The human vaginal microbial community dysbiosis contributes to the urinary tract infections during pregnancy: Case study of Gisenyi District Hospital, Rwanda

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ABSTRACT

Background: Urinary tract Infections (UTIs) are the common infections during pregnancy. About 150 million UTIs occur every year globally, and 30% is attributed to pregnant women. **Aims and Objective:** The study was carried out to observe the association with vaginal microbial community imbalance and urinary tract infections among pregnant women. **Materials and Methods:** A total of 80 pregnant women were recruited. Of the 80 women, 40 were pregnant with UTI, and the remaining 40 were women without UTI. About 80 vaginal swab samples were collected and transported to INES clinical microbiology laboratory for microbiological analysis. Laboratory techniques including culture, gram stain, and biochemical tests were performed. ANOVA-2 was used for comparison, while chi square (χ^2) was used to test for association. **Results:** *E. coli* was predominant among women with UTIs while *Lactobacilli* predominated among women without UTIs. There was a statistical significance association with vaginal microbial community imbalance and urinary tract infection among pregnant women to *Escherichia coli* ($\chi^2 = 9.97$, p = 0.0015), *Staphylococcus epidermidis* ($\chi^2 = 5.12$, *p* = 0.023), *Proteus spp* ($\chi^2 = 4.96$, P = 0.025), *Citrobacter spp* ($\chi^2 = 32.51$, P < 0.00001), *Streptococcus pyogenes* ($\chi^2 = 5.11$, P = 0.023), *Staphylococcus sapropyticus* ($\chi^2 = 4.3$, p = 0.038) and *Lactobacilli species* ($\chi^2 = 13.7$, p = 0.00021). The overall association ($\chi^2 = 94.879$, p < 0.00001) with all isolated microorganisms and urinary tract infections was statistically significant. The odd ratio of pathogenic microorganisms to non-pathogenic was OR = 4.98 > 1. For ANOVA-2, there was a higher microbial variation or differences among women with UTIs (F = 7.241842) compared to women without UTIs (F = 4.71) in pregnancy trimesters. **Conclusion:** Pregnancy is associated with vaginal microbial community imbalances which predispose women to urinary tract infections. Pregnant women should seek for medical assistance during pregnancy for early detection of urinary tract infections.

Key words: Microbiota; urinary tract infections; microorganisms; pregnancy

INTRODUCTION

Urinary tract infections (UTIs) are the major clinical threat across the lifespan of women.[1] In 2010, national ambulatory medical care survey reported about 10 million outpatient visits for urinary tract diagnosis occurs annually in the United States for both men and women. The vaginal anatomical structure makes it the main site of urinary tract infection pathogenesis among women.[2] The vaginal microbiota is a critical factor

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for vaginal health, and its imbalance contributes to adverse vaginal health conditions including urinary tract infections. The vaginal microbial community dysbiosis is characterized by the loss of *Lactobacillus* spp which protects the vagina against pathogenic microorganisms. The alterations in vaginal microbiota may result from hormonal changes (estrogen and progesterone) during pregnancy, antimicrobial therapy use, contraceptive use, or other causes.[3] The reduction of urinary tract infections could be attributed to the restore of protective *lactobacilli* in the vagina during pregnancy.[4] The derangement in vaginal microbiota during pregnancy is associated with the high occurrence of urinary tract infections among women.[5] Currently, it is evidenced that the healthy vaginal microbiota is predominated by *Lactobacillus* species.[3] Urinary tract infections (UTIs) is a major contributor of morbidity among women, and one of problems facing gynecologists and family physicians.[6] Adverse physiological, anatomical, and personal factors contribute to this health problem during pregnancy.[7] Personal hygiene could be also the exposure to urinary tract infections. Clinical presentation of UTIs including bacteriuria which is the presence of bacteria in the urine, bacteriuria is asymptomatic condition for urinary tract infections. The clinical stage of urinary tract infection composed of lower tract (acute cystitis) and upper tract (acute pyelonephritis) infections.[8] UTI contributes to serious obstetrical complications such as poor maternal and perinatal health conditions including intrauterine growth restriction, pre-eclampsia, cesarean delivery, and preterm delivery. The early detection of urinary tract infections, proper management and control, and the proper use of therapeutics are important strategies to prevent complications during pregnancy.[1]

Each year, about 150 million UTIs occur globally, and 30% is attributed to pregnant women. The high incidence of UTIs was reported among young women during adolescents.[9] Almost 25%-30% of women developed initial infections in the United States.[10] The urinary tract infections (UTIs) is defined as a collective term for pathogenic invaders of any part of urinary tract.

