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Original Article

Pregnancy-associated asymptomatic bacteriuria and drug resistance

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الملخص

أهداف البحث: يرتبط تجرثم البول بمخاطر ملحوظة للأم والجنين في الدول النامية. والظهور السريع لمقاومة المضادات الحيوية يستدعي الرصد المستمر لنمط المقاومة للعزلات البكتيرية. نعرض هنا النتائج التي توصلنا إليها حول العزلات البكتيرية لالتهاب المسالك البولية ونمط مقاومة الأدوية بين النساء الحوامل.

طرق البحث: أجريت الدراسة على ١٣٥٨ سيدة حامل تراجع عيادة ما قبل الولادة بقسم أمراض النساء والتوليد، في الفترة بين يوليو ٢٠١٣م وأغسطس ٢٠١٤م. تم تجهيز عينات البول لعزل وتحديد أنواع البكتريا باستخدام الطرق الميكروبيولوجية القياسية. كما استخدم اختبار انتشار القرص لتحديد أنماط مقاومة مضادات الميكروبات للعزلات البكتيرية في المختبر المركزي لعلم الأحياء الدقيقة بكلية طب نيبال جونج، نيبال.

النتائج: كانت ٣١٧ من العزلات موجبة للبكتيريا بشكل ملحوظ. كما لوحظت المقاومة للإريثرومايسين (٥٨.٦٪)، وكو-ترايموكسازول (٥٧.٤٪) وسيبروفلوكساسين (٥٠.١٪). كان ٢٠٣ من العزلات (٦٤٪) من السيدات في الفئة العمرية ٢١-٣٠ عاما وهذه المجموعة ذات دلالة إحصائية (قيمة ب <٠.٠٥) بالمقارنة للفئات العمرية الأخرى.

الاستنتاجات: تجرثم البول منتشر بين السيدات الحوامل، مما يستدعي الفحص الروتيني بواسطة استنبات البول. الإشريكية القولونية كانت الجرثومة الأكثر شيوعا تليها الكلبسيلة الرئوية. وكانت السيدات من الفئة العمرية (٢١-٣٠) هن الأعلى خطورة. لا ينبغي استخدام الإريثرومايسين، وكو-ترايموكسازول وسيبروفلوكساسين تجريبيا كأدوية الصف الأول لعلاج التهاب المسالك البولية. الرصد المحلي المستمر لنمط المقاومة ضروري للاختيار المناسب للعلاجات المضادة للميكروبات.

الكلمات المفتاحية: السيدات الحوامل؛ التهاب المسالك البولية؛ تجرثم البول؛ مقاومة الدواء

Abstract

Objectives: In developing countries, bacteriuria is associated with significant maternal and foetal risks. Rapid emergence of antibiotic resistance warrants continuous monitoring of the susceptibility patterns of bacterial isolates. In this study, we report our findings regarding the drug resistance patterns of bacteria isolates from pregnant women with urinary tract infections (UTI).

Methods: This study included 1358 pregnant women attending the antenatal clinic at the Department of Obstetrics and Gynecology between July 2013 and August 2014. Urine specimens were processed for isolation and identification of bacterial species following standard microbiological methods. The disc diffusion test was used to determine the antimicrobial resistance patterns of the recovered isolates at the Central Laboratory of Microbiology of Nepalgunj Medical College, Nepal.

Results: Three hundred and seventeen isolates were positive for significant bacteriuria. *E. coli, K. pneumonia, P. aeruginosa, E. faecalis, S. aureus, P. mirabilis, CoNS,* and *P. vulgaris* accounted for 61.5%, 17%, 7.5%, 5.3%, 2.8%, 2.5%, 1.8%, and 1.2% of bacterial isolates,

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respectively. Resistance to erythromycin (58.6%), co-trimoxazole (57.4%) and ciprofloxacin (50.1%) was observed. Among the 317 positive isolates, 203 (64%) were from women in the 21–30-year-old age group, and the rate of bacteriuria in this group was statistically significantly more than those for the other age groups ($P < 0.05$).

