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Pregnancy-related asymptomatic bacteriuria at Kampala International University Teaching Hospital, Bushenyi Uganda

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Abstract

Background: Pregnancy-related asymptomatic bacteriuria remains a potential health danger to women of reproductive age because of the possible emergence of urinary tract infections during pregnancy. Surveillance will generate data for effective intervention to avert the devastating health impact of urinary tract infection in pregnancy, especially in a resource-limited setting.

Objective: This study was designed to assess pregnancy-related asymptomatic bacteriuria as potential pathogens for urinary tract infections. at Kampala International University Teaching Hospital, Bushenyi, Uganda.

Methods: In this cross-sectional study, 362 aseptically collected midstream urine specimens of pregnant mothers were analyzed using standard bacteriological methods for significant bacteria in urine, and antibacterial sensitivity of isolates recovered from mid-stream urine samples of consenting participants. Structured questionnaires were used to obtain sociodemographic, clinical, and obstetric data. Data were analyzed descriptively using STATA 14.2

Results: The overall prevalence of ASB among the studied pregnant women attending ANC clinic at KIU-TH was 15.5% and out of this 15.5% prevalence, 51.8% were E.coli, 19.6% were *Staph aureus* 17.9% were *Klebsiella*, 8.9% were P*seudomonas* while 1.8% were P*roteus species*). Most of the isolates were sensitive to Amikacin, Imipenem, Gentamicin, and Levofloxacin. The factors that were significantly associated with ASB were gravidity (Gravida 1 or prime gravidas) and WOA of the 1st trimester and 3rd trimester. Prevalence of ASB varied directly with gravidity (p-value=0.015, OR = 2.1, 95% CI =1.15-3.93). Thus pregnant women with gestation of 1-12 weeks were more likely to develop ASB compared to those of 13-28 weeks of pregnancy (OR=4.0, 95% CI=1.64-9.83).

Conclusions The study found that 15.5% of pregnant women attending ANC clinic at KIU-TH had asymptomatic bacteriuria mostly during the 1st or 3rd trimester and 51.8% of the bacteria were Escherichia coli followed by 19.6% Staphylococcus and other enteric bacteria.

Background

While the global struggle to provide minimum healthcare to the needy remains below expectation, people in resource-limited settings are faced with worst-case scenarios where a significant population still falls sick, gets worst, and dies without medical attention (1-5). Skeletal interventions directed towards some vulnerable population in resource-poor settings have highlighted the magnitude of the problem especially in hard-to-reach rural communities of Africa. Targeting vulnerable populations (6) such as pregnant women for intervention is one way of ensuring equitable distribution of available services with the ultimate goal of impacting the morbidity and mortality index. Reduction of urinary tract infections (7) in pregnancy is one of the objectives of antenatal care because infection in pregnancy is a threat to mother and child and infection can become invasive causing complicated urinary tract infections (8-9).

There is a discrepancy between the population that: needs pregnancy now, does not need pregnancy, and those who need pregnancy at a later time in life. This discrepancy defines the various arguments about abortion laws in different healthcare policies globally (10). However, the population in need of pregnancy remains high and so can do almost anything within their power to keep the pregnancy. In Africa, people seek healthcare when they know the danger associated with present illness thus making illnesses and associated danger, key in defining the rate at which people seek

healthcare (11). In the absence of illnesses as a driving force for the high rate of healthcare seekers, defining the population of bacteria that are potential dangers to mother and child is difficult (12).

Asymptomatic bacteriuria (ASB) is the presence of a significant quantity of bacteria in the urine without symptoms of a lower or upper urinary tract/kidney infection (13-14). Prevalence of ASB in premenopausal and ambulatory women is 2%–10% (13) but due to anatomical and physiological changes higher rates of ASB during pregnancy are expected and a greater chance of progression to UTI (13, 15). The physiological and anatomical changes during pregnancy facilitate the growth of bacteria in women both symptomatic and asymptomatic.