Escherichia coli is the major cause of urinary tract infections. It was isolated by different in previous studies, and observed to be predominant during pregnancy.[11] UTIs is the common cause of admission in obstetrical wards.[12] During pregnancy, Urinary tract infections could be the persecutor of adverse maternal and neonatal outcomes. Untreated UTIs could contribute to serious obstetric complications and lifelong reproductive impairment.[8] Therefore, this study was conducted to evaluate the association of vaginal microbiota dysbiosis and UTIs among pregnant women at Gisenyi district hospital.

MATERIALS AND METHODS

Study area
The study was carried out at Gisenyi District Hospital, located in Nengo cell, Gisenyi sector, Rubavu district, Western Province in Rwanda

Study design
This cross-sectional study was carried out from October 2020 to January 2021.

Target population and sample size
The study population consisted pregnant women with Urinary Tract Infections at Gisenyi district hospital. About 40 pregnant women with UTIs accepted to participate in the study were recruited. The control group of 40 women without UTIs also was recruited. Both groups make a total of 80 pregnant women.

Ethical consideration
The permission to conduct the research was granted by both Gisenyi district hospital and INES Ruhengeri ethical committees. Pregnant women were informed about the study to get their consent for participation. The right to privacy and confidentiality was respected. Collected specimens were assigned anonymous codes and data generated were solely used for the purpose of the study.

Collection of vaginal swab specimens
The vaginal swab samples were collected with sterile cotton stick and placed them in appropriate container contained normal saline. The collected samples were transported to the clinical microbiology laboratory for analysis at INES-Ruhengeri.

Laboratory analysis
Macroscopic of vaginal swab
This is an observation of swab specimen using a naked eye. The identified abnormalities of the samples were based smell and color. The normal vagina discharge is milky or white and odorless. The reduction of the protective lactobacilli favored the growth of pathogenic microorganisms which caused the change in color of the vaginal discharge.

Culture media preparation
Blood Agar (HIMEDIA® Ref M073-500G), Mannitol Salt Agar (HIMEDIA® Ref M118-500G), MacConkey Agar (HIMEDIA® Ref M081-500G), and Sabouraud Dextrose Agar (TM Media Ref TM 387) were prepared by dissolving 40.0g, 111.02g, 51.53g and 65g respectively to 1000 ml of distilled water according to instructions for use. Heated with repeated stirring and boiled for 1 minute to 2 minutes to dissolve completely. Then the prepared solution was

autoclaved at 121^0C for 15 minutes, and 15 PSI, then cooled down and distributed in the Petri dish and waited for culture medium to solidify.

Inoculation and incubation

Streak plate method was used for inoculation of bacterial samples on sterile Petri dishes of Blood agar, Mannitol salt agar, MacConkey agar media. The plates were aerobically incubated at 35-37^0C for 18-24 hrs. Bacterial growth was observed on the basis of colony characteristics.

Smear preparation and gram stain

The smear was prepared before staining. A colony was picked up from Petri dish and mixed with the drop of normal saline u sing a sterile inoculating loop. The slide was heat fixed over a blue flame. The smear was flooded the solution of crystal violet and waited for 1minute. Tap water was used to wash the slide, then iodine solution was applied on the smear and waited for 1 minute. The iodine solution was washed off and rinsed the slide with running water slightly and shaking off the excess water from the slide. Then, a few drops of decolorizer, ethanol, was added on the slide and washed with tap water for 5 seconds. The counterstain, safranin was flooded on the slide for 30 seconds and washed off with water and making the slide air dried in room temperature. Then, the stained smear was examined under light microscope and oil immersion was used.