Conclusions: Bacteriuria is frequent among pregnant women, which generates a need for routine urine culture screening. In this study, *E. coli* was the most predominant bacterial species identified followed by *K. pneumonia*. Furthermore, women in the 21–30-year-old group were at a higher risk of UTI. Erythromycin, co-trimoxazole and ciprofloxacin should not be empirically used as first-line drugs in the treatment of UTIs. Continuous local monitoring of resistance patterns is necessary to determine the appropriate empirical antimicrobial therapy.

Keywords: Bacteriuria; Drug resistance; Pregnant women; Urinary tract infection

Introduction

Bacteriuria is the presence of bacteria in the urine. Bacteriuria is said to be significant in the presence of $\geq 10^5$ colony forming units (CFU)/mL. One issue with bacteriuria is that it does not always present with symptoms.[1] Occult infection occurs in approximately 2–7 % of pregnancies, and 30–40 % of cases develop acute pyelonephritis later into their pregnancy.[2] Additionally, there are associations between maternal pregnancy complications and pyelonephritis, including hypertension, preeclampsia, anaemia, amnionitis, and endometritis.[3] Pyelonephritis can lead to renal scarring, hypertension and renal failure in the long term.[4] In pregnancy, pyelonephritis increases the risk of preterm labour and delivery, which results in premature delivery and low birth weight (LBW) with high perinatal morbidity and mortality.[2] Another study showed that asymptomatic bacteriuria (ASB) is independently associated with preterm delivery, hypertensive disorders, recurrent abortions, intrauterine growth restriction (IUGR), polyhydramnios and oligohydramnios, premature rupturing of membranes, and labour induction.[5] Additionally, ASB increases the risk of developing pyelonephritis in the puerperium.[6] The most commonly reported etiologic agent of bacteriuria is *Escherichia coli* (*E. coli*) (80–90 %), followed by *Proteus mirabilis* (*P. mirabilis*), *Klebsiella pneumonia (K. pneumonia)* and *Pseudomonas aeruginosa (P. aeruginosa)*.[7] Gram-positive organisms, including *B streptococci*, *Enterococcus faecalis (E. faecalis)* and coagulase-negative staphylococci (*CoNS*), are less commonly recognised as etiologic agents of bacteriuria.[8] Urinary tract infection (UTI) cases have shown increasing antimicrobial drug resistance in recent years.[9] Accurate bacteriologic records of culture results may help guide the determination of empirical therapies before sensitivity patterns are available. This study was performed to determine the common bacteria that cause UTIs in pregnant women and the antibiotic susceptibility pattern of these uropathogens. The prevalences and resistance patterns of pathogens causing UTI and the risk factors associated with the identified pathogens are reported in this study. The results of this study could be important for the planning and development of appropriate strategies to control and prevent UTIs in pregnant women.

Materials and Methods

This study included 1358 pregnant women who attended the antenatal clinic at the department of Obstetrics and Gynaecology between July 2013 and August 2014. Specimens were processed at the Central Laboratory of Microbiology of Nepalgunj Medical College, Nepal. The samples were collected from asymptomatic pregnant females with a gestation period of 28 weeks or less. Prior to sample collection, socio-demographic and clinical data were collected by face-to-face administration of structured questionnaires. Pregnant women with a history of UTI symptoms (e.g., dysuria, frequency and urgency, etc), pregnancy induced diabetes mellitus/hypertension, a history of antibiotic therapy taken within two weeks prior to the study, pyrexia of unknown origin and known congenital anomalies of the urinary tract were excluded from this study. Ethical clearance from the Ethics Committee of Nepalgunj Medical College, Nepalgunj was obtained before commencing the study. Informed consent was obtained from all patients. Participants were advised to collect a clean catch of 10–20 ml of midstream urine (MSU) using sterile disposable leak proof containers and using aseptic collection techniques.

Culturing of specimens

Aliquots of urine samples were centrifuged at 500 G for five minutes. The sediment from the sample was streaked onto culture media using a sterile standard nichrome loop of 28 SWG with an internal diameter 3.26 mm and a volume holding capacity of 0.004 ml. The samples were cultured on blood agar (BA), mannitol salt agar (MSA) and MacConkey agar (MA) plates. Then, the plates were incubated aerobically at 37 °C for 24 h.[10]

Identification of isolated organisms

Colony-forming units (CFUs) were estimated, and bacterial isolates with growth of $\geq 10^5$ CFU/mL of urine (i.e., 400 colonies or more) were considered to indicate significant bacteriuria. The organisms were identified following standard procedures.[10] Colonies on plates with significant growth were classified as Gram-positive or Gram-negative. The genera and species of bacteria were identified using the Analytic Profile Index (API) 20E system (BioMé rieux, 69280 Marcy-l'Etoile, France).

