASB was found to be more prevalent among the self-employed 5(55.6%) and married 8(88.9%) pregnant women.

11.5 Accuracy as determined from the sensitivity, specificity, predictive values and likelihood ratios of the dipstick test for detection of ASB.

Table 4a: Sensitivity, specificity, predictive values and likelihood ratios of the leucocyte esterase test.

Leucocyte esterase	**Culture positive (N = 9)**	**Culture negative (N = 123)**	**Total**
Positive	6	31	37
Negative	3	90	93
Total	9	121	130

Sensitivity = 6/9 x 100 = 66.7%

Specificity = 90/121 x 100 = 74.4%

PPV = 6/37 x 100 = 16.2%

NPV = 90/93 x 100 = 96.8%

Positive LR = 66.7/ (1-74.4) = 2.61

Negative LR = (1-66.7)/74.4 = 0.45

Compared to the culture test results, the LE test was able to detect 6 true positive and 90 true negative cases. There were 31 false positive and 3 false negative cases. The Sensitivity, specificity, NPV and PPV of LE test was 66.7%, 74.4%, 16.2% and 96.8% respectively.

Table 4b: Sensitivity, specificity, predictive values and likelihood ratios of the nitrite test.

Nitrite	Culture positive (N = 9)	Culture negative (N = 123)	Total
Positive	4	3	7
Negative	5	118	123
Total	9	121	130

Sensitivity = 4/9 x100 = 44.4%

Specificity = 118/121 x 100 = 97.5%

PPV = 4/7 x 100 = 57.1%

NPV = 118/123 x 100 = 95.9%

Positive LR = 44.4/ (1-97.5) = 17.76

Negative LR = (1-44.4)/97.5 = 0.57

The nitrite test detected 4 true positive and 118 true negative cases. There were 5 false negative and 3 false positive cases. This gave a sensitivity of 44.4%, specificity of 97.5%, NPV of 95.9% and PPV of 57.1%.

The sensitivity of LE (66.7%) was higher than that of nitrite (44.4%) test. Both the nitrite and LE tests had high specificity values (97.5% and 74.4% respectively) and high NPV (96.8% and 95.9%, respectively).

Table 4c: Sensitivity, specificity, predictive values and likelihood ratios of the combined test (leucocyte esterase and/or nitrite).

Combined leucocyte esterase and nitrate test (leucocyte esterase and/or nitrite)	Culture positive (N = 9)	Culture negative (N = 123)	Total
Positive	8	34	42
Negative	1	87	88
Total	9	121	130

Sensitivity = 8/9 x 100 = 88.9%

Specificity = 87/121 x 100 = 71.9%

PPV = 8/42 x 100 = 19%

NPV = 87/121 x 100 = 98.9%

Positive LR = 88.9/ (1-71.9) = 2.3

Negative LR = (1-88.9)/71.9 = 0.46

With the combined LE and nitrite tests (any one of the two tests positive) there were 34 false positive and one false negative case. However this combination had an improved sensitivity of 88.9% compared to considering each test alone.

Table 4d: Sensitivity, specificity, predictive values and likelihood ratios of the combined test (both leucocyte esterase and nitrite).

Combined leucocyte esterase and nitrate (Both leucocyte esterase and nitrite)	Culture positive (N = 9)	Culture negative (N = 123)	Total
Positive	2	0	2
Negative	7	121	128
Total	9	121	130