Biochemical tests

Kligler's Iron Agar test (KIA) test

Kligler's Iron Agar (HIMEDIA® Ref M078-500G) was used for the identification of *Enterobacteriaceae*, based on double sugar fermentation and hydrogen sulphide production. A sterilized inoculating needle was used to pick the suspected organism from MacConkey or Blood agar plate then stabbed into the medium up to the butt of the KIA tube and then it was streaked back and forth along the surface of the slant. Again the neck of the KIA test tube was flamed, capped and incubated for 24 hours at 37 °C. Therefore, lactose and glucose sugar fermentation were observed as well as hydrogen sulfide (H2S) production.

Simon's Citrate Agar test

To differentiate between members of *Enterobacteriaceae* capable of utilizing citrate as a carbon source Simon's Citrate Agar (HIMEDIA® Ref M099-500G). Using sterilized inoculating needle suspected organism from MacConkey or Blood agar plate was picked then stabbed into the medium up to the butt of citrate tube and then it was streaked back and forth along the surface of the slant. Then Incubate at 37 °C for 18 to 24 hours.

Urease test

Urea Broth (HIMEDIA® Ref M111-500G) was also used to determine the ability of isolated microorganism to split urea, through the production of the enzyme urease. The colony growing on MacConkey or Blood Agar plate was stabbed into Urea Broth using sterilized inoculating needle. Then incubated at 37 °C for 18 to 24 hrs.

Sulfide-Indole-Motility medium

To determine bacteria microorganism which have the ability to reduce sulfates, the ability to produce indoles and motility, Sulphide Indole Motility (HIMEDIA® Ref M181-500G) medium was used. The isolated colonies from MacConkey plate were stabbed into the medium SIM. Then incubated at 37 °C for 18 to 24 hrs. Then after, to check for indoles production two to three drops of kovac's reagent were added.

Germ tube test

Germ tube test was used to confirm *Candida albicans*. A colony of yeast cells grew on Sabouraud Dextrose Agar was suspended into 0.5 ml of human serum in the test tube. The tube was then incubated at 37°C between 2 to 4 hours. Therefore, one drop of the serum was transferred to a slide for examination. The short hyphal (filamentous) extension arising laterally from a yeast cell (Pseudohyphae) confirming the *Candida albicans*.

Catalase test

Slide method was applied to differentiate *staphylococcus* (catalase-positive) from *streptococcus* (catalase-negative). 2 drops of 6% Hydrogen Peroxide (Faholo B/No: 32017 FHP) were put onto a clean glass slide using a dropper, a pure colony of the organism was picked from Mannitol Salt Agar or Blood Agar plate using a wire loop. Placing the colony on the hydrogen peroxide on the glass slide; emulsification was done. Observation for bubble formation was done within 30 seconds.

Coagulase test

To confirm *Staphylococcus aureus*. 0.5ml of diluted Coagulase plasma (HIMEDIA® Ref FD248-5VL) was put in a small tube using Pasteur pipette. By using sterilized wire loop 2-3 colonies from Mannitol Salt Agar plate was suspended into tube. Followed by incubation of the tube at 37 °C for 2 to 4 hours to examine clot formation absence or present.

Statistical analysis

We analyzed the association with vaginal microbial community imbalance and the occurrence of urinary tract infections among pregnant women. The vaginal microbial community imbalance was also analyzed and compared in pregnancy trimesters. The ratio of pathogenic microorganisms was analyzed between the two groups. Both SPSS version 22 and

Excel were used for data analysis. Chi square (x^2) test was used to test for association with vaginal microbial community imbalance and UTIs, ANOVA-2 was used for vaginal microbial community mean difference in pregnancy trimesters, and odd ratio (OR) for pathogenic microorganisms' presence in both groups. Tables were used for result presentation.

RESULTS

Age and pregnancy trimesters distribution of participants

The table1 shows Age and pregnancy trimesters distribution of participants with their frequencies and percentages. Then the most dominant age was between 26-32 followed by the range of age between 33-39 and age under 26 and finally the least age was above 39.