Table 1: Result of culture.

Result of culture	Number of cases	Percentage (%)
Significant bacteriuria	317	23.34
Insignificant bacteriuria	106	7.80
Contamination	184	13.54
Sterile	751	55.30
Total	1358	100

Antibiotic susceptibility testing

The standardised Kirby–Bauer disc diffusion test of the Clinical And Laboratory Standards Institute (formerly NCCLS) was used for antibiotic susceptibility testing on Mueller-Hinton agar, and the results were interpreted accordingly.[11] The antibiotics tested included ampicillin (10 μg), amikacin (30 μg), cefepime (50 μg), ceftriaxone (30 μg), ciprofloxacin (5 μg), nitrofurantoin (300 μg), co-trimoxazole (25 μg), cefuroxime (30 μg), erythromycin (15 μg), and imipenem (10 μg). All drugs and media were manufactured by Hi-Media Lab. Pvt Ltd, Mumbai, India.

Statistical analysis

The data obtained were analysed using the Statistical Package for Social Sciences (SPSS) software (version 16, SPSS, Inc, Chicago, IL, USA). Associations between age-groups and prevalences of different bacterial species were assessed using the chi-square test. P values of <0.05 were considered to indicate statistically significant differences.

Results

A total of 1358 urine samples were screened, and 317 of them (23.34%) were positive for significant bacteriuria (CFU $\geq 10^5$/mL) (Table 1). Bacterial species were isolated from patients that were 20–50 years of age. A high prevalence of bacteriuria (64.04%) was identified in the 21–30 year-old age group, and the prevalence in this age group was statistically significantly higher than those of other age groups ($P < 0.05$). The following bacterial species were identified: *E. coli*, 195 isolates (61.51%); *K. pneumonia*, 54 isolates (17.03%); *P. aeruginosa*, 24 isolates (7.57%); *E. faecalis*, 17 isolates (5.36%); *S. aureus*, 9 isolates (2.84%); *P. mirabilis*, 8 isolates (2.52%); *CoNS*, 6 isolates (1.89%); and *P. vulgaris*, 4 isolates (1.26%) (Table 2). *E. coli* was the predominant isolate of the samples examined in this study. The resistance pattern of bacterial species isolated from UTIs from July 2013 to August 2014 is shown in Table 3. Over 50% of bacterial isolates were resistant to two or more antibiotics, including erythromycin, ciprofloxacin and co-trimoxazole. All isolates from the 41–50-year-old age group were resistant to all 3 of those drugs. The maximum resistant isolates were observed in 21–30 and 31–40-year-old age groups. No resistance to imipenem was observed in the samples examined in this study.

Discussion

Asymptomatic bacteriuria (ASB) in pregnant women is an important causative factor of premature birth, low birth weight, postpartum UTIs and higher foetal mortality rates. Women with bacteriuria have a 20–50-fold increased risk of developing pyelonephritis compared to women who do not have bacteriuria.[12] Women who have positive urine cultures should be treated based on the antimicrobial sensitivity patterns of the bacteria isolated from their samples to prevent maternal and foetal morbidities. In this study, the prevalence of asymptomatic bacteriuria was 23.34%, which was similar to that observed by a study in Chitwan, Nepal conducted by Neupane et al., (26%) and that observed by a study in Cameroon conducted by Mokube M.N. et al. (23.5%).[13,14] In contrast, some studies found lower prevalences than our study,[12,15–17] and a study by Imade et al., (45.3%) reported a higher prevalence than our study.[1] These varying results may have been due to differences in the areas being studied, in the social habits of the communities being studied and in the socio-economic statuses, standards of personal hygiene and education levels of the patients being studied. The current study that the 21–30-year-old age group had the highest prevalence of infection (64.04%), followed by the 31–40-year-old age group (22.71%), and these results were similar to those of a study conducted in India by Sujatha R. et al.[17] Alghalibi et al.,[18] reported a higher prevalence of UTIs in pregnant women who were 21–25 years of age and Turpin et al.,[15] reported a higher prevalence of ASB in pregnant women who were 35–39 years of age. Advanced maternal age (of

Table 2: Distribution of bacterial isolates recovered from different age groups.