Sensitivity = 2/9 x 100 = 22.2%

Specificity = 121/121 x 100 = 100%

PPV = 2/2 x 100 = 100%

NPV = 121/128 x 100 = 94.5%

Positive LR = 22.2/ (1-100) = 22.2

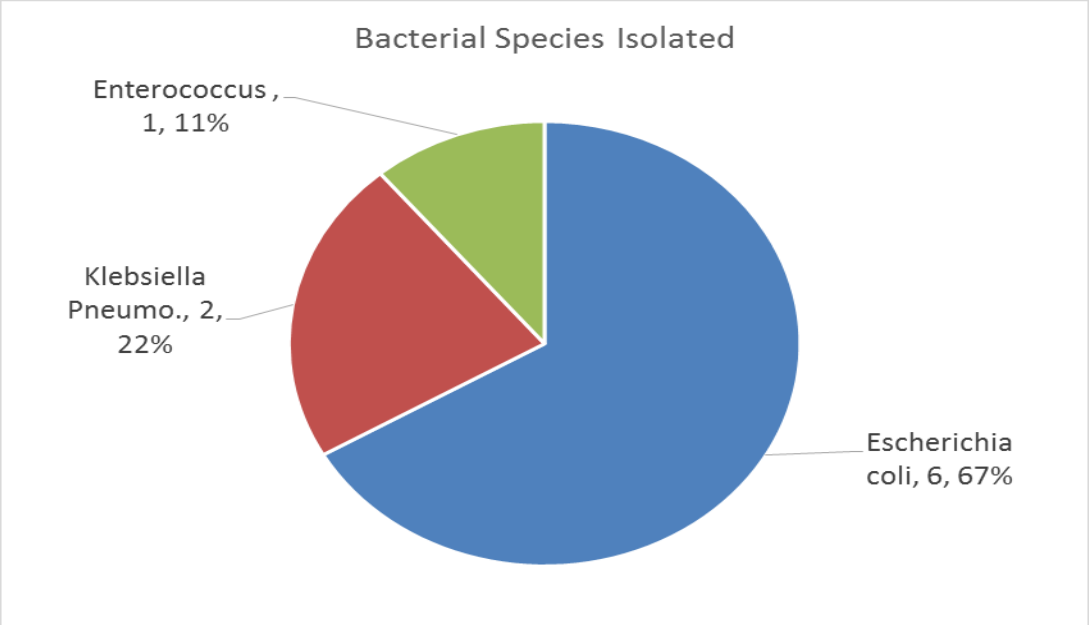
Negative LR = (1-22.2)/100 = 0.78

Combined LE and nitrite (both tests positive), indicated 7 false positive results. There were no false negative results. The sensitivity also decreased to 22.2% compared to when each test was considered separately.

All the positive likelihood ratios were greater than 1 indicating that the positive test results were associated with the presence of ASB, whereas negative likelihood ratios were less than 1 indicating that the negative test results were associated with the absence of the disease. However, a positive nitrite test was strongly predictive of a diagnosis of ASB as the likelihood ratio was substantially higher than 10.

11.6 Bacterial isolates.

Figure 2: Bacterial isolates from pregnant women receiving ANC at KNH.



All the bacteria isolated during culture were gram negatives. The commonest being Escherichia Coli (66.7%), followed by Klebsiella pneumonia (22.2%) and Enterococcus at (11.1%) as shown in figure 2 above.

Table 5: Correlation between the dipstick test results and bacterial species isolated from pregnant women receiving ANC at KNH.

Leucocyte esterase	**NITRITE**	**ORGANISM**
+	Positive	Escherichia Coli
++	Positive	Klebsiella
negative	Positive	Klebsiella
+++	Negative	Escherichia Coli
+++	Negative	Enterococcus
negative	Negative	Escherichia Coli
+++	Negative	Escherichia Coli
negative	Positive	Escherichia Coli
++	Positive	Escherichia Coli

11.7 Correlation between the dipstick test results and bacterial species isolated.

The nitrite test was positive for both cases of Klebsiella isolated, whereas for the enterococcus strain, only the LE test was positive. Both tests were each able to detect about half of the Escherichia coli strains. Only one out of six cases of Escherichia coli isolated had not been detected by either LE or the nitrite test as shown in table 5 above.

Table 6: Antibiotic sensitivity pattern of the bacterial isolates from women receiving ANC at KNH.

