Original Article

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Diabetes Mellitus has no Significant Influence on the Prevalence of Antenatal Asymptomatic Bacteriuria

Microbiology Section

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ABSTRACT

Introduction: Diabetes is a known risk factor for asymptomatic bacteriuria (ASB). However, the influence of diabetes on antenatal ASB was previously not addressed.

Aim: The prevalence of ASB, effect of risk factors and type of isolates and susceptibility patterns were studied in diabetic pregnancy.

Materials and Methods: A total of 311 pregnant women were recruited for this study of which 103 were diabetic and 208 non-diabetic. A clean catch midstream urine samples were collected and cultured. The isolates were identified and antibiotic sensitivity was studied. The data was analysed by Chi-square test.

Results: The prevalence of ASB in diabetic pregnancy was 38.83% (40/10^3; 95% CI: 23.73 - 53.94) and in non-diabetic pregnancy was 37.98% (79/208; CI: 27.28- 48.68). The odds ratio was not significant 1.0225 (95% CU: 0.65 – 1.599; p=0.922) and associated factors such as age and gestational period had no effect. The major isolates were *Escherichia coli* (25.0%), *Staphylococcus aureus* (22.5%), Coagulase negative *staphylococci* (CONS) (20.00%), and *Klebsiella pneumonia* (20.00%) in diabetic pregnancy and CONS (31.7%), *E.coli* (24.0%) and *K.pneumonia* (16.5%) in non-diabetic pregnancy. The isolates of diabetic pregnancy showed highest susceptibility to nitrofurantoin (56.4%), gentamicin (38.5%) and cotrimoxazole (38.5%) whereas that of non-diabetic pregnancy to gentamicin (43.0%), azithromycin (32.9%) and norfloxacin (30.4). There was no significant ($p<0.05$) difference in the type and susceptibly of the isolates between diabetic and non-diabetic pregnancy.

Conclusion: Diabetes has no significant influence on the prevalence of ASB in diabetic pregnancy both in terms of isolates and antibiotic susceptibility pattern.

Keywords: Pregnancy, *Escherichia coli*, Gentamicin

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic endocrine disorder which leads to several acute and chronic complications [1], especially infection of urinary tract, respiratory tract, and soft tissues [2-5]. Urinary tract is the easily accessible for infections due to the presence of high amount of glucose in urine, which serves as a medium for pathogenic microorganisms. Further, DM is known to predispose urinary tract to bacterial infection [6]. Further, the presence of asymptomatic bacteriuria (ASB) in patients with Type 2 diabetes is considered as a predictor for subsequent urinary tract infection (UTI) in later stages [7]. Development of asymptomatic UTI in diabetic women has been reported to be three or four times more common in diabetic than in non-diabetic women or men [8-13]. The prevalence of ASB has been reported to be as high as 30% in diabetic women [14].

Female urinary tract undergoes several changes during pregnancy, which increase the risk of urinary tract infection. Following the development of ASB, several complications can develop such as UTI, pyelonephritis, pre-eclampsia, anaemia, low birth weight of foetus, retarded intrauterine growth, preterm labour, premature rupture of membrane and post-partum endometritis [15,16]. In developed countries, the awareness of ASB has led to screening and treatment of ASB during early pregnancy [17], but similar awareness is lacking in developing countries despite the widespread prevalence in Indian subcontinent [18-20]. Further, the prevalence of ASB in diabetic pregnant women was hitherto not addressed.

AIM

Hence, this study is taken up to assess the prevalence of ASB in diabetic pregnant women attending antenatal out-patient department of government tertiary hospital.

MATERIALS AND METHODS

Outpatient recruitment

This study was conducted during January 2013 to December 2014 on diabetic pregnant women attending antenatal OPD at government tertiary hospital, who were willing to participate in the study. Ethical committee clearance was obtained prior to the start of the study.

Pregnant diabetic and non-diabetic women in their first, second and third trimesters without a history of urinary tract infection were included. Detailed history was obtained from each patient using a pre-designed proforma. Patients with fever or genitourinary complaints such as dysuria, urinary hesitancy, urgency, frequency, incontinence, incomplete voiding, flank/supra-pubic/hypogastric pain and patients on antibiotics were excluded from the study. After considering the history and inclusion criteria, a total of 103 pregnant diabetic women and 208 pregnant non-diabetic women were included in the study. Initially, urine sample was collected from all the participants. However, after culturing the urine, during subsequent check-ups, a second urine sample was collected only from patients with significant bacteriuria (10^5 organisms /mL of urine).

