

Characterization of aerobic vaginitis in late pregnancy in a Chinese population

A STROBE-compliant study

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Abstract

This study aimed to analyze the clinical characteristics, responsible pathogens, and antibiotic sensitivity of aerobic vaginitis (AV) infection in women in late pregnancy in western China.

We enrolled 246 pregnancy with AV (≥ 35 weeks gestation) and 204 reproductive non-pregnancy with AV from West China between January 2019 and December 2019. Then, bacterial culture, identification and antibiotic sensitivity testing were performed. Subsequently, we retrospectively analyzed the vaginal microbiota of 250 healthy pregnant women with no AV and compared the maternal features and pregnancy outcomes.

Regarding bacterial diversity, *Streptococcus* and *Lactobacillus* were highly abundant in women with AV in late pregnancy, whereas *Staphylococcus* spp. and other bacteria were significantly more abundant in reproductive non-pregnant women with AV. In addition, 82.5% (343/416) of the single isolate comprised *Escherichia coli*, group B *Streptococcus*, *Enterococcus faecalis*, and *Staphylococcus aureus*. Among the top 4 isolates, 13.4% (46/343) were multidrug-resistant, but all isolates were highly susceptible to nitrofurantoin. *Escherichia coli* was 100% susceptible to amikacin, meropenem, ertapenem, and imipenem (100%, 157/157), and gram-positive cocci were 100% (186/186) susceptible to vancomycin and linezolid. Finally, we found that pregnant women with AV had high rates of histories of vaginitis, premature rupture of membranes and neonatal infection.

Our study reveals new insights into AV infection during pregnancy and highlights the different vaginal bacterial microbiome compositions between pregnant and reproductive non pregnant women with AV, these results may translate to treatments that are more cost-effective than current standard treatments.

Abbreviations: AV = aerobic vaginitis, CoNS = coagulase-negative staphylococci, GBS = group B *Streptococcus*, MRSA = methicillin-resistant *Staphylococcus aureus*, PROM = premature rupture of membranes.

Keywords: aerobic vaginitis, antibiotic sensitivity, multidrug-resistant, pathogens, pregnancy

1. Introduction

The vaginal microbiome is a complex system that is affected by microorganisms, ethnicity and genes.^[1] When aerobic bacteria (or facultative anaerobes) predominate in vaginal flora and the flora lacks lactobacilli, aerobic vaginitis (AV), which is a common vaginal

microbiome disorder in females of reproductive age, occurs.^[2] AV was first named by Donders et al in 2002 and is characterized by aerobic bacterial infection, vaginal inflammation and parabasal epitheliocyte presence.^[3] Among bacterial vaginitis, desquamative inflammatory vaginitis (severe AV) was first proposed in 1965 by Gray and Barnes.^[4] The most frequent pathogens responsible for AV are *Escherichia coli*, *Staphylococcus aureus*, and coagulase-negative staphylococci (CoNS), such as *Staphylococcus epidermidis*, group B *Streptococcus* (GBS), and *Enterococcus faecalis*.^[5-7]

However, little is known about AV during pregnancy. Few studies have been conducted on the microbial diversity differences between pregnant and nonpregnant women with AV.^[5] Moreover, the antibiotic sensitivity of pathogens responsible for AV infection is not well known. AV in pregnant women is associated with complications of pregnancy, particularly an increased risk of preterm labor and premature rupture of membranes (PROM).^[8,9] The diagnosis and treatment of AV during pregnancy may reduce the risk of negative pregnancy outcomes. For this reason, we aimed to analyze the clinical characteristics, pathogen composition and antibiotic sensitivity of AV infections in women in late pregnancy in western China to identify candidates for prophylaxis and to prevent severe maternal and neonatal outcomes.

2. Methods

2.1. Study design and patients

The case-control study was conducted from January 2019 to December 2019 in the Obstetric and Gynecological Department

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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of West China Second University Hospital, Sichuan University, China. The study was reviewed and approved by the ethics committee of West China Second University Hospital of Sichuan University (Sichuan China).