The microorganisms isolated from vagina among pregnant women

The Table2 indicates the microorganisms isolated from vaginal swab samples of women with and without urinary tract infections and their respective percentages at Gisenyi district hospital. The microorganisms isolated such as *E. coli* (14.29%, 3%), *Staphylococcus aureus* (12.86%, 7.46%), *Staphylococcus epidermidis* (10%, 2.99%), *Streptococcus pyogenes* (10%, 2.99%), *Proteus species* (7.14%, 1.49%), *Pseudomonas species* (5.71%, 1.49%), *Lactobacilli species* (5.71%, 22.39%), *Citrobactor species* (4.29%, 0.00%), *Candida albicans* (11.43%, 22.39%), *Klebsiella species* (4.30%, 1.50%), *non- albicans Candida* (11.43%, 25.37%), *Staphylococcus saprophyiticus* (2.86%, 8.96%).

Vaginal microbial variation based on pregnancy trimesters

The table 3 shows the variation of vaginal microbial community in pregnancy trimesters between pregnant women with and without UTIs. ANOVA-2 was used to test for the vaginal microbial community mean difference in pregnancy trimesters. There was a higher microbial variation or differences among women with UTIs (F=7.241842) compared to women without UTIs (F = 4.71) in pregnancy trimesters.

Association with Vaginal microbial community imbalance and UTIs

Table 4 shows the association with vaginal microbial community variation in the two groups and urinary tract infections. There was a statistical significance association with *Escherichia coli* (x^2=9.97, p=0.0015), *Staphylococcus epidermidis* (x^2=5.12, p=0.023), *non- albicans Candida* (x^2=7.2, p=0.00729), and *Lactobacilli species* (x^2=13.7, p=0.00021), *Proteus ssp* (x^2=4.96, p=0.025), *Citrobactor ssp* (x^2=32.51, p<0.00001), *Strep.pyogenes* (x^2=5.11, p=0.023), *Staphylococcus saprothiticus* (x^2=4.3, p=0.038), and *Candida albicans* (x^2=4.89, p=0.027). *Klebsiella spp, Staphylococcus aureus,* and *Pseudomonas*

ssp were not statistically significant. The overall association (x^2=94.879, p<0.00001) with all isolated microorganisms and urinary tract infections was statistically significant.

Ratio of pathogenic microorganisms among women with UTIs compared to women without UTIs

Table 5 shows Ratio of pathogenic microorganisms among women with UTIs compared to women without UTIs. The risk ratio (RR) and odd ratio (OR) of pathogenic and non-pathogenic bacteria were 3.14 and 4.98 respectively. Since these epidemiological measurements of association are above 1, it implies that vaginal microbial community dysbiosis contributed to urinary tract infection.

DISCUSSION

The study was carried out to analyze the vaginal microbial differences among women with and without UTIs. The highest imbalance in vaginal microbial community between the two groups was observed to different microorganisms such as *E. coli* which was 5 times among women with UTIs compared to the control group, *Proteus ssp* was also 5 times among women with UTIs compared to women without UTIs. *Lactobacilli spp* and *Proteus ssp* were predominant among women

Table 1: Age and pregnancy trimester distribution of participants

Parameter	Frequency	Percentage
Grouped age		
21-25	12	15
26-32	46	57.5
33-38	12	15
39-43	10	12.5
Total	40	100
Trimester		
1st	46	57.5
2nd	26	32.5
3rd	8	10
Total	40	100

Table 2: Isolated microorganisms in pregnant women with and without UTIs

Microorganisms	Pregnant with UTI	Pregnant without UTI
E.coli	14.29%	3%
Klebsiella spp	4.30%	1.50%
Staphylococcus aureus	12.86%	7.46
Staphylococcus epidermidis	10%	2.99%
Proteus spp	7.14%	1.49%
Pseudomonas	5.71%	1.49%
Citrobactor spp	4.29%	0.00%
Streptococcus pyogenes	10%	2.99%
Staphylococcus saprophiticus	2.86%	8.96%
Lactobacilli spp	5.71%	22.39%
Candida albicans	11.43%	22.39%
Non albicans Candida	11.43%	25.37