Name of isolate	Age groups (years) distribution				Total No.(%)
	<20 No.(%)	21–30 No.(%)	31–40 No.(%)	41–50 No.(%)	
E. coli	15	129	49	2	195 (61.51)
K. pneumonia	3	39	12	0	54 (17.03)
P. aeruginosa	6	11	6	1	24 (7.57)
E. faecalis	3	9	3	2	17 (5.36)
S. aureus	2	6	1	0	9 (2.84)
P. mirabilis	2	4	1	1	8 (2.52)
CoNS	3	2	0	1	6 (1.89)
P. vulgaris	1	3	0	0	4 (1.26)
Total No.(%)	35 (11.04)	203 (64.04)	72 (22.71)	7 (2.29)	317 (100)

Table 3: Resistance of the bacterial isolates to a panel of ten antibiotics.

Name of isolates	Antimicrobial agent									
	AMP % (No)	COT % (No)	AK % (No)	NIT % (No)	E % (No)	CIP % (No)	CTR % (No)	CXM % (No)	CPM % (No)	IPM % (No)
E. coli	31.03	56.16	19.21	15.27	68.97	61.08	10.84	11.82	00	0
(N = 203)	(63)	(114)	(39)	(31)	(140)	(124)	(22)	(24)	–	–
K. pneumonia	44.44	51.85	00	12.96	29.63	22.22	7.41	11.11	3.70	0
(N = 54)	(24)	(28)	–	(7)	(16)	(12)	(4)	(6)	(2)	–
P. aeruginosa	100	54.17	20.83	75	70.83	29.16	66.66	29.16	58.33	0
(N = 24)	(24)	(13)	(5)	(18)	(17)	(7)	(16)	(7)	(14)	–
E. faecalis	58.82	52.94	11.76	35.29	29.41	17.65	00	5.88	00	0
(N = 17)	(10)	(9)	(2)	(6)	(5)	(3)	–	(1)	–	––
S. aureus	55.56	77.78	33.33	00	44.44	00	22.22	33.33	11.11	0
(N = 9)	(5)	(7)	(3)	–	(4)	–	(2)	(3)	(1)	–
P. mirabilis	12.5	50	00	50	25	87.5	00	12.5	0	0
(N = 8)	(1)	(4)	–	(4)	(2)	(7)	–	(1)	–	–
CoNS	16.67	83.33	50	00	33.33	50	16.67	00	0	0
(N = 6)	(1)	(5)	(3)	–	(2)	(3)	(1)	–	–	-
P. vulgaris	00	50	00	50	00	75	00	0	0	0
(N = 4)	–	(2)	–	(2)	–	(3)	–	–	–	–
Total	40.38	57.42	16.40	21.45	58.68	50.16	14.20	13.25	5.36	00
(N = 317) % (No)	(128)	(182)	(52)	(68)	(186)	(159)	(45)	(42)	(17)	(00)

Abbreviations: AMP = Ampicillin, AK = Amikacin, CPM = Cefepime, CTR = Ceftriaxone, CIP = Ciprofloxacin, NIT = Nitrofurantoin, COT = Co-trimoxazole, CXM = Cefuroxime, E = Erythromycin, IPM = Imipenem.

≥35years) was reported as a risk factor for asymptomatic bacteriuria.[19] The observed trend of bacteriuria in pregnant women in this study and other studies showed that the 21–40 year-old age group is a high risk group for the development of UTIs during pregnancy. The bacteria which are responsible for asymptomatic bacteriuria are of faecal origin and colonise the periurethral area. The predominant bacterial isolates observed in this study were *E. coli* (61.51%), followed by *K. pneumonia* (17.03%) and *P. aeruginosa* (7.57%). The predominance of *E. coli* was reported previously by Chandel et al.,[16] Imade et al.,[1] and Sujatha R. et al.,.[17] *K. pneumonia* was found to be the second most prevalent pathogen in this study, and this result is in agreement with those of studies recently conducted in the Sudan, Ethiopia, India, Cameroon and Nigeria.[1,14,20–22] However, Muharram S. H. et al reported a higher incidence of *K. pneumonia* than was observed in this study.[23]