Written informed consent forms were obtained from all the participants. We collected maternal vaginal discharge from women after 35 weeks of gestation because Schoenmakers et al suggested that this was the optimal time to influence pregnant outcomes.^[10] The inclusion criteria were as follows:

- a) a singleton pregnancy,
- b) ≥ 35 weeks gestation and
- c) a vaginal smear AV score ≥ 3 according to Donders' microscopic diagnostic criteria.^[3]

This AV scoring system combines microscopic assessment about lactobacillary grades, number of leukocytes, proportion of toxic leukocytes, background flora, and proportion of parabasal epitheliocytes. The control group comprised reproductive women with AV (20–50 years) from the same gynecological department. The exclusion criteria were as follows:

- a. other specific pathogens, including fungal, viral, mycoplasma, chlamydia, or other microbial infections, such as bacterial vaginosis in the female reproductive system;
- b. severe medical diseases, such as hypertension, diabetes mellitus, malignant tumor, abnormal immune function, etc,
- c. the use of antibiotics within 7 days or
- d. unavailable follow-up, such as psychiatric illness. A second control group comprised healthy pregnant women with no AV at ≥ 35 weeks gestation who underwent regular prenatal check-ups in the same period. They were age-matched to the age ranges of the pregnant women with AV.

2.2. Vaginal discharge collection

We collected vaginal discharge under direct visualization during a speculum examination by using three sterile nylon-flocked swabs (MRC Science and Technology Ltd., Shenzhen, China), the discharge was taken from the posterior fornix or vaginal wall. All sterile nylon-flocked swabs were put into sterile tubes (DIRUI Industrial Company, Changchun, China) immediately and sent to the Department of Laboratory Medicine, West China Second University Hospital, Sichuan University.

2.3. Microscopic observation

One smear was mixed with 1 droplet of saline and then examined by 2 laboratory microbiologists under a 400-field CKX41 inverted microscope (Olympus, Japan). The results of their observations were consistent. Observations and documentation followed the guidelines of both the National System for External Quality Assessment (NSEQA) and the College of American Pathologists (CAP). We used Donders' AV saline wet mount microscopic diagnostic criteria.^[3] If the AV score was ≥ 3 , the other swabs containing vaginal discharge were used for culture and identification. Finally, we identified 246 pregnant and 204 reproductive non pregnant eligible women with AV.

2.4. Microbiological tests

The second swabs were inoculated onto chromID Strepto B agar (Zhuhai Dier Science and Technology Development Limited

Company, Zhuhai, China). After incubation for 8 to 48 hours at 35°C to 37°C, characteristic orange isolates were subcultured on blood agar plates. According to the manufacturer's instructions, 3 quality control stains were performed, *Streptococcus agalactiae* (the positive control), *E. faecalis* (gram-positive bacteria as the negative control) and *E. coli* (gram-negative bacteria as the negative control) to verify the availability of chromID Strepto B agar. The third swabs were analyzed using Columbia agar and 5% sheep blood (Mérieux Shanghai Science and Technology Development Limited Company, Shanghai, China), and microorganisms were identified by VITEK matrix-assisted laser desorption/ionization time of flight mass spectrometry. For the drug susceptibility tests, a VITEK 2 Compact AST-GP system was used for *Staphylococcus* spp. and *Enterococcus* spp.; the quality-control strains were *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212. ATBS TREP5 expression was detected for *Streptococcus* spp., and the quality-control strain was *Streptococcus pneumoniae* ATCC 49619. In addition, the quality-control strains for chromID Strepto B agar were *Streptococcus agalactiae* ATCC 12386, *E. faecalis* ATCC 29212 and *E. coli* ATCC 25922. The VITEK2-COMPACT GN13 and K-B methods were applied for Enterobacteriaceae, and the quality-control strains were *E. coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853.

