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ORIGINAL ARTICLE

Aerobic vaginitis in late pregnancy and outcomes of pregnancy

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Abstract

The purpose of this study was to investigate the risk factors and pregnancy outcomes for aerobic vaginitis (AV) in late pregnancy. A total of 624 pregnant women who were treated in the perinatal unit at Tianjin Medical University General Hospital and 365 nonpregnant women who were evaluated at a health management center from January 2015 to June 2016 were recruited for this case-control study. A questionnaire covering personal hygiene habits and sociodemographic factors was administered to pregnant women to analyze risk factors for AV. Bacterial vaginosis, AV, vulvovaginal candidiasis, and Trichomonas vaginitis were scored according to standardized definitions. Pregnancy outcomes were followed up and recorded. The chi-square test and univariate and multivariate logistic regression analyses were used for statistical evaluation. The prevalence of vaginal infection in pregnant and nonpregnant women were 27.9% and 15.3%, respectively ($P < 0.05$). AV was identified more frequently in pregnant women than in nonpregnant women (4.2% vs. 1.4%; $P < 0.05$). A history of vaginal infection within 1 year (odds ratio [OR] = 3.219, 95% confidence interval [CI] 1.103–9.346) and external hemorrhoids (OR = 11.233, 95% CI 4.647–27.155) were independent risk factors for AV during pregnancy. A higher incidence of premature rupture of membranes (PROM) was significantly associated with AV ($P < 0.05$). AV is common in late pregnancy. Clinicians should pay more attention to vaginal microbiota evaluations during pregnancy.

Keywords Pregnancy · Vaginal microbiota · Aerobic vaginitis · Prevalence · Preterm birth

Introduction

The vaginal microbiota is composed of several microbial species, mainly *Lactobacillus* spp. [1]. The balance and interactions among vaginal microbes are critical for a healthy vaginal microenvironment. When this balance is disturbed, pathological conditions may occur, such as bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and Trichomonas vaginitis (TV). Distinct from the vaginal infections above, aerobic vaginitis (AV) is a recently recognized clinical entity. The definition of AV was first proposed by Donders et al. in 2002 [2], and the prevalence of AV during pregnancy is in the range of 4–8% [3]. AV is characterized by abnormal vaginal microflora containing aerobic enteric bacteria, increased vaginal inflammation, and deficient epithelial maturation [3]. Inadequate understanding of AV may lead to treatment failure and result in perinatal complications, such as preterm birth (PTB) and fetal infection [4]. This study aimed to investigate the risk factors and pregnancy outcomes for AV in late pregnancy. In this study, we demonstrated the potential benefits of vaginal microbiota evaluation for preventing adverse pregnancy outcomes.

Cha Han and Huiyang Li contributed equally to this work.

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Materials and methods

Participants and procedures

During the period January 2015 to June 2016, the study was implemented at Tianjin Medical University General Hospital in China. Pregnant women in their third trimester presenting for their regular prenatal visits at the perinatal unit of Tianjin General Hospital in Tianjin, China, were consecutively enrolled in this study to investigate the prevalence of vaginal infection and to explore the underlying association between AV and pregnancy outcomes. The inclusion criteria were as

follows: (a) intrauterine pregnancy, (b) singleton pregnancy, and (c) intact fetal membranes. Control participants were selected from among women of reproductive age who presented for routine examinations at a health management center, and all were age- and time-matched to the pregnant patients. The exclusion criteria were as follows: (a) lactation, sexual intercourse, or vaginal douche that occurred within the previous 3 days; (b) use of antibacterial (topical or systemic) therapy in the previous 7 days; (c) other specific vaginal infection including VVC, BV, TV and mixed vaginal infections, cervicitis, pelvic inflammatory disease, or any sexually transmitted disease or genital skin abnormalities diagnosed before enrollment; (d) congenital genital tract deformity; or (e) other comorbid diseases (hypertension, diabetes mellitus, etc.). Ultimately, 624 pregnant patients and 365 control participants were consecutively enrolled. Prior written informed consent was obtained, and the study was approved by the Ethical Committee of Tianjin Medical University General Hospital in China.