Collection of samples

A clean voided mid-stream urine specimen was collected into sterile specimen bottles and labelled with patient details. Initial Gram's staining and motility tests were done. The samples were processed without delay on to Cysteine Lactose Electrolyte Deficient (CLED) medium and blood agar for semi-quantitative analysis. Patients were advised to undergo follow up after one week time. During follow up, a second urine sample was collected from women diagnosed

Ingredient	Quantity(µg/disc)
1) Ampicillin (AMP)	10
2) Gentamicin (GEN)	10
3) Cephalexin (CN)	30
4) Ceftriaxone (CTR)	30
5) Ofloxacin (OF)	5
6) Norfloxacin (NX)	10
7) Cotrimoxazole (COT)	1.25 / 23.75
8) Nitrofurantoin (NIT)	300
9) Vancomycin (VA)	30
10) Linezolid (LZ)	30
11) Amoxycillin/Clavulanic acid (AMC)	20 / 10
12) Cefoperazone/Sulbactam (CFS)	75 / 10

[Table/Fig-1]: List of antimicrobial used for sensitivity testing.

Age group	Diabetic Pregnant women	Non-Diabetic Pregnant women	Significance (p)
18-22 years	37.50 (18/48) {15.13-59.87}	40.63(26/64) {21.75-59.50}	0.990
23- 27 years	52.00(13/25) {24.84-79.16}	38.10(32/84) {21.27-54.92}	0.673
28-32 years	30.00(09/30) {0.06-59.94}	35.00(21/60) {14.60-55.40}	0.973
Sig	0.723	0.994	

[Table/Fig-2]: Prevalence of asymptomatic bacteriuria in different age groups.
Values in ( ) are actual numbers and in { } are 95% Confidence Intervals; Chi-square test for between and within group values using SPSS software 19.0 V (P<0.05)

with significant bacteriuria (>10^5 organisms /mL). Samples were not obtained from patients without significant bacteriuria during follow up.

Culturing of urine samples

A quantity of 0.01 mL of urine sample was inoculated on to CLED agar and Blood agar plates for semi-quantitative cultures using standard loop. The plates were incubated at 37°C overnight in an incubator. Bacterial counts were performed in a colony counter. Bacterial counts of more than 10^5organisms /mL were considered as significant bacteriuria. Lower bacterial counts were considered insignificant and growth of more than two types of organisms was considered as contamination.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was done for the isolates using Kirby-Bauer method (disc diffusion). Three to four similar colonies were selected and transferred to five mL of Mueller-Hinton broth and incubated at 37° C for 4 hours. The broth was diluted to match the optical turbidity of 0.5 McFarland standard. Using a sterile swab, the broth was streaked on the surface of Mueller-Hinton (MH) agar. The inoculum was allowed to dry for 5-15 min and antibiotic discs were placed (6 discs per plate) on the surface [Table/Fig-1]. The plates were incubated at 37°C overnight. The zone of inhibition for the respective antibiotics was recorded using Vernier callipers.

RESULTS

The prevalence of ASB in diabetic pregnancy was 38.83% (40/103; 95% CI: 23.73 - 53.94) and in non-diabetic pregnancy was 37.98% (79/208; CI: 27.28- 48.68). The odds ratio was 1.0225 (95% CI: 0.65 – 1.599; p=0.922) indicating that the odds of acquiring ASB was not significantly different in diabetic pregnancy compared to non-diabetic pregnancy. A chi-square test of independence showed no significant (p<0.05) difference in the prevalence of asymptomatic bacteriuria between the two groups (X^2=0.021; DF=1; Sig=0.884). Further, there was no significant (p<0.05) difference in the prevalence of ASB between different age groups in diabetic pregnancy and non-diabetic pregnancy and between the groups [Table/Fig-2]. Similarly, there was no significant (p<0.05) difference in the prevalence of ASB between different periods of gestation in diabetic pregnancy and non-diabetic pregnant women and between the groups [Table/Fig-3]. Majority of the patients in diabetic pregnancy (88.35%; 91/103) and non-diabetic pregnancy (91.35%; 190/208) were from rural back ground and belonged to lower and middle class.