2.5. Retrospective reconsideration information

The pregnant women with AV were asked about their history of vaginitis and followed to evaluate pregnancy outcomes including delivery mode; delivery condition, for example, PROM, referring to membrane rupture before labor;^[11] birth weight; Apgar score (low Apgar score^[12]); stillbirth (delivery ≥ 28 weeks with no signs of life at birth),^[13] and neonatal infections were recorded for 28 days after delivery. Neonatal infection was defined by laboratory-confirmed bacterial infection (positive culture of blood, cerebral spinal fluid, or urine),^[14] clinical signs of infection (pneumonia, fever, hypothermia, respiratory distress, etc) or administration of antibiotics for ≥ 10 days.^[15] Then, we collected the data of healthy pregnant women with no AV (the control group) from electronic medical records and/or telephone interviews; this data included vaginal microbiota test results, patient demographics, medical history, delivery mode, delivery condition, birth weight, Apgar score, and neonatal infection status.

2.6. Statistical analysis

The data analysis was performed with SPSS Statistics ver. 20.0 (SPSS Inc., Chicago, IL). Student *t* test was used to analyze continuous variables, while the comparisons of different species and different positive rates were analyzed by Chi-squared or Fisher exact probability tests. All graphics were accomplished using GraphPad Prism 5.0 (GraphPad Software Inc., CA).

3. Results

3.1. Different vaginal microbial community compositions in AV in pregnant and reproductive non pregnant women

A total of 4.2% (246/5857) of pregnant women (≥ 35 weeks gestation) were positive for simple AV infection compared to 4.8% (204/4234) of reproductive non pregnant women with AV ($\chi^2 = 2.542, P = .061$). They also have no severe medical diseases.