The third most prevalent pathogen in this study was *P. aeruginosa* (7.57%), and this result is consistent with those of recent studies conducted in Cameroon, Nigeria and India.[1,14,22] Additionally, *P. aeruginosa* is the epitome of an opportunistic pathogen of humans and is notorious as an etiologic agent of nosocomial infections. In this study, there was a considerable prevalence (5.36%) of *E. faecalis*, which was probably due to pregnancy and contamination. Naturally, the urethra is closer to the anus in females than in males[24]; moreover, in pregnant women, the distension of the abdomen makes anal cleaning more cumbersome. The other organisms isolated during this study included those of *S. aureus*, *CoNS*, and Proteus species, and these species less commonly cause UTIs than others.[6] Antimicrobial sensitivities and resistance patterns vary from community to community and from hospital to hospital due to the emergence of resistant strains caused by the indiscriminate use of antibiotics. In this study, the isolates showed 100% sensitivity to imipenem. Most of the uropathogens isolated in our study were most susceptible to cephalosporins, such as cefepime, ceftriaxone, and cefuroxime. Isolates identified by Njunda et al.[25] also showed a high sensitivity to cephalosporin. This finding is unlike those of other studies that found that isolates had greater sensitivities to fluoroquinolones, such as ciprofloxacin.[1,26] It is worth noting that the administration of cephalosporins is relatively safer than the administration of fluoroquinolones during pregnancy; thus, fluoroquinolone treatment during pregnancy is contraindicated, unless no other treatment alternatives are available.[27] In our study, the bacterial isolates showed greater sensitivities to nitrofurantoin than to fluoroquinolones. Okonko et al. also found that bacterial isolates had high sensitivities to nitrofurantoin,[28] but the findings of Mokube M. N. et al. regarding nitrofurantoin sensitivity differed from those of our study.[14] The isolates in our study showed the lowest sensitivities to cotrimoxazole and erythromycin, which is in agreement with the findings of Akoachere et al.[14,17] The resistance to cotrimoxazole and erythromycin in our study can be explained by their widespread over-the-counter use in the location of our study. In mid-western and far-western Nepal, isolates exhibited considerable susceptibility to antibiotics used for the empirical treatment of UTI in pregnancy, such as ampicillin and amikacin. The considerable susceptibility to amikacin observed in that study correlates with findings of Mokube M. N. et al. and Lone T.A et al.[14,22] In a study conducted by G Nath et al., a significantly higher rate of LBW babies was observed in women with UTIs (22.4%) than in women without UTIs (7.7%).[29] The incidence of premature birth and LBW babies may be greater in patients with untreated UTIs. Furthermore, according to a study by the World Health Organization (WHO) on the global burden of disease, LBW and perinatal causes of LBW are

the leading causes of death and disability in newborns. To counter the high rates and disproportionate world burden of neonatal morbidity and mortality, the WHO developed the MOTHER BABY PACKAGE as a universal instrument for the safe motherhood initiative.[30] This initiative may drastically reduce the financial burden caused by pregnancy complications, as screening and treatment for asymptomatic bacteriuria costs approximately US $5.00–6.00, while managing complications, such as pre-term birth and IUGR, costs approximately US $60–70 per case in Nepal.[31] Therefore, it is beneficial to screen and treat pregnant females with asymptomatic bacteriuria to avoid complications linked to this disease.

Conclusions

Pregnancy associated bacteriuria is a common entity. The common pathogens responsible for bacteriuria are of faecal origin, and the most common uropathogen that has been isolated from pregnant women by this and other studies is *E. coli*. The pattern of antibiotic resistance varied according to bacterial species, and multi-resistant isolates were observed. For all antenatal women, routine urine cultures and antibiotic sensitivity tests should be performed to detect asymptomatic bacteriuria and determine the resistance patterns of isolated uropathogens. It is necessary to stop the culture of antimicrobial abuse, and continuous surveillance of multidrug resistant strains is highly important to follow changes in antibiotic susceptibility patterns over time.

Conflict of interest statement

We declare that we have no conflicts of interest.

Ethical approval and funding

Ethical approval for the study was taken from institutional research ethical committee.

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