Period of gestation	Diabetic Pregnancy	Non-Diabetic Pregnancy	Sig
First trimester	47.92(23/48) {27.50-68.33}	30.61(30/98) {14.12-47.10}	0.243
Second Month	27.78(05/18) {-11.48-67.04}	37.50(18/48) {15.13-59.87}	0.908
Third Trimester	32.43(12/37) {5.95-58.92}	50.00(31/62) {32.40-67.60}	0.405
Sig	0.664	0.299	

[Table/Fig-3]: Prevalence of asymptomatic bacteriuria in different periods of gestation.
Values in ( ) are actual numbers and in { } are 95% Confidence Intervals; Chi-square test for between and within group values using SPSS software 19.0 V (P<0.05)

Organism	Diabetic pregnancy	Non-diabetic pregnancy	Sig
Coagulase negative *Staphylococci*	20.00(8/40)	31.65(25/79)[b]	0.615
Escherichia coli	25.00(10/40)	24.05(19/79)[b]	0.998
Enterobacteraerogenes	2.50(1/40)	5.06(4/79)[a]	0.933
Klebsiella oxytoca	7.50(3/40)	7.59(6/79)[a]	0.999
Klebsiella pneumonia	20.00(8/40)	16.46(13/79)[ab]	0.972
Pseudomonas aeruginosa	2.50(1/40)	5.06(4/79)[a]	0.933
Staphylococcus aureus	22.50(9/40)	10.13(8/79)[a]	0.344
Chi-square test Sig.	0.179	0.001	0.001

[Table/Fig-4]: Type of isolates from urine samples from diabetic and non-diabetic pregnancy.
Values in parenthesis are actual numbers; Chi-square test for between group and within group values using SPSS software 19.0 V; Alphabets indicate significant difference between isolates within each group (p<0.05)

In diabetic pregnant women, *Escherichia coli* (25.00%), *Staphylococcus aureus* (22.50%), Coagulase negative *staphylococci* (20.00%), and *Klebsiella pneumonia* (20.00%) were the major contributors for ASB. In non-diabetic pregnant women, Coagulase negative *staphylococci* (32.00%), *Escherichia coli* (24.00%), *Klebsiella pneumonia* (16.50%) and *Staphylococcus aureus* (10.00%) were involved in ASB. The percent of isolates for each organism showed no significant (p<0.05) difference between diabetic and non-diabetic pregnant ASB [Table/Fig-4].

The isolates from diabetic pregnant urine samples showed highest susceptibility to nitrofurantoin (56.4%), gentamicin (38.5%), followed by cotrimoxazole (38.5%), norfloxacin (33.3%). The isolates from non-diabetic pregnant urine samples showed highest susceptibility to gentamicin (43.0%), azithromycin (32.9%) followed by norfloxacin (30.4%) and nitrofurantoin (25.3) [Table/Fig-5,6].

DISCUSSION

Asymptomatic bacteriuria (ASB) in pregnancy is defined as the presence of more than 10^5 organisms per millilitre (mL) of urine taken from a clean catch mid-stream urine specimen with no symptoms referable to the genito-urinary tract [21,22]. Normally, urine is not conducive for the growth of bacteria due to acidic pH and high osmolality and urea content. The chances of occurrence of infection are further reduced due to free antegrade flow of urine in urinary tract. But in pregnancy, profound physiological and anatomical changes in urinary tract enhance the chances of infection [23-25]. Hence, the chances of ASB are much more common during pregnancy than normal condition. If untreated, ASB can progress to actual infection leading to adverse maternal and foetal outcomes [21,26].

Organism	CONS	*E.coli*	*Enterobacter*	*K.oxytoca*	*K.pneumonia*	*P.aureginosa*	*S.aureus*	Total
LZ	5(62.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(44.4)	9(23.1)
NX	1(12.5)	8(80.0)	0(0.0)	0(0.0)	2(25.0)	0(0.0)	2(22.2)	13(33.3)
COT	1(12.5)	5(50.0)	1(100.0)	0(0.0)	3(37.5)	1(100.0)	4(44.4)	15(38.5)
NIT	1(12.5)	9(90.0)	1(100.0)	1(33.3)	3(37.5)	1(100.0)	6(66.7)	22(56.4)
GEN	3(37.5)	6(60.0)	0(0.0)	1(33.3)	5(62.5)	0(0.0)	0(0.0)	15(38.5)
CN	3(37.5)	3(30.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	6(15.4)
OF	2(25)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(5.1)
VA	2(25)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(22.2)	4(10.3)
AZM	0(0.0)	3(30.0)	0(0.0)	0(0.0)	6(75.0)	0(0.0)	0(0.0)	9(23.1)
CTR	0(0.0)	3(30.0)	1(100.0)	0(0.0)	0(0.0)	1(100.0)	4(44.4)	9(23.1)
AK	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
AMC	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(25.0)	0(0.0)	2(22.2)	4(10.3)
CFS	0(0.0)	0(0.0)	0(0.0)	0(0.0)	3(37.5)	0(0.0)	0(0.0)	3(7.7)
No. of isolates	8	10	1	3	8	1	9	39