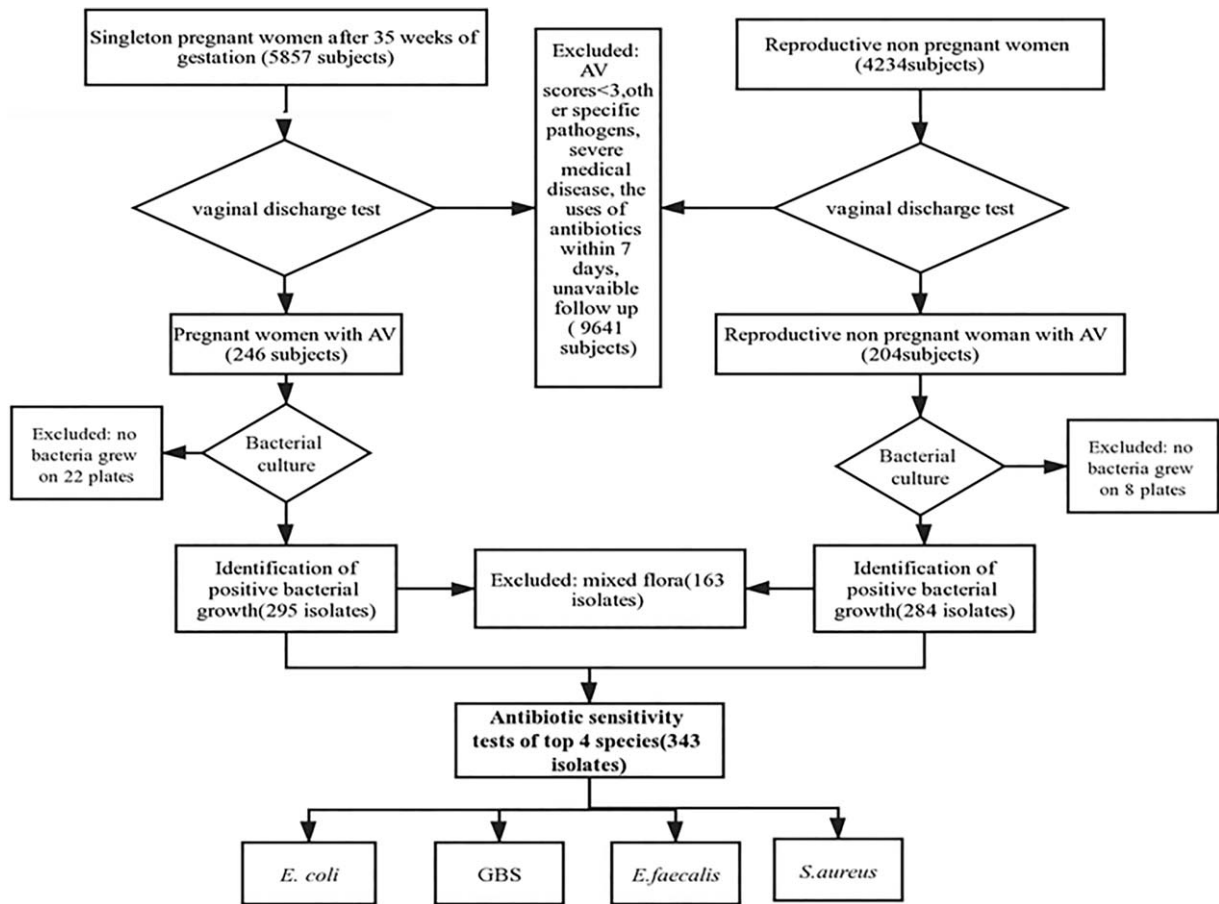


Figure 1. Flow diagram of the subjects analyzed. AV=aerobic vaginitis, GBS=group B Streptococcus.

The mean age of the pregnant women with AV was 31.1 ± 3.8 years, which was similar to that of the reproductive non pregnant women with AV (32.1 ± 7.7 years, $t=1.79$, $P=.075$). A total of 295 isolates were identified from 224 pregnant women with AV; no bacteria grew on 22 plates and multiple species grew (*E. faecalis* / CoNS / *E. coli* / *lactobacilli*) on 71 plates. We cultured 284 isolates, including 92 with mixed flora (*E. faecalis* / CoNS / *E. coli* / *lactobacilli*). A total of 8 women in 204 reproductive non pregnant women with AV had no growth on plates. Flow diagram of the subjects analyzed was shown in Figure 1. The majority (94.3%, 546/579) of isolates belonged to *E. coli* (32.4%, 177/546), *Staphylococcus* spp. (21.8%, 119/546), *Enterococcus* spp. (19.4%, 106/546), *Streptococcus* spp. (18.7%, 102/546) and *Lactobacillus* (7.7%, 42/546). In particular, there were no differences between the 2 groups in bacterial diversity, but the constituent ratio significantly differed ($\chi^2=32.326$, $P<.001$). We observed a relatively high abundance of *Streptococcus* spp. ($\chi^2=13.812$, $P<.001$) and *Lactobacillus* ($\chi^2=16.034$, $P<.001$) in pregnant women with AV. In contrast, *Staphylococcus* spp. ($\chi^2=37.159$, $P<.001$) and other bacteria ($\chi^2=1.59$, $P=.14$) were found at significantly higher abundances in reproductive non pregnant women with AV than in pregnant women with AV (Figure 2). Other bacteria isolated from pregnant women with AV were *Gardnerella vaginalis* (1.7%, 5/295), *Candida albicans* (0.7%, 2/295), *Enterobacter cloacae* (0.3%, 1/295), *Enterobacter aerogenes* (0.3%, 1/295), and *Klebsiella pneumoniae* (0.3%, 1/295). Other bacteria isolated from