Antibiotic / Bacterial species	**Escherichia Coli**		**Klebsiella**		**Enterococcus**	
	R	**S**	**R**	**S**	**R**	**S**
Ampicillin	3 (50%)	3 (50%)	2 (100%)	0(0%)	0(0%)	1(100%)
Amoxicillin /Clavulanic acid	2 (25%)	4 (75%)	1 (50%)	1 (50%)	0(0%)	1(100%)
Ampicillin/Sulbactam	3 (50%)	3 (50%)	1 (50%)	1 (50%)	0(0%)	1(100%)
Piperacillin/Tazobactam	1 (17%)	5 (83%)	1 (50%)	1 (50%)	0(0%)	1(100%)
Amikacin	0(0%)	6 (100%)	0(0%)	2 (100%)	0(0%)	1(100%)
Gentamicin	0(0%)	6 (100%)	0(0%)	2 (100%)	0(0%)	1(100%)
Nitrofurantoin	0(0%)	6 (100%)	1 (50%)	1 (50%)	1(100%)	0(0%)
Ciprofloxacin	2 (25%)	4 (75%)	0(0%)	2 (100%)	0(0%)	1(100%)
Triamethoprim/Sulfonamide	3 (50%)	3 (50%)	1 (50%)	1 (50%)	1(100%)	0(0%)
Cefazolin	2 (25%)	4 (75%)	0(0%)	2 (100%)	1(100%)	0(0%)
Cefuroxime	2 (25%)	4 (75%)	0(0%)	2 (100%)	1(100%)	0(0%)
Ceftriaxone	2 (25%)	4 (75%)	0(0%)	2 (100%)	1(100%)	0(0%)
Cefepime	2 (25%)	4 (75%)	0(0%)	2 (100%)	1(100%)	0(0%)
Aztreonam	2 (25%)	4 (75%)	0(0%)	2 (100%)	0(0%)	1(100%)
Meropenem	0(0%)	6 (100%)	0(0%)	2 (100%)	0(0%)	1(100%)
Imipenem	0(0%)	6 (100%)	0(0%)	2 (100%)	0(0%)	1(100%)

**R- Resistant,*S- Sensitive*

11.8 Antibiotic sensitivity patterns.

As shown in table 6 above, all the organisms isolated showed 100% sensitivity to meropenem, imipenem, amikacin and gentamicin. Only Escherichia coli showed 100% sensitivity to nitrofurantoin as resistance was observed with Klebsiella pneumonia (50%) and to the Enterococcus strain isolated. The rate of resistance to ampicillin, co-trimoxazole, amoxicillin-clavulanic acid and cephalosporins among E. coli strains was 50%, 50%, 25% and 25%, respectively.

Only Klebsiella Pneumoniae strains were 100% sensitive to the cephalosporins. Resistance to ampicillin, amoxicillin-clavulanic acid, nitrofurantoin and co-trimoxazole was 100%, 50%, 50%, 50% respectively.

The only Enterococcus strain isolated was sensitive to ampicillin, amoxicillin-clavulanic acid, amikacin, gentamicin, aztreonam, imipenem and meropenem but resistant to nitrofurantoin, co-trimoxazole and cephalosporins.

12.0 DISCUSSION.

The prevalence of ASB among pregnant women receiving antenatal care at KNH in this study based on the culture result was 6.9% whereas that based on the LE test was 28.4% signifying a high number of false positive results. About a quarter (n = 31) of the women with LE positive result, did not have bacterial growth on culture testing. The high false positive results meant that treatment based on the presence of LE would expose 23.6% of the mothers and their fetuses to unnecessary antibiotics with the associated adverse effects and attendant costs. Similar findings have been suggested by other studies(16)(50). In India, Khanna et al recently reported a 25% false positive rate (50 false positive cases) associated with the use of LE test(50). The high false positive rate could be due to the fact that presence of LE signifies pyuria and not an absolute indicator of bacteriuria. Pyuria may occur with other inflammatory disorders of the urinary tract (e.g cystitis) or may continue for a while after bacteriuria has been cleared(33).

The prevalence of ASB of 6.9% indicates that about 7% of pregnant women are at a risk of developing symptomatic urinary tract infections, preterm deliveries, low birth weight infants, foetal growth restrictions, preterm premature rupture of membranes and pre-eclampsia if ASB is left untreated. The prevalence is comparable to that of studies done in other countries with prevalence of ASB quoted in literatures varying from 2-10%(13). In Delhi, northern India it was reported as 5% (16), 4% in Gazi university hospital, Turkey(17), 12.5% in Cairo, Egypt(19), 4.8% in Sharjah, United Arab Emirates(18), 7.3% in Kumasi, Ghana(20) and 7.8% in Buea, southwest Cameroon(21). However a very high prevalence of 40% was reported in Ilorin, Nigeria by Ajayi et al(22). The high prevalence was attributed to the fact that only women who booked around the peak gestational age for bacteriuria (20 weeks) were recruited for the study unlike in our study where the participants were of varied gestational

ages. The discrepancies between countries may also be explained by variations in the study population's social, economic and cultural habits or differences in bacterial ecologies or study setting(51).