[Table/Fig-5]: Susceptibility of isolates obtained from diabetic pregnant urine samples.
Values in parenthesis are percentages; CONS: Coagulase negative *staphylococci*; AMP:Ampicillin; GEN: Gentamicin; CN: Cephalexin; CTR: Ceftriaxone; OF: Ofloxacin; NX: Norfloxacin; COT: Cotrimoxazole; NIT: Nitrofurantoin; VA: Vancomycin; LZ: Linezolid; AMC: Amoxycillin/Clavulanic acid; CFS: Cefoperazone/Sulbactam.

Organism	CONS	*E.coli*	*Enterobacter*	*K.oxytoca*	*K.pneumonia*	*P.aureginosa*	*S.aureus*	Total
IZ	10(40.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(50.0)	14(17.7)
NX	4(16.0)	6(31.6)	2(50.0)	2(33.3)	6(46.2)	0(0.0)	4(50.0)	24(30.4)
COT	0(0.0)	2(10.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(50.0)	6(7.6)
NIT	0(0.0)	12(63.2)	0(0.0)	2(33.3)	4(30.8)	0(0.0)	2(25.0)	20(25.3)
GEN	6(24.0)	14(73.7)	2(50.0)	4(66.6)	8(61.5)	0(0.0)	0(0.0)	34(43.0)
CN	4(16.0)	2(10.5)	0(0.0)	0(0.0)	0(0.0)	2(50.0)	2(25.0)	10(12.7)
OF	10(40.0)	2(10.5)	0(0.0)	2(33.3)	0(0.0)	0(0.0)	2(25.0)	16(20.3)
VA	4(16.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(25.0)	6(7.6)
AZM	8(32.0)	4(21.0)	4(50.0)	2(33.3)	6(46.2)	0(0.0)	2(25.0)	26(32.9)
CTR	0(0.0)	2(10.5)	0(0.0)	2(33.3)	2(15.4)	0(0.0)	0(0.0)	6(7.6)
AK	0(0.0)	2(10.5)	0(0.0)	2(33.3)	0(0.0)	0(0.0)	0(0.0)	4(5.1)
AMC	4(16.0)	2(10.5)	0(0.0)	0(0.0)	2(15.4)	0(0.0)	2(25.0)	10(12.7)
CFS	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
No. of isolates	25	19	4	6	13	4	8	79

[Table/Fig-6]: Susceptibility of isolates obtained from non-diabetic pregnant urine samples.
Values in parenthesis are percentages; CONS: Coagulase negative *staphylococci*; AMP:Ampicillin; PI: Piperacillin; GEN: Gentamicin; CN: Cephalexin; CTR: Ceftriaxone; OF: Ofloxacin; NX: Norfloxacin; COT: Cotrimoxazole; NIT: Nitrofurantoin; VA: Vancomycin; LZ: Linezolid; AMC: Amoxycillin/Clavulanic acid; CFS: Cefoperazone/Sulbactam.

Several factors occurring during pregnancy contribute to the development of bacterial infections during pregnancy. Enlarging uterus compresses ureter leading to hydro uterus and hydro nephrosis. Similarly, progesterone causes relaxation of smooth muscles in urinary tract leading to reduced peristalsis of ureter, relaxation of urinary bladder and retention of urine [27,28]. Decreased maternal immunity also contributes to the colonization of commensal and pathogenic bacteria in urinary tract [29]. In such cases, ASB is very likely to occurs leading to adverse maternal and foetal effects such as UTI in 30 to 40% women [30] and premature birth, low birth weight, intrauterine growth restriction and perinatal mortality in foetus [31,32]. If asymptomatic bacteriuria is left untreated 30% of mothers develop acute pyelonephritis compared with 1.8% of non-bacteriuric controls [33].

In developing countries like India, the prevalence of ASB is considered widespread [16-20]. In this study, the prevalence of asymptomatic bacteriuria during pregnancy ranged from 38.83% in non-diabetic pregnant women to 37.98% in diabetic pregnant women. Earlier, ASB was reported to account for about 2 to 10% pregnancies in developed countries [34] and up to 86.6% in developing and under-developed countries [35]. Earlier studies have reported the prevalence of ASB to be 4.00% to 23.90% during pregnancy [18,22,36]. The prevalence of ASB in this study was higher as majority of the patients included in the study belonged to middle and lower classes. The association of socio-economic status and rural background were reported to be associated with higher prevalence of ASB due to poor sanitation, lack of general hygienic and failure to attend ante-natal clinic [34,37-39].