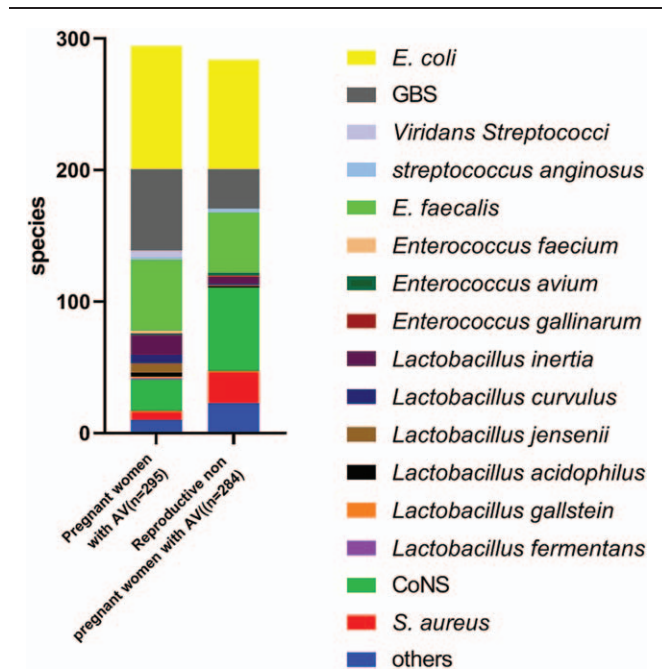


Figure 2. Distribution of bacterial isolates in pregnant and reproductive non pregnant women with aerobic vaginitis. AV=aerobic vaginitis, GBS=Group B Streptococcus, CoNS=Coagulase negative Staphylococci.