Numerous risk factors for ASB in pregnancy have been identified to include low socioeconomic status, higher parity, a history of recurrent UTI, diabetes, and anatomical abnormalities of the urinary tract (13, 14, 16). ASB was associated with an increased risk of preterm delivery and it has been found that treating ASB does not only reduce the risk of maternal pyelonephritis but also reduces the risk of preterm birth (17). Pregnancy is an aggravating factor for the asymptomatic bacteriuria to become symptomatic (18). Hormonal effects particularly increase the risk for urinary tract bacterial colonization throughout pregnancy. Asymptomatic bacteriuria in pregnancy is among the commonest (1.9% to 9.5%) health problems globally and 14% in low-income countries (19-21). In Tanzania, the prevalence of ASB was 15.5% (22), and 13.3% in Uganda (23).

Objective

The objective of this study is therefore to evaluate pregnancy-related asymptomatic bacteriuria at Kampala International University Teaching Hospital, Bushenyi district of Uganda with the ultimate goal of providing a database for use designing the effective future intervention. Again this study will provide the knowledge of asymptomatic bacteriuria burden in pregnancy, needed to predict the potential emergence of future symptomatic urinary tract infection.

Materials and Methods

In this cross-sectional study, 362 aseptically collected midstream urine specimens were analyzed for significant bacteria in the urine that may serve as potential pathogens for urinary tract infections. All pregnant women attending antenatal clinics at Kampala International University Teaching Hospital were selected while pregnant (adult and emancipated) mothers attending antenatal clinics without any signs or symptoms of urinary tract infection were selected were included. Pregnant women with a history of antibiotic therapy in the previous two weeks ~~and~~ a history of structural urogenital anomalies were excluded. The 362 patients samples analyzed were obtained using the formulae $n= (z_{\alpha}+z_{\beta})\ ^2P\ (1-P)/d^2$ Where $\alpha=0.05$, $Z\alpha$ =z-static at $\alpha=1.96$, Power=80%, $\beta=0.2$, $Z_{\beta}=0.84$, p=13.3%. Consenting respondents were selected using systematic random sampling (ballots). Pre-tested questionnaires were administered to each participant for information on socio-demographic and gynecological factors. A detailed

gynecological history was taken and urine samples were inoculated on a sterile CLED medium, Blood agar, Chocolate agar, and MacConkey agar plates and were incubated at 37º C for 24-48 hours and isolate identification made using Bergey's manual of systematic bacteriology (24).

Antibiotics susceptibility test

Susceptibility testing was carried out according to standard clinical laboratory guidelines of Kirby Bauer diffusion methods (25). Pure colonies of the organisms were tested for their antimicrobial drug susceptibility against six commonly used antibiotics including ceftriaxone (30ug), amikacin (30ug), penicillin G. (30ug), pefloxacin (30ug), nalidixic acid (30ug), gentamycin, Oxacillin, nitrofurantoin and erythromycin using Kirby-Bauer disc diffusion (26) as modified by the clinical laboratory standard institute (27). Overnight bacterial broth suspension was made to match with 0.5% McFarland turbidity standard. A sterile inoculation glass rod was used to spread the surface of Muller-Hinton agar plates homogenously with the diluted broth suspension of bacterial colonies. Antibiotic discs were placed onto the inoculated Muller-Hinton agar and incubate at 37℃ for 24 hours. The zones of inhibition were measured and compared to a standard chart (28). A pre-tested questionnaire was used to collect data on demographics, obstetric, genetic, and socioeconomic status. Data obtained from the questionnaire were used to determine the Cronbach's coefficient alpha and an index of more than 0.8, which was considered to indicate that the items of the questionnaire are reproducible and consistent (29).

Statistics

With the aid of STATA version 14.1, binary logistic regression analysis was done at the bivariate level to report crude odd ratios and at a multivariate level to obtain unbiased adjusted odd ratios for potential predictors. The adjusted odds ratio was reported together with their respective 95% confident intervals and p-values. Variables with p-values ≤ of 0.05 were considered statistically significant.

Ethics Declaration

The present study was approved by the Research and Ethical Committee of Kampala International University Teaching Hospital (KIUTH) and also by the Uganda Council for Science and Technology. Participation in this study was completely anonymous and based on written informed consent.

Competing interests { None

Results

Socio-demographic findings

Table 1: Majority (79%) of the pregnant women were aged between 20-30 years followed by: 97.2% of the women that we're married and 2.8% that were single. About 43.1% of the women had secondary education while 23.9% and 22.2% had primary and tertiary education respectively. The majority 46.1% and 37.8% were Protestants and were Catholics respectively. About 42.3% of the men were peasants and 28.2% were unemployed.