The nitrite test showed a low sensitivity of 44.4%, but a high specificity of 97.5%. Varying sensitivities of the nitrite test have been reported, 35.7% in the study done in Northwest Ethiopia (52), 8% in southwest Cameroon(21) and 82.5% in Delhi, India(16) while the specificities were 98%, 98.7% and 99.9%, respectively. The nitrite test relies on the breakdown of urinary nitrates to nitrites. The variation in sensitivity and specificity in the different studies done may be due to differences in prevalence and type of uropathogens as not all organisms possess nitrate reductase, the enzyme capable of reducing nitrates to nitrites to allow for its detection by the test kit. The low sensitivity (44.4%) in our study implies a high false negative rate making the nitrite test when used alone, a poor screening tool for ASB. This could be due to the fact we did not utilize the early morning voided urine sample or ensure that the urine was in the bladder for at least four hours before collection to allow for the conversion of nitrates to nitrites(13). Such conditions are not adhered to in the routine local set up.

Sensitivity of LE was 66.7%, specificity of 74.4%, PPV of 16.2% and NPV of 96.8%. This correlates with the studies by Titoria et al in Delhi, India that showed sensitivity of LE to be 60% and specificity of 96.1% and that by Cakir et al in Turkey that noted the sensitivity and specificity of LE to be 70% and 92% respectively(16)(17). Morike et al in Cameroon however reported a lower sensitivity of 20.8% and this was attributed to presence of fastidious organisms like Neisseria gonorrheae that produce sterile pyuria(21). Sensitivity of LE in our study was higher than that of the nitrite test. This meant the LE test was better in detecting those with ASB than the nitrite test, a finding reported in various other studies (22)(16)(18). On the contrary the study by Titoria et al found the nitrite test to have a higher

sensitivity of 82.5% than that of the LE test 27.5%(16). The sensitivity of the nitrite and LE test improved to 88.9% and specificity 100% when combined in parallel (any one of the test positive). This is higher than considering each test alone or when both tests are positive. Two previous studies, by Khanna et al and Titoria et al also reported an improved sensitivity of 93.3% (50) and 87.3%(16) respectively considering either test positive. On the contrary a study by Tincello in Liverpool noted no added value in combining the two tests as this gave a sensitivity of 33.3%(53). The high NPV's noted with LE (96.8%), nitrite test (95.9%) and combined test (98.9%) correlated well with that reported in various other studies (16)(17)(21)(50).

All organisms isolated were gram negatives. Sevki et al in their study reported gram negative isolates to be at 95 percent(54). The commonest bacterial isolate was Escherichia coli (66.7%), followed by Klebsiella pneumonia (22.2%) and Enterococcus faecium at (11.1%). Comparable findings of Escherichia Coli as the most prevalent organism have been reported in Sharjah, 66.7% (18), in Cairo, Egypt, 70%(19) and in Jos, Nigeria, 66.7% (55). It is the predominant bacteria in human intestine, the close proximity of the female genital tract and anal region aids easy transfer of the bacteria to the vagina and urethra. Specific E. Coli virulence factors, such as the P-fimbriae and S fimbriae adhesions and pregnancy related urinary stasis enable them to colonize, invade and attach to the urinary epithelium, allowing for multiplication(35). Other studies reported Staphylococcus aureus (22) and klebsiella species(56) as the most prevalent causative agents. Geographical distribution and epidemiological factors could have a role in this variation.

There was no evidence to suggest significant association between maternal age, occupation, marital status, parity, gestational age, highest education level attained, history of UTI in current pregnancy and ASB in this study. This is in line with findings made by Morike et al(21).On the contrary several other studies have identified the predictors of ASB to be past

history of UTI, advanced maternal age, anaemia, advanced gestational age, level of education, low socioeconomic status, immunosuppressive diseases and multiparity (34)(57)(58). The failure to identify significant predictors of ASB in our study could be attributed to the setting of the study (tertiary care centre) and that not all risk factors were assessed.