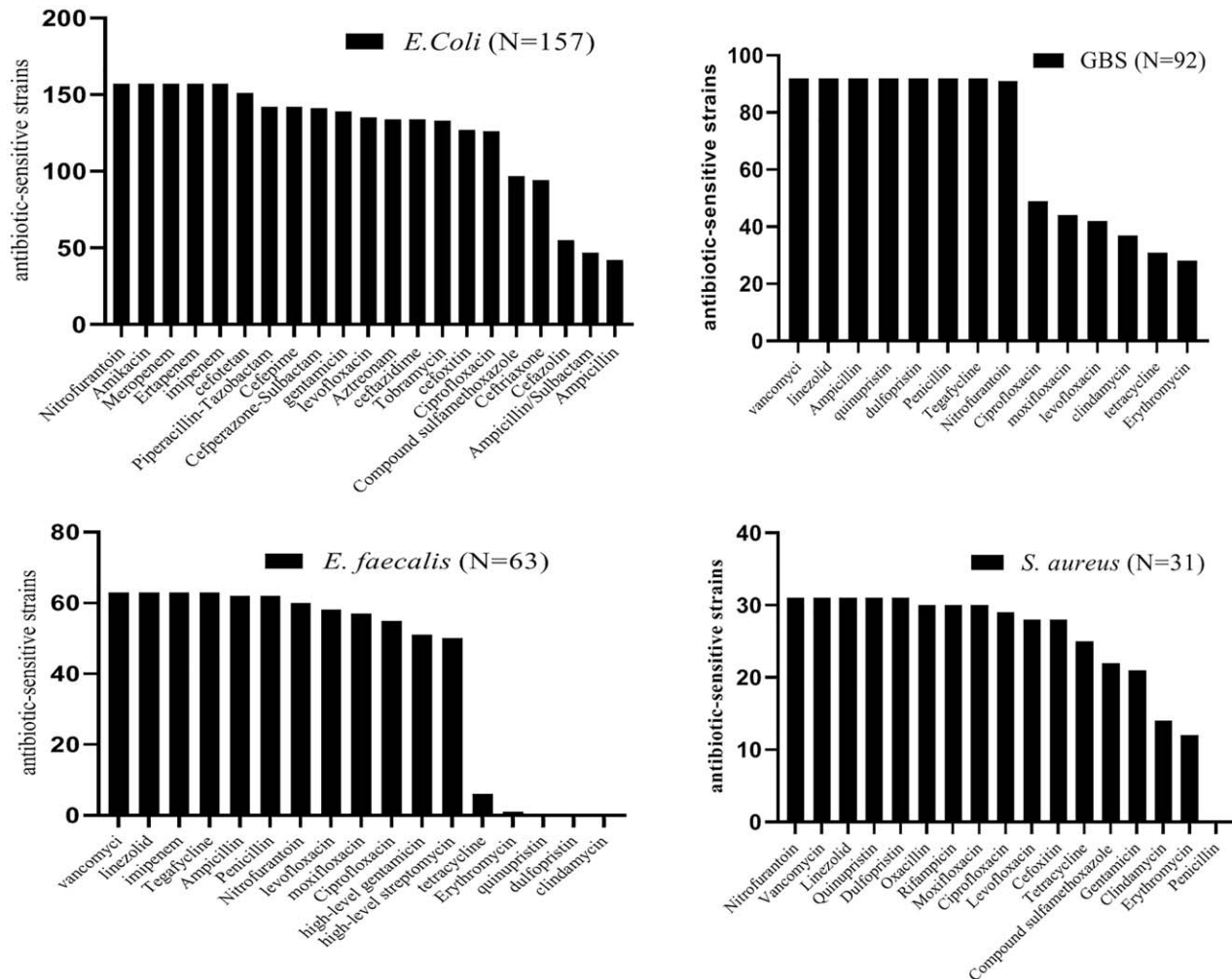


Figure 3. Antibiotic sensitivity tests of the top 4 species in aerobic vaginitis-positive women. GBS=*group B Streptococcus*.

reproductive non pregnant women with AV were *Pseudomonas aeruginosa* (3.2%, 9/284), *K. pneumoniae* (1%,3/284), *G. vaginalis* (1%,3/284), *C. albicans* (1%,3/284), *E. aerogenes* (0.7%,2/284), *E. cloacae* (0.4%,1/284), *Candida parapsilosis* (0.4%,1/284), and *Proteus vulgaris* (0.4%,1/284).

3.2. Antibiotic sensitivity tests in maternal AV infection

Antibiotic susceptibility tests were performed on 82.5% (343/416) of the isolates, excluding 163 isolates which belonged to mixed flora (64CoNS, 37Enterococcus feces, 20E coli which considered of opportunistic pathogens and 42 Lactobacillus), and other species (some species have no tests standard)did not perform antibiotic susceptibility tests. We found that the majority pathogen species were *E. coli*, GBS, *E. faecalis* and *S. aureus*. Out of 343 isolates, 13.4% were antimicrobial-resistant; 11.5% (18/157) of *E. coli* were extended spectrum beta-lactamase producers, 4.3% (4/92) of GBS were multidrug-resistant, 19% (12/63) of *E. faecalis* were high-level gentamicin resistance, 20.6% (13/63) of *E. faecalis* were high-level streptomycin resistance, and 9.7% (3/31) of *S. aureus* were methicillin-resistant *Staphylococcus aureus* (MRSA). All isolates were highly susceptible to nitrofurantoin. *E. coli* were 100% (157/157)

susceptible to amikacin, meropenem, ertapenem, and imipenem, and resistance to ampicillin, ampicillin/sulbactam, and ceftazolin was less than 40%. Gram-positive cocci were 100% (186/186) susceptible to vancomycin and linezolid and above 50% isolates resistant to erythromycin and clindamycin. Among them, GBS and *E. faecalis* were highly susceptible to tigecycline and penicillin but resistant to tetracycline. GBS and *S. aureus* were 100% (94/94) susceptible to quinupristin and dalfopristin. GBS were 100% (92/92) susceptible to ampicillin and more than 50% resistant to levofloxacin and moxifloxacin (Fig. 3).

3.3. Clinical characteristics of AV-positive and healthy pregnant women

Clinical characteristics, including age, history of vaginitis, PROM, delivery mode, birth weight, Apgar score, stillbirth, and neonatal infection, were recorded after delivery (Table 1). The groups were matched by age and time of delivery. Interestingly, the pregnant women with AV had higher rates of history of vaginitis, PROM and neonatal infection than healthy pregnant women. We found no significant differences between AV-positive and healthy pregnant women with no AV in age, delivery mode, birth weight, or Apgar score ($P > .05$). No

Table 1
Clinical factors and pregnancy outcomes of women with aerobic vaginitis and health vaginal microbiota.