Vaginal microbiota evaluation

At enrollment, every pregnant participant underwent a transabdominal ultrasound examination to confirm the gestational age of the fetus. All the participants also underwent gynecological examinations and vaginal discharge collection. An unlubricated sterile speculum was inserted before further examination in order to prevent any interference with the examination of vaginal discharge. Sterile long cotton swabs were used to obtain samples of vaginal discharge from the upper lateral vaginal wall for vaginal pH measurements (special indicator paper, pH 3.8–5.4; Shanghai SSS Reagent Co. Ltd., Shanghai, China) and microscopic examinations. After the speculum examination was performed, the characteristics (quantity, color, appearance, and odor) of the vaginal discharge, appearance (redness, ulcer, and swelling) of the vaginal mucosa, and the presence of congestion or purulent secretions in the cervix were recorded.

Discharge smears were spread on three glass slides for immediate microscopic examination. One smear was mixed with one droplet of saline while another was mixed with one droplet of 10% potassium hydroxide and then examined at × 400 magnification with a phase contrast microscope (*Olympus*, Japan). The third slide was Gram stained.

Questionnaire

Each pregnant participant completed a standardized and structured questionnaire containing the following information: sociodemographic factors (age, education level), obstetric history, last menstrual period, past history of diagnosed genital tract infection, history of clinical diagnosis of sexually transmitted infection, smoking habits, alcohol intake, personal hygiene habits, and health behaviors.

Follow-up

Pregnant patients were followed up to evaluate pregnancy outcomes. Pregnancy outcomes were recorded as normal delivery, premature rupture of membranes (PROM), PTB, etc.

Diagnostic criteria

PTBs are those that occur at a gestational age of less than 37 weeks' gestational age [5]. Stillbirth is defined as a baby born with no signs of life at 28 weeks' gestation or more [6]. Low birth weight is defined as a weight at birth of less than 2500 g (irrespective of gestational age) [7]. The definition of PROM is rupture of membranes before the onset of labor. Membrane rupture before labor and before 37 weeks of gestation is referred to as preterm PROM [8]. Neonatal asphyxia is defined as (1) risk factors of neonatal asphyxia presented, (2) Apgar score ≤ 7 after birth at 1 min or 5 min, (3) umbilical arterial pH < 7.15, and (4) other causes of low Apgar score must be ruled out [9].

As described previously, AV was diagnosed when a composite AV score ≥ 3 was determined by saline wet mount microscopy [2]. The microscopic diagnostic criteria for AV are shown in Table 1. BV was confirmed if the Nugent score was ≥ 7 on Gram-stained vaginal smears [10]. TV was diagnosed when Trichomonas vaginalis was microscopically detected in the saline wet mount smear [11]. VVC was determined by direct observation of budding yeast or hyphae on a 10% potassium hydroxide preparation slide in the presence of vaginal discharge or vulvovaginal pruritus [11]. Mixed vaginal infection was defined as ≥ 2 kinds coexisting vaginal infection. Well-trained doctors strictly adhered to the above inclusion and diagnostic criteria when enrolling participants. All smears were evaluated by an experienced microscopist.

Statistical analysis

SPSS 20.0 software (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Data are presented as the mean ± standard error of the mean (SEM). The strength of the associations of these factors was analyzed using odds ratios (ORs) with 95% confidence intervals (95% CI). $P < 0.05$ was considered statistically significant. Independent associations between potential factors with $P < 0.05$ in the univariate analysis and AV were further evaluated in a multivariate logistic regression analysis.