Isolates from this study were highly sensitive (100%) to imipenem, meropenem, amikacin and gentamicin. Mohammed et al in Cairo, Egypt(56) and Sevki et al in Turkey(54) reported 100% sensitivity to similar antibiotics. The high sensitivity may be attributed to the drugs' potent activity against the gram negative organisms and that they are less frequently abused locally due to their intravenous or intramuscular routes of administration. Highest resistance was noted with ampicillin and trimethoprim. This concurs with the study by Sevki et al where resistance to ampicillin was 57% (54). Isolates in our study exhibited variable susceptibility to antibiotics like cephalosporins, nitrofurantoin and amoxicillin-clavulanic acid commonly used for empirical treatment of ASB in pregnancy. E. coli was 100% sensitive to nitrofurantion but resistance was observed with klebsiella pneumonia (50%) and enterococcus (100%). Considerable sensitivity of E.coli (75%) and klebsiella pneumonia (100%) to cephalosporins was reported but there was resistance to the Enterococcus strain. Sensitivity to amoxicillin-clavulanic acid was 75% with E.coli, 50% with klebsiella pneumonia and 100% with Enterococcus. This is not in line with the study by Mohammed et al who reported a very low sensitivity of cephalexin to all the isolates, but sensitivity to other classes of cephalosporins was 88% (56). The antibiotic resistance could be due to the specific drugs widespread prescription for empirical treatment of ASB or self-medication in the localities(56).

13.0 CONCLUSION.

This study demonstrates that the urine dipstick test is useful to exclude the presence of ASB at the point of care if the results of both nitrites and LE are negative owing to the high specificity and NPV of the tests. Sensitivity of either test alone was insufficient to allow use as a screening tool for detecting ASB hence a positive test would require confirmation with culture instead of empirical treatment. This would ensure a high diagnostic performance and save on laboratory costs and workload as not all samples will be sent for culture analysis. The urine dipstick test method is thus not optimal in detecting ASB among pregnant women and that urine culture should be used for confirmatory testing. Highest sensitivity (100%) was noted with imipenem, meropenem, amikacin and gentamicin while highest resistance was noted with ampicillin and co-trimoxazole. Cephalosporins, amoxicillin- clavulanic acid and nitrofurantoin exhibited variable susceptibility.

14.0 RECOMMENDATIONS.

We recommended that:

1. The prevalence of ASB of 6.9% is high enough to warrant continued routine screening of all pregnant women.

2. Urine dipstick test should be done as an initial test to rule out ASB on all pregnant women. Those who test negative are unlikely to have ASB, whereas those who test positive are then sent for confirmatory testing via urine culture. Given a low prevalence of ASB of 6.9% and low sensitivity of the nitrite and LE tests, there is no justification for empirical treatment of pregnant women who are dipstick positive. As this would mean that approximately 25% of women with LE positive would receive unnecessary antibiotic treatment due to the numerous false positive results associated with this test.

3. Antibiotic sensitivity patterns showed nitrofurantoin can be used as first line drug for empirical treatment. The second line being the cephalosporin.

5. Further larger studies can be done to evaluate the accuracy of other screening methods for ASB i.e microscopy and also on the microbial and sensitivity patterns among our different population groups.

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16.0 APPENDICES.

16.1 APPENDIX 1; CONSENT FORM.

I will be given a copy of this consent form.

Study title: The accuracy of urine dipstick test in detecting asymptomatic bacteriuria among Pregnant women receiving ANC at KNH.

Participant's study number; Name;

Introduction:

Principle investigator: Dr. Muli Alice

Institution: University of Nairobi

Department: Obstetrics and Gynaecology

Registration no.: H58/75017/2014

Contacts: 0725271666

This research project is done as a part of the requirements for the award of the master's degree.

Supervisors; Professor Koigi Kamau – Professor in the Department of Obstetrics and Gynaecology/ UON

Dr Alfred Osoti – Lecturer/ Consultant Department of Obstetrics and Gynaecology/ UON

Dr Peter Michoma – Consultant Obstetrics and Gynaecology/KNH

Investigator's statement.

I invite you to participate in this research study. This consent form will give you information about the study, in order to enable you make a decision on whether to participate or not.

Introduction

The urinary system entails the kidneys, ureters, bladder and urethra. Bacterial infections of the urinary system can occur among pregnant women without symptoms hence investigations are done on the urine to detect them. When detected and treated with antibiotics the associated pregnancy related complications like pyelonephritis, preterm deliveries, low birth weight infants, intrauterine growth restriction and pre-eclampsia can be avoided.

Purpose of study

This study will help us know how common these infections are in our set up and determine how accurate the urine dipstick test is in detecting the pregnant women with urinary tract infections and those without.

Voluntary participation

Your participation in this research study is voluntary. Any participant willing to withdraw from the study will be free to do so at any stage without being penalized or victimized. Your participation will involve answering questions related to you and the pregnancy and also providing a urine sample.

Risks:

There are no short or long term risks associated with participation in this study.