Characteristic	AV (n=246)	Control (n=250)	χ^2	P value
Age (y)			1.245	.162
<35	208 (84.5)	220 (88)		
≥35	38 (15.5)	30 (12)		
History of vaginitis (n, %)			13.49	<.001*
Yes	53 (21.5)	24 (9.6)		
No	193 (78.5)	226 (90.4)		
PROM (n, %)			26.105	<.001*
Yes	63 (25.6)	21 (8.4)		
No	183 (74.4)	229 (91.6)		
Delivery mode (n, %)			0.136	.39
Cesarean section	131 (53.3)	129 (51.6)		
Vaginal delivery	115 (46.7)	121 (48.4)		
Birth weight (g) (n, %)			0.917	.632
1500–2500	14 (5.7)	18 (7.2)		
2500–4000	223 (90.6)	220 (88)		
>4000	9 (3.7)	12 (4.8)		
Apgar score (n, %)			/	.306 ^a
Low Apgar score	3 (3.70)	1 (9.09)		
≥7	243 (96.30)	249 (90.91)		
Stillbirth (n, %)			/	.746 ^a
Yes	1 (0.4)	1 (0.4)		
No	245 (99.6)	249 (99.6)		
Neonatal infection (n, %)			5.32	.021*
Yes	21 (8.6)	9 (3.6)		
No	224 (91.4)	240 (96.4)		

AV = aerobic vaginitis, PROM = premature rupture of membranes.

* indicates statistical significance.

^a indicates Fisher exact test.

significant differences in PROM, Apgar score, neonatal infection were observed among different bacteria of AV. The maternal infection with *E. coli* exhibited their infants birth weights lower than average (Table 2).

4. Discussion

This was one of the largest observational studies investigating the characterization of AV in late pregnancy, and we found that the isolated pathogens differed between AV-positive pregnant women and reproductive non pregnant women. Furthermore, to our knowledge, this was the first study to evaluate the association between antibiotics and different pathogens in vaginal discharge. Finally, we further strengthened the evidence linking AV with negative neonatal outcomes.

The findings in the current study were consistent with Donders et al's review of the prevalence of AV during pregnancy, which ranged from 4% to 8% but was slightly lower than the 7% to 13% found in non-pregnant women,^[16] their prevalence rates were higher than ours possibly because we excluded other types of vaginitis by including only AV-positive women or because the incidence of AV in non pregnant women in western China is lower than that in other areas.

The vaginal bacterial community in women with AV is characterized by high loads of aerobes and low concentrations of *Lactobacilli*.^[16] We also observed a variable mixed flora of *E. faecalis*, CoNS, *E. coli*, *Lactobacilli* in AV-positive women. Several studies concluded that the most common AV-associated organism, or at least the most commonly identified gram-negative

Table 2
Effect of different bacterial isolates types on pregnancy outcome of pregnant women with aerobic vaginitis (n).

	Total	<i>E. coli</i>	GBS	<i>E. faecalis</i>	<i>S. aureus</i>
PROM	63	22	14	10	2
NPROM	183	68	48	32	5
χ^2	/	0.101	0.399	0.086	/
P value	/	.75	.527	.769	.558 ^a
Low birth weight	14	9	2	1	1
Normal birth weight	223	81	60	41	6
χ^2	/	4.373	/	/	/
P value	/	.037*	.241 ^a	.253 ^a	.351 ^a
Low Apgar score	3	1	1	0	1
Apgar score ≥7	243	89	61	42	6
χ^2	/	/	/	/	/
P value	/	.697 ^a	.583 ^a	.569 ^a	.083 ^a
Neonatal infection	21	10	6	2	1
Uninfected neonates	224	80	56	40	6
χ^2	/	1.171	0.130	/	/
P value	/	.279	.719	.264 ^a	.47 ^a

AV = aerobic vaginitis, GBS = group B Streptococcus, low birth weight = Birth weight < 2500 g, low Apgar score = Apgar score < 7, PROM = premature rupture of membranes, S.aureus = Staphylococcus aureus.

* indicates statistical significance.