Table 3: Isolated microorganisms from the vagina based on pregnancy trimesters

Microorganism	Pregnant with UTI			Pregnant without UTI		
	1st Term	2 nd Term	3 rd Term	1st Term	2 nd Term	3 rd Term
E.coli	4	10	6	0	2	2
Klebsiella	0	6	0	2	0	0
Staph.aureus	6	6	6	4	4	2
Staph epidermidis	6	8	0	2	0	2
proteus spp	4	6	0	0	2	0
Pseudomonas ssp	4	4	0	2	0	0
Citrobactor ssp	2	4	0	0	0	0
Strep.pyogenes	6	4	4	2	2	0
Lactobacilli	4	2	2	10	18	2
Staph saprothiticus	4	0	0	4	8	0
Candida albicans	8	6	2	16	12	2
Non albicans Candida	8	8	0	20	12	2
ANOVA-2						
SS			76.2			133
Df			2			2
MS			38.11			66.77
F			7.241842			4.71
P			0.003833			0.019
F-crit			3.443357			3.41

SS=Sum Square   Df=Degree of freedom   MS=Mean Square

Table 4: Microorganisms associated with urinary tract infection

Microorganism	P. W with UTI		P.W without UTI		Total	Df	χ^2	P-Value
	O	E	O	E				
E.coli	20	12.26	4	11.73	24	1	9.97	0.0015
Klebsiella	6	4.08	2	3.91	8	1	1.83	0.17
Staphylococcus aureus	18	14.3	10	13.69	28	1	1.94	0.16
Staphylococcus epidermidis	14	9.19	4	8.8	18	1	5.12	0.023
Proteus spp	10	6.13	2	3.91	12	1	4.96	0.025
Pseudomonas spp	8	5.1	2	4.89	10	1	3.349	0.06
Citrobactor spp	6	3.065	0	29.7	6	1	32.51	<0.00001
Strep.pyogenes	14	9.19	4	8.8	18	1	5.11	0.023
Lactobacilli ppp	8	19.41	30	18.58	38	1	13.7	0.00021
Staphylococcus saprothiticus	4	8.1	12	7.82	16	1	4.3	0.038
Candida albicans	16	23.5	30	22.39	46	1	4.89	0.027
Non-albican Candida	16	25.5	34	24.5	50	1	7.2	0.00729
Total	140		134		274	11	**94.879**	**<0.00001**

Table 5: Ratio of pathogenic microorganisms among women with UTIs compared to women without UTIs

	P. women with UTI	P. women without UTI	TOTAL
TOTAL	124	134	258
Non Pathogenic microorganisms	46	100	146
Pathogenic microorganisms	78	34	112
Risk in cases	**R=0.629**		
Risk in controls		**R=0.274**	
Risk Ratio			**RR=3.14**
Odd Ratio			**OR=4.98**

RR=Risk Ratio OR=Odd Ratio

without UTIs compared to women with UTIs (Table 2 and 3). Considering the contribution of *E. coli* to urinary tract infections, its predominance occurrence among women with UTIs was not critical because of its dominance in urinary tract infection etiology compared to other microorganisms.[13] *Lactobacilli spp* was also the most predominant microorganism among women without UTIs. Healthy vaginal microbiota is dominated by *Lactobacilli spp* which protects the vagina against pathogenic microorganisms and their effects.[14] The low occurrence of *Lactobacilli spp* favored the growth of pathogenic microorganisms among women with UTIs. The findings of Kzar reported the high occurrence of *Escherichia coli* 17(34%) and K*lebsiella* ssp.11(22%) among pregnant women with urinary tract infections.[15] The similar findings conducted by Demilie & Beyene revealed that *E. coli (*45.7%) coagulase negative (17.1%), and S. *aureus* (8.6%), *Proteus* ssp (17%), and the least isolated microorganisms were K*lebsiella* ssp. G. *vaginalis* and *Enterococci* ssp.[16] Another study carried

out in Tanzania at Muhimbili National Hospital reported *E. coli* (33.3%), *Klebsiella* ssp (21.4%), *Proteus* ssp (7.1%), *S. aureus* (14.3%), coagulase negative st*aphylococcus* (16.7%), and E*nterococcus* ssp (7.1%) among pregnant women with UTIs.[17] *E. coli, enterococcus species*, *Klebsiellaspeci*es, Group B *Streptococcus* species were reported as the predominant etiologic agents of urinary tract infections among pregnant women.[18] The study conducted by Brubaker, et al. at Harvard Medical School isolated different microorganisms among pregnant women with UTI, and the *E. coli*, *S. aureus*, *Klebsiella* ssp, and *Pseudomonas* ssp showed a significant association with urinary tract infection.[19] The current study and previous studies isolated common microorganisms among with UTIs despite some differences in frequencies from one study to another depending on the region or the country where the study was conducted from. *E. coli* was observed to be the leading cause of urinary tract infection among women with UTIs regarding the findings of the current study and that of the previous studies.