First, the chi-square analysis was performed to assess the different prevalence of vaginal infection in pregnant patients and nonpregnant controls. Second, univariate logistic regression analysis was performed to assess the association between potential predictive variables and AV. The following predictive variables were used for that purpose: (1) education level

Table 1 Diagnostic criteria of AV (×400magnification, phase contrast microscope)

AV score	LBG	Number of leukocytes	Proportion of toxic leukocytes	Background flora	Proportion of PBC
0	I and IIa	≤ 10/hpf	None or sporadic	Unremarkable or cytolysis	None or < 1%
1	IIb	> 10/hpf and ≤ 10/epithelial cell	≤ 50% of leukocytes	Small coliform bacilli	≤ 10%
2	III	> 10/epithelial cell	> 50% of leukocytes	Cocci or chains	> 10%

LBG, lactobacillary grade; *PBC*, parabasal epitheliocytes; *hpf*, high-power field

I: Numerous pleomorphic lactobacilli, no other bacteria

IIa: Mixed flora, but predominantly lactobacilli. IIb: Mixed flora, but proportion of lactobacilli severely decreased due to increased number of other bacteria.

III: Lactobacilli severely depressed or absent because of overgrowth of other bacteria.

A composite AV score of < 3 corresponds to "no signs of AV," 3–4 to "light AV," 5–6 to "moderate AV," and any score > 6 to "severe AV"

(college or less, university, or above), (2) history of genital tract infection (no, yes), (3) history of vaginal infection within 1 year (no, yes), (4) history of AV (no, yes), (5) history of sexually transmitted infection (no, yes), (6) smoking habits (no, yes), (7) alcohol consumption (no, yes), (8) presence of hemorrhoids (no, yes), (9) underwear type (cotton, synthetic), and (10) underwear washing method (alone, with clothes, with clothes or socks).

Results

All the participants enrolled were age-matched, and the average age of participants was 30.12 ± 3.57 years old. Of the 624 pregnant women, 174 (27.9%) had vaginal infections. However, only 56 (15.3%) of the 365 nonpregnant women had vaginal infections. Of the 174 pregnant women with vaginal infections, 120 had a single form of vaginal infection, and 54 had mixed vaginal infections. Of the 56 nonpregnant women with vaginal infections, 43 had a single form of vaginal infection, and 13 had mixed vaginal infections. The prevalence of vaginal infections in pregnant women was higher than that in nonpregnant women ($P = 0.02$).

The prevalence of AV in pregnant women and nonpregnant women were 4.2% (26/624) and 1.4% (5/365), respectively ($P = 0.015$). The prevalence of VVC in pregnant women and nonpregnant women were 11.1% (69/624) and 4.9% (18/365), respectively ($P = 0.001$). The prevalence of BV and TV in

Table 2 Prevalence of different vaginal infection in pregnant and non-pregnant group

Variables	Pregnant group *n* (%)	Nonpregnant group *n* (%)	χ^2	*P* value
AV			5.933	*0.015*
Yes	26 (4.2)	5 (1.4)		
No	598 (95.8)	360 (98.6)		
VVC			10.773	*0.001*
Yes	69 (11.1)	18 (4.9)		
No	555 (88.9)	347 (95.1)		
BV			1.445	0.229
Yes	24 (3.8)	20 (5.5)		
No	600 (96.2)	345 (94.5)		
TV			–	1.000
Yes	1 (0.2)	0 (0.0)		
No	623 (99.8)	365 (100.0)		
Single vaginal infection			9.286	*0.002*
Yes	120 (19.2)	43 (11.8)		
No	504 (80.8)	322 (88.2)		
Mixed vaginal infection			9.455	*0.002*
Yes	54 (8.7)	13 (3.6)		
No	570 (91.3)	352 (96.4)		

Italicized values indicate statistical significance

pregnant and nonpregnant women were not significantly different (Table 2).

Of the 54 pregnant women with mixed vaginal infections, 28 (51.9%) had AV combined with VVC, 11 (20.4%) had VVC combined with BV, 10 (18.5%) had AV combined with VVC and BV, 4 (7.4%) had AV combined with BV, and only 1 (1.9%) had VVC combined with TV.