^a indicates Fisher exact test.

pathogen, was *E. coli*.^[16,17] Our study confirmed these findings. *E. coli* was the most common pathogen among all women, including pregnant women, however *Staphylococcus* spp. were the most commonly identified gram-positive pathogen in non-pregnant women and their compositions varied in different reports. The prevalence of *Streptococcus* spp., *S. aureus*, CoNS, and *Enterococcus* spp. varied from 0.7% to 58.7%, 6% to 37.4%, 0.2% to 41.7%, and 0.3% to 78.3%, respectively.^[16,18,19] In particular, GBS,^[20] *S. aureus*,^[21] and *E. faecalis*^[19] were found to be the most frequently isolated pathogenic bacteria in different reports. GBS (*S. agalactiae*) and *S. aureus* were the predominant gram-positive organisms in nonpregnant women in Nepal.^[22] Our study demonstrated that *Staphylococcus* spp., *Enterococcus* spp., and *Streptococcus* spp. dominated in the majority of the AV-positive groups. Among these dominant genera, *Staphylococcus* and *Streptococcus* were substantially dissimilar between the pregnant and nonpregnant AV women.

Although not concerning vaginal microbiota, Khan et al found that the gut bacterial community composition differed between pregnant and non pregnant Saudi women, and an increased proportion of antibiotic resistance was observed during pregnancy.^[23] To date, there has been little agreement on this. Dammeyer et al^[24] found that 3.5% (23/651) of healthy pregnant women harbored antimicrobial-resistant bacteria and 14.3% (93/651) harbored methicillin-susceptible *S. aureus* (MSSA); the MRSA:MSSA ratio was 3.1%. However, Hetsa^[25] reported a high prevalence (76%–100%) of vaginal colonization with antibiotic-resistant isolates among pregnant women.

In our study, 13.4% (46/343) of women harbored antimicrobial-resistant bacteria; 11.5% had extended spectrum beta-lactamase-producing bacteria, 4.3% had multidrug-resistant bacteria, 19% had high-level gentamicin resistance bacteria, 20.6% had high-level streptomycin resistance bacteria, and 9.7% MRSA. The MRSA:MSSA ratio equaled 10.7%. Due to ethnicity and genes, there are possible explanations for the differences. Clindamycin is often used in clinical practice, but considering the

emerging resistance to antibiotics, the administration of ampicillin, ampicillin/sulbactam, cefazolin, erythromycin, and clindamycin is insufficient to control relevant bacteria. In theory, we could empirically use nitrofurantoin^[26] because there is a low rate of resistance in all AV-associated bacteria; amikacin,^[27] meropenem, ertapenem, and imipenem^[28] for gram-negative bacilli; and vancomycin and linezolid^[29] for gram-positive cocci. We do not recommend levofloxacin or moxifloxacin therapy for GBS which is in accordance with Ji W et al's report.^[30] Importantly, consequences for the unborn fetus should be considered. Finally, pregnancy outcomes relates to various factors such as abnormal vaginal flora,^[31,32] gestational diabetes,^[33] etc our study supports previous research, but we demonstrate that pregnant women without complications (such as gestational diabetes) who suffered from simple AV also had worse pregnancy outcomes. AV maybe as a independent risk factor is associated with adverse pregnancy outcomes. It is feasible to assess the effect of the four main pathogens *E. coli*, GBS, *E. faecalis* and *S. aureus* on pregnancy and neonatal outcome. However, the present study contained too few samples to allow us to draw definite conclusions about the effects of different bacteria on pregnancy and neonatal outcome. Moreover, animal experiment, which is the direct evidence, should be performed in the future, and further research should be conducted to investigate the association between additional risk factors and pregnancy outcomes in women with AV to prevent and/or treat AV early.

In conclusion, our study reveals new insights into AV infection during pregnancy. This finding has implications for future studies designed to explore AV infection and treatment and, in particular, highlights that the isolates of AV infection were different between pregnant and nonpregnant women, which may translate to treatment that is a more cost-effective than current standard treatments.

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