Table 1: Socio-demographic characteristic of the study subject

Variable	Frequency (n)	Percentage (%)
Age		
< 20 years	15	4.1
21-30 years	289	79.9
>31years	58	16.0
Education level		
None	40	11.0
Primary	86	23.8
Secondary	156	43.1
Tertiary	80	22.1
Occupation		
Unemployed	102	28.2
Peasant	153	42.3
Professional	57	17.7
Business	50	13.8
Religion		
Protestant	167	46.1
catholic	137	37.8
Moslem	36	9.9
born-again/advent	22	6.2
Marital status		
Married	352	97.2
Single	10	2.8

Obstetric and other characteristics

The majority (56%) of the women were of gravida 2-4, while 32.3% were of gravida 1 and 11% were of gravida 5. Many (82%) of the women had never aborted their previous pregnancies and only 18.4% had aborted their pregnancies before the study. On the other hand, the majority of women were more than 28weeks (3rd trimester) of gestation age in their pregnancy while 40.6% were 13-28 weeks (2nd trimester) of gestation age in their pregnancy and 10.2% were 0-12 week (1st trimester) of gestation age in their pregnancy. A small proportion 2.9% of the women were HIV positive

Asymptomatic bacteria prevalence in the studied population

Of the 362 urine samples in this study, 56 (15.5%) had significant bacteria with a colony count of 10^5CFU/ml. *E.coli* was 51% prevalent followed by 19.6% S*taph aureus,* 17.9% of *Klebsiella species* 8.9% *Pseudomonas* species, and lastly 1.8% *Proteus species* respectively.

Susceptibility status to conventional antibiotics of the bacteria isolated from the urine of study participants

Most bacteria isolate 56 (15.5%) were sensitive to Amikacin, Levofloxacin, Imipenem, and Gentamycin and were higher resistant to Ampicillin, Ceftriaxone, and Ciprofloxacin. E.coli was 100% resistant to Ampicillin, and most 65.5%. Sensitive to Amikacin. Staphylococcus aureus was 100% resistant to Ceftriaxone, Perfloxacin, and Ciprofloxacin but 63.6% sensitive to Amikacin. Klebsiella species were 100% resistant to Ampicillin, Ceftriaxone, Ceftrixine, Gentamycin, and Ciprofloxacin. But it was most sensitive to Imipemum and Levofloxacin at 40.0% each. Pseudomonas was 100% resistant to Ampicillin, Ceftriaxone, Ceftrixine, Gentamycin, and Perfloxacin. But most sensitive to Amikacin and Imipemim at 70.0% and 60.0% respectively. Proteus was most sensitive to Gentamycin, and Imipemim. It was resistant to all the other antibiotics.

Table 2: Susceptibility status of bacteria to conventional antibiotics

Conventional Antibiotics	E. coli (n=29)	Staph aureus(n=11)	Klebsiella (n=5)	Pseudomonas(n=10)	Proteus (n=1)
Amikacin	19(65.5%)	7(63.6%)	1 (20.0%)	7 (70.0%)	0 (0.0%)
Ampicillin	0(0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Levofloxacin	6 (20.7%)	5 (45.5%)	2 (40.0%)	2 (20.0%)	0 (0.0%)
Ceftriaxon	3 (10.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ceftrixine	2 (6.9%)	2 (18.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gentamycin	5 (17.2%)	3 (27.3%)	0 (0.0%)	1 (10.0%)	1 (100.0%)
Imipemum	7 (24.1%)	4 (36.4%)	2 (40.0%)	6 (60.0%)	1 (100.0%)
Perfloxacin	2 (6.9%)	0 (0.0%)	1 (20.0%)	0 (0.00%)	0 (0.0%)
Ciprofloxacin	3 (10.3%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)

Socio-demographic characteristics

In table 3 below all listed socio-demographic variables were not significantly (p>0.05) impact on the acquisition and urinary tract colonization. The prevalence of ASB varied inversely with age. With education, the uneducated were at low risk of developing ASB compared to those primary, secondary and tertiary. Though those primaries were at high risk to develop ASB than those of secondary and tertiary. Regarding occupation, comparing the peasants with unemployed they were at equal risk of getting ASB while the professionals were 2 times more likely to develop ASB compared to unemployed. Whereas businesswomen were 20% less likely to develop ASB compared to unemployed. On comparing the protestants with Catholics, Muslims, and born again/adverts, the Muslims were at equal risk of getting ASB compared to protestants though the Catholics and born again/adverts were 2 times more likely to develop ASB compared to protestants.