Of the 624 pregnant women who underwent a vaginal microbiota evaluation, 26 had AV alone. The control participants were 450 pregnant women with normal vaginal microbiota evaluations. Univariate logistic regression analysis was performed to determine the risk factors for AV. Based on the results of the analysis (Table 3), we found that underwear washing method, history of vaginal infection, and presence of external hemorrhoids were positively associated with an increased risk of AV ($P < 0.05$). Multivariate logistic regression analysis revealed that history of vaginal infection and presence of external hemorrhoids were independent risk factors for AV ($P < 0.05$) (Table 3).

Fifteen out of 26 AV patients had positive bacteria culture. Among them, *Enterococcus faecalis* (6/15, 40%) is the most frequently isolated pathogenic bacteria. Other bacteria found in AV patients also include *Staphylococcus epidermidis* (4/15, 27%), *Escherichia coli* (2/15, 13%), *Corynebacterium* (2/15, 13%), *Streptococcus agalactiae* (1/15, 7%), and *Lactobacillus acidophilus* (1/15, 7%). One case was positive for both *Enterococcus faecalis* and *Staphylococcus epidermidis*.

Among the 624 pregnant participants who underwent vaginal microbiota evaluations, 573 completed follow-up. Among them, 26 had AV alone, and 412 had normal vaginal microbiota. The chi-square test showed that AV was associated with a higher incidence of PROM ($P < 0.05$) (Table 4).

Discussion

The dynamic balance and interactions between vaginal microbes are critical to female vaginal health. Lactobacilli, which dominate in the vaginas of the majority of healthy women, play a vital role in protecting the host from genital tract infections [12, 13].

In our study, the observed prevalence of vaginal infections in pregnant women was significantly higher than that in controls, especially for AV and VVC. AV combined with VVC was the most common form of mixed vaginal infection during pregnancy. This may be because AV unbalanced the vaginal microbiota making it easier for other pathogenic microorganisms, such as *Candida*, to survive, invade, and grow.

Our previous work showed that the use of an intrauterine device, long-term use of antibiotics, and frequent vaginal douching were independent risk factors for AV [14]. In this study, we found that a history of vaginal infection within 1 year and the presence of external hemorrhoids were independent risk factors for AV during pregnancy. In addition, the size of

Table 3 Risk factors associated with AV during pregnancy

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
History of vaginal infection		*0.017*		*0.032*
No	1		1	
Yes	3.253 (1.232~8.588)		3.219 (1.109~9.346)	
External hemorrhoids		*< 0.001*		*< 0.001*
No	1		1	
Yes	12.443 (5.276~29.346)		11.233 (4.647~27.155)	
Underwear washing method		*0.012*		0.062
No	1		1	
Yes	9.292 (1.621~53.275)		7.038 (0.906~54.659)	
Pad use in pregnancy		0.104		
No	1			
Yes	0.407 (0.138~1.203)			
Educational level		0.260		
University or above	1			
College or less	1.617 (0.701~3.730)			
Age		0.177		
≤ 30	1			
≥ 31	1.749 (0.777~3.937)			

Italicized values indicate statistical significance

Table 4 Pregnancy outcomes of women with single AV and normal vaginal microbiota

	AV *n* (%)	Control *n* (%)	χ^2	*P* value
PROM			8.829	*0.003*[b]
Yes	7 (26.9)	32 (7.8)		
No	19 (73.1)	380 (92.2)		
pPROM			–	0.265[a]
Yes	1 (3.8)	4 (1.0)		
No	25 (96.2)	408 (99.0)		
PTB			1.407	0.236[b]
Yes	3 (11.5)	18 (4.4)		
No	23 (88.5)	394 (95.6)		
Low birth weight			–	0.155[a]
Yes	2 (7