The contribution of vaginal microbiota imbalance to the occurrence of urinary tract infection at Gisenyi district hospital was analyzed. There was statistical significant association with vaginal microbiota change and UTI (x^2=1378.52, p=0.00001) (Table 4). The study conducted by Kline, et al. observed the significant association in the vaginal microbiota variation and vaginal UTI, in her study the change in the characteristics of vaginal microbiota resulted from the loss of normal protective *lactobacilli* ssp which increased the risk of UTIs among pregnant women.[20] The *E. coli* which was predominant in the current study, was also predominant in the study of Kline and stood at 80% of isolated microorganisms. The same findings of Chen, et al. showed a significant association with the vaginal microbiota dysibiosis and urinary tract infection. *E. coli* (p=0.011), K*lebsiella* ssp (p=0.04) and P*seudomonas* ssp (p= 0. 029) were observed as contributor of urinary tract infections.[21] This shows that vaginal microbial dysibiosis leads to urinary tract infection. Lewis, et al. reported a significant different between isolated microorganisms. *E. coli*, *Klebsiella* and S. *aureus* were significantly contributed to UTI among pregnant women.[22] The study analyzed the ratio of pathogenic bacteria among pregnant women. The epidemiological measurement techniques including odd ratio and risk ratio were performed. The odd ratio value of 3.7>1 shows that the ratio of pathogenic bacteria is higher among pregnant women. The current study isolated pathogenic microorganisms that contributes to urinary tract infection among women including *E. coli*, *Klebsiella*, *S. aureus*, and others (Table 2&5). The same microorganisms were isolated by the study conducted in Bangladesh by Anne Lee et al., where the high frequency of pathogenic bacteria was observed to *E. coli*, *Staphylococcus* ssp, K*lebsiella* ssp and *S. aureus*.[23] This implies that microbiota imbalance

predisposes pregnant women to urinary tract infections. The findings of the study on asymptomatic bacteriuria among pregnant women in Iran identified different microorganisms associated with asymptomatic bacteriuria including *E. coli* which was the commonest bacteria followed by *Staphylococcus ssp* and *S. aureus*.[24] Derese et al., conducted a study of bacteria profile of urinary tract infection and antimicrobial susceptibility pattern among pregnant women, in his findings he compared pathogenic bacteria among symptomatic and asymptomatic UTI, where *E. coli* stood at 19.2% in symptomatic while 15.4% in asymptomatic, Coagulase negative *Staphylococcus* stood at 11.5% in symptomatic while 7.7% in asymptomatic and *Citrobactor* ssp stood at 3.8% in symptomatic while 0% in asymptomatic.[25] The percentages of isolated microorganisms are high in symptomatic UTI compared to asymptomatic UTI. Considering asymptomatic UTI condition free from UTI, it does not make differences from what the current study investigated as pathogenic bacteria were high in symptomatic UTI.

CONCLUSION

This was a cross section study to vaginal microbiota dysbiosis among pregnant women with urinary tract infection at Gisenyi district hospital. There were vaginal microbial community differences among pregnant women with and without urinary tract infection in pregnancy trimesters. Vaginal microbial community variation was the persecutor of urinary tract infections among pregnant women. The microbial imbalance in the vagina during pregnancy observed that *E. coli*, *Citrobactor spp*, S. *epidermidis* and P*roteus* ssp, *Strep. pyogenes, Lactobacilli ppp, Staphylococcus saprothiticus, Candida albicans, and Non-albicans Candida* were associated with the occurrence of urinary tract infection among pregnant women. The ratio of pathogenic microorganisms for pregnant women with UTIs was greater than that of pregnant women without UTIs. Pregnant women should seek for gynecologists for early detection of urinary tract infections.

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