Table 3: Results of Univariate analysis for social demographic characteristics

Variable	No ASB (negative) n (%)	ASB (positive) n(%)	Un adjusted OR (95% CI)	P-value
Age				
< 20 years	12(80.0)	3(20.0)	3.4 (0.67-17.09)	0.142
20-30 years	240(83.0)	49 (17.0)	2.8 (0.95-7.96)	0.061
31-50 years	54 (93.1)	4 (6.9)	1.0	
Education level				
None	37 (92.2)	3(20.0)	1.0	
Primary	71 (82.6)	15 (17.4)	3.8(0.82-17.54)	0.087
Secondary	130 (83.3)	26 (16.7)	3.6 (0.82-15.89)	0.091
Tertiary	68 (85.0)	12 (15.0)	3.2 (0.67-14.97)	0.144
Occupation				
Unemployed	87 (85.3)	15 (14.7)	1.0	
Peasant	130 (85.0)	23 (15.0)	1.0 (0.49-2.08)	0.976
Professional	45 (78.9)	12 (21.1)	1.7 (0.72-4.05)	0.219
Business	44(88.0)	6 (12.0)	0.8 (0.28-2.17)	0.633
Religion				
Protestant	143 (87.0)	21 (12.8)		
Catholic	111 (82.2)	24 (19.8)	1.5 (0.78-2.78)	0.233
Moslem	30 (85.7)	4 (14.3)	1.1 (0.39-3.25)	0.814
born-again/Advent	18 (81.8)	4 (18.2)	1.5 (0.47-4.91)	0.490

Obstetric and other characteristics

In table 4 below, the distribution of asymptomatic bacteria in the urine of respondents was significantly ($p<0.05$) dependent on the Gravidity and weeks of gestation. Prevalence of ASB varied directly with gravidity (p-value=0.015, OR = 2.1, 95% CI =1.15-3.93). Thus pregnant women with gestation of 1-12 weeks were more likely to develop ASB compared to those of 13-28 weeks of pregnancy (OR=4.0, 95% CI=1.64-9.83). HIV status and blood group were not statically significant. Although the positive HIV case was at higher risk of developing ASB. In addition, pregnant women of blood group A, B, and AB were protective to develop ASB compared to blood group O.

Table 4: Results of Univariate analysis for obstetric and other characteristics

Variable	No ASB (negative) n (%)	ASB (positive) n (%)	Un adjusted OR (95% CI)	P-value
Gravidity				
1	171 (81.0)	40 (19.0)	2.1 (1.15-3.93)	0.015
2-4	91(89.2)	11 (11.8)	1.0	
5	44 (89.8)	5 (10.2)	1.0 (0.36-2.85)	0.973
WOA				
1-12 weeks	29 (70.7)	12 (29.3)	4.0 (1.64-9.83)	0.002
More than 28 weeks	137 (91.3)	13 (8.7)	2.0 (1.02-3.93)	0.043
13-28 weeks	140 (81.9)	31 (18.1)	1.0	
HIV status				
Negative	298 (85.0)	54 (15.0)	1.0	
Positive	8 (80.0)	2 (20.0)	1.4 (0.29-6.88)	0.664
Blood group				
A	69 (91.5)	13 (15.9)	0.4 (0.126-1.00)	0.050
B	87 (88.8)	11 (11.2)	0.5 (0.201-1.170)	0.107
AB	32 (80.0)	8 (20.0)	0.8 (0.278-2.409)	0.715
O	119 (83.8)	24 (16.9)	1.0	

Multivariate binary logistic regression: Factors associated with ASB among the study group

The multivariate analysis was achieved using a backward stepwise selection method of the model. With this model factors which were independently associated with ASB among pregnant women were being prime gravida (Gravida 1), being in either the 1st or 3rd trimester (1-12 weeks or more than 28 weeks). The odds of having ASB were higher among prime gravida mothers as compared to multigravida (OR=2.0, 95% CI= 1.07-3.74). The odds of having ASB were higher among pregnant women of 1st trimester as compared to those of 2nd trimester (OR=3.8, 95% CI=1.51 - 9.56). Lastly the odds of having ASB were 2 times higher among pregnant women of 3rdtrimester as compared to those of 2nd trimester (OR=2.1, 95% CI=1.06 - 4.27).