Earlier, the prevalence of ASB was reported to be three times higher in diabetic women than in non-diabetic women [40-43]. However, some studies reported no significant difference between diabetic and non-diabetic women [44,45]. In this study, the prevalence of ASB in diabetic pregnancy revealed no significant difference with normal pregnancy. The similarity in the prevalence of ASB between normal and diabetic pregnancy can be explained by the fact that glucosuria, which is common in diabetics also occurs in 70% of pregnant women encourages bacterial growth in urine [46,47]. Similarly, we found no significant difference in the prevalence of age and period of gestation on ASB. However, previously, factors such as diabetes and anatomical abnormalities of the urinary tract [48], increasing maternal age, increasing period of gestation, multiparity, anaemia, gestational diabetes, past urinary tract infection, multiparity, advanced maternal age, lower education level, advanced gestational age and lower socioeconomic status [49], race, sickle cell disease, age and parity [50,51] were positively correlated with the prevalence of ASB. However, the effect of these factors on prevalence of bacteriuria is less clear and much controversy exists in literature [44,45].

In this study, a significantly ($p<0.05$) higher isolates of Coagulase negative *Staphylococci* and *Escherichia coli* were observed in urine

samples of diabetic pregnancy. Earlier studies have observed that the major etiologic agent responsible for ASB is *E. coli* followed by other Gram negative organisms like *Proteus* and *Klebsiella*, Gram positive organisms like group B *Streptococcus* and *Staphylococcus* [23]. Several studies indicated that *Escherichia coli* is the most common pathogen associated with both symptomatic and asymptomatic bacteriuria, representing 70–80% of isolates [25,52,53] and up to 90% in one study [54]. Specific virulence determinants in uropathogenic strains of *E. coli* were reported to be associated with invasive infection and pyelonephritis in pregnancy [55]. Diabetes has been associated with increased incidence of urinary tract infections [3] with *Staphylococcus aureus* being the most common uropathogen isolated from both diabetics and non-diabetics with ASB [56]. However, some studies [57] found that coagulase-negative *staphylococci* (36.3%) were most prevalent in diabetes mellitus. Individuals with diabetes are reported to have increased carriage of *Staphylococcus aureus*, especially those using insulin [58,59], which increases the risk of staphylococcal bacteraemia and mortality [60]. In diabetics, ASB could lead to renal infections such as *staphylococcus* induced renal carbuncles, renal cortico-medullary abscesses and the rare but dangerous emphysematous pyelonephritis, associated with gas formation within the kidney [61].

Epidemiological studies support the relationship between the treatment of asymptomatic bacteriuria and prevention of pyelonephritis. Hill et al., observed that the incidence of hospitalization for acute pyelonephritis in pregnancy decreased after screening for asymptomatic bacteriuria became routine [62]. Treatment of bacteriuric pregnant women prevented pyelonephritis and avoided up to 20% of preterm deliveries [33,63]. However, clear consensus on the duration and choice of antibiotic is lacking in literature. The antibiotic chosen should be safe, efficacious and have low resistance rates. In this study, the isolates from both diabetic and non-diabetic pregnancy showed highest susceptibility to gentamicin. Common therapeutic regimens such as ampicillin plus gentamicin or a cephalosporin is advocated for ASB whereas ampicillin is less favoured due to high resistance rates [64-66]. The use of aminoglycoside such as gentamicin has the advantage of reaching high renal parenchymal concentrations but also poses the risk of ototoxicity and nephrotoxicity in the foetus because the drug crosses the placenta. However, gentamicin does not cause congenital anomalies, ototoxicity or nephrotoxicity after in utero exposure [67]. There exists immense scope to investigate the utility of novel antibacterial agents, which are reported to have enhanced activity over traditional antibiotics [68,69].

CONCLUSION

ASB is found more commonly in pregnant women due to hormonal and anatomical changes promoting growth of bacteria in urinary tract. Diabetes and other risk factors showed no association with increased prevalence. However, low socioeconomic status is strongly associated with ASB. The major isolates in ASB are *Escherichia coli* and *Streptococcus* species, which did not differ from diabetic to non-diabetic women. Gentamicin was equally efficient on the isolates from both groups.

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