Potential benefits:

Participants will benefit by having urine microscopy, culture and sensitivity tests done at no extra cost.

Protection of confidentiality

Only those involved in the study will be allowed access to any data collected. True participant's identity will not be revealed in data analysis or in any publication resulting from this study. Only their unique coded numbers will be used. The urine sample availed will be used only for the investigations described in the study.

Contact information

Please contact Dr. Muli on 0725271666 if you have any questions or concerns about the study. In case of any questions concerning your rights as a research subject you can contact the KNH-UON Ethics& Research Committee on 02726300.

Consent by Participant:

I have read this consent form, understood it fully, was given the opportunity to ask questions and assured of confidentiality. I voluntary give my informed consent to participate in this study.

Participant's signature_____ Date: _____

Person conducting the consenting process:

I have provided the required information and ensured that the participant understood the study as described in this consent form.

Signature_____ Date: _____

16.2 APPENDIX 2; QUESTIONNAIRE.

Study title: Accuracy of the urine dipstick test in detecting asymptomatic bacteriuria among pregnant women receiving ANC at KNH.

This questionnaire is to be filled by the investigator or research assistant by circling only one of the various options given for each question as per the participant's response. This is after the participant confirms full understanding of the question.

Consent filled; yes - no

Study number;

File no;

Date;

1. Age in years;

2. Residence;

3. Occupation; Housewife - unemployed - self-employed - formal employment.

4. Marital status: single- married- divorced- widowed

5. Highest education level attained: none- primary- secondary- tertiary

6. Obstetric history;

a) LNMP:

b) Gestation by dates (in weeks);

c) Gestation by ultrasound (in weeks);

d) Number of pregnancy;

7. Medical history:

a) Have you received any antibiotics in the last one month? Yes - no

b) Have you been treated for a urine infection in this pregnancy? Yes – no – I don't know

8. Present symptoms;

Do you have any of the following symptoms?

a) Pain on passing urine? Yes – no

b) Lower abdominal pain? Yes – no

c) Fever/ hotness of body? Yes - no

d) Blood stained urine? Yes - no

e) Loin pains? Yes – no

9. Physical examination;

a) Temperature; febrile – afebrile

b) Abdominal tenderness; present - absent

c) Fundal height;

16.3 APPENDIX 3; DIPSTICK TEST FORM.

Study title: Accuracy of the urine dipstick test in detecting asymptomatic bacteriuria among pregnant women receiving ANC at KNH.

Participant's study number;

File no;

Sample type;

Time of sample collection;

Date of sample collection;

Gross sample description;

RESULTS

Leucocytes

Nitrites

Glucose

Bilirubin

Ketones

Protein

Blood

Ph

Urobilinogen

16.4 APPENDIX 4; LABORATORY FORM.

Study title: Accuracy of the urine dipstick test in detecting asymptomatic bacteriuria among pregnant women receiving ANC at KNH.

Participant's study number; File no;

Sample type;

Time of sample collection;

Date of sample collection;

Gross sample description;

Bacterial species isolated

Escherichia Coli Klebshiella

Proteus Citrobacter

Enterococcus Streptococcus

Staphylococcus

Antibiotic sensitivity results.

Ampicillin	Cefuroxime	Amikacin	Imipenem
Amoxicillin/ Clavulanic acid	Piperacillin/ Tazobactam	Ciprofloxacin	
Ampicillin/ Sulbactam	Augmentin	Cefazolin	
Gentamycin	Ceftriaxone	Cefepim	
Nitrofurantoin	Meropenem	Aztreonam	

16.5 APPENDIX 5; ERC APPROVAL FORM

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14th December 2016

Dr. Muli Alice Mwikali
Reg. No. H58/75017/2014
Department of Obstetrics and Gynecology
School of Medicine, UoN
College of Health Sciences
University of Nairobi

Dear Dr. Muli,

REVISED RESEARCH PROPOSAL- ACCURACY OF URINE DIPSTICK TEST IN DETECTING ASYMPTOMATIC BACTERIURIA AMONG PREGNANT WOMEN RECEIVING ANTENATAL CARE AT KENYATTA NATIONAL HOSPITAL (P684/09/2016)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above revised proposal. The approval period is from 14th December 2016 - 13th December 2017.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the rehewal*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.

Protect to discover

g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website http://www.erc.uonbi.ac.ke

Yours sincerely,

PROF M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
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