Discussion

Prevalence of ASB among the study group

The prevalence of asymptomatic bacteriuria among pregnant women in this study was 15.5%. These findings were relatively consistent with a 10% to 20% range from Cairo, global, East Africa, and other prevalence reports (21, 30-36). The fact that the result of this study is relatively similar to reports from major studies globally shows that Uganda and indeed, Kampala International University Teaching Hospital (KIUTH) are moving in the right direction in medical practice and discharge of their corporate health responsibilities to the general public.

KIUTH is a private not-for-profit tertiary hospital acting as a major referral hospital to five districts of southwestern Uganda including Bushenyi, Shema, Rubiriizi, Mitooma, and Buhweju districts respectively. Its major health policy is a public-private partnership in which the Uganda government built a magnificent edifice at the hospital premises where it provides comprehensive free health services (pediatrics, surgery, medical, obstetrics, and gynecology) to the people with government-employed doctors posted to do this work. In return, KIUTH trains its undergraduate and postgraduate medical students there. This arrangement gives KIUTH strategic and regional advantage placing it at par with other regional referral hospitals like Mbarara Kabale and Masaka referral hospitals respectively.

On the other hand, our result was lower, than two reports from Ethiopia, 21.5% and 26%

respectively (22, 37), India reports of 25.3%-30.5% (38-39), and Kenya report of 21.5% (40). Ethiopia, Kenya, and many parts of India are underdeveloped, with a severe scarcity of health resources including human resources for health. The vulnerability of mother and child to poverty-related and neglected tropical disease, in the presence of limited resources is the source of concern and impacts the acceptance and uptake of hospital-directed health services to the general public.

The public-private partnership (PPP) health concept is not common in Africa its advantages over public and/or private healthcare centers are numerous including but not limited to higher acceptance and uptake of hospital services, good health education and promotion, moderately resourced antenatal care services, good inter-hospital referral network system, free services and no stock-out of tools for good healthcare delivery among others. The above factors underlying the policy of heath delivery at KIUTH must have impacted the lower result of this study compared to the reports of Ethiopia, India, and Kenya respectively. Again Senait et al (41), suggested geographical variations between the regions where the pregnant women live, and social habit of the community vis-à-vis pregnancy affects the microecology of the urinary system and the population structure of colonizing asymptomatic bacteria in pregnancy. Though 15.5% was lower than Ethiopia, India, and Kenya reports, it hard to accept that 15.5% of pregnancy healthcare seekers harbor potential bacteria pathogens capable of initiating urinary tract symptomatic infections during or after 9 months of pregnancy. Stepping up interventions to reduce this prevalence is recommended.

We also found that gravida-one (Primi-gravida) mothers were more likely to acquire and be colonized with asymptomatic bacteria in their urinary tract than multigravida mothers, (OR=2.0, 95% CI= 1.07-3.74). This study result was in agreement with 53.89% report by Karur, (42) and Ajayi *et al*., (30). Primi-gravida women are expected to be relatively more exposed to complex genital manipulation including intensive sexual intercourse and most times at younger age compared to their multigravida counterparts. Thus early and intensive sexual intercourse is known to cause minor urethral trauma and transfer of both resident and contaminating bacteria from the perineum into the bladder raising the stakes for asymptomatic bacteria in the urinary tract of pregnant women in this locality (43).

In this study, asymptomatic bacteria acquisition and colonization of the urinary tract of consenting participants were significantly

($p<0.05$) influenced by the trimester of pregnancy. Thus, participants that were in either the 1st or 3rd trimester (1-12 weeks or more than 28 weeks) of pregnancy were more likely to present with asymptomatic bacteriuria compared to their counterparts in the 2nd trimester. This fact is supported by: Adeliade, (40) in Kenya, Chandel *et al*., (44) in India, Bankole Oladeinde, (45) in Nigeria, and Tadesse *et al*, (22) in Ethiopia respectively but different from the report of Omer *et al*,(46) in Sudan (OR=3.8, 95% CI=1.51 - 9.56). Higher ASB in 1st trimester may be due to increasing progesterone and estrogen hormones and compressed bladder due to increasing uterus in the pelvic region which causes urine stasis and ureter dilatation, a factor known to encourage bacteria migration retention and colonization of the urinary tract with the ultimate goal of establishing urinary tract infection in pregnancy (47). Numerous anatomical and hormonal variations in pregnancy lead to urethral dilation and urinary inertia which encourages bacteria acquisition, migration, and colonization of the urinary tract in the 3rd trimester of pregnancy a fact supported by Bankole, (45), (OR=2.1, 95% CI=1.06 - 4.27).

Escherichia coli (51.8%) was the most prevalent bacteria followed by 19.6% *Staphylococcus aureus*, 17.9% *Klebsiella species*, 8.9% *pseudomonas species*, and 1.8%. *Proteus* species respectively. This result is in line with the reports of Gayathree, (20) in India, Prasanna1, (48) in India, Bankole, (45) in Nigeria, Omer *et al*,(46) in Sudan, Mike *et al*,(49) in Cameroon, Senait *et al*, (41) in Ethiopia, Moses *et al*, (50) in Tanzania and Adelaide *et al*, (40) in Kenya respectively. E coli together with *Klebsiella species* and other bacteria isolates in this study are entro-bacteria found in stool samples. One explanation of 51.8% E coli predominance and other enterobacteria isolates in the urinary tract is poor hygiene whereby most women passing feces prefer to clean up the anus towards the open vagina thereby loading the stool samples and its bacteria content in the genital and urinary tract.

Again, *E coli* strains which are relatively normal flora of the lower intestine become pathogenic when they gain access to the urinary tract Abdullahi, et al (51). Though this study was not in line with the report of Amiri, (8) and Manasi, (39) who showed *Klebsiella* to be the most predominant isolate, E coli and Klebsiella species can contaminate the genital and urinary tract due to poor hygiene. The concept of low immunity induced by pregnancy could also explain the observed predominance of staff and enteric bacteria in pregnancy Mor and Cardenas, (52)

Generally, there was greater sensitivity of bacterial isolates to Amikacin, levofloxacin, pefloxacin, and imipenem which were similar to a study by Prasanna, (48), but different from nitrofurantoin, gentamicin, cefuroxime, and ceftazidime reported by Ajayi (30). Klebsiella species and E. coli showed resistance against Penicillin, Ampicillin, Pefloxacin, and Amoxicillin. This may be because in our setting these drugs are overused routinely (31). Asymptomatic bacteria resistance can be explained by exposure to a sub-lethal dose of antimicrobial agents especially when treating other symptomatic bacteria disease.

Limitation: It was difficult to convince pregnant mothers to participate in this study as they found it hard to consent since there was no sign or symptoms to generate the fear factor central in driving patients to seek healthcare. It was also hard to define the status of asymptomatic bacteria, normal flora, contaminants, and opportunistic bacteria as well as the resistance profile of bacterial isolates in an asymptomatic pregnant population. However, the mothers were educated on the dangers of risking the emergence of disease by asymptomatic bacteria during the nine months of pregnancy. Standard aseptic protocols and significant bacteria in urine were used to minimize spurious laboratory results about contaminants and resistance to contaminating bacteria. A primary school teacher of the locally spoken language (Runyankole language) who also works as a social worker was recruited to overcome the language barrier and reduce the magnitude of the problem enabling us to get all information we needed

Conclusion.

Exactly 15.5% of pregnant women attending ANC clinic at KIU-TH had asymptomatic bacteriuria mostly during the 1st or 3r^{d} trimester and 51.8% of the bacteria were Escherichia coli followed by 19.6% Staphylococcus and other enteric bacteria. Even though in pregnancy, asymptomatic bacteria isolates are considered potential agents of emerging urinary tract infection, a high index of suspicion is needed to decipher how to administer sensitive antimicrobial agents outlined in this study to pregnant women with the ultimate goal of protecting mother and child unexpected complications.

Raw database

The data sets generated during the current study have all been included in the main text above. Any other questions can get be addressed by the research team through the corresponding author as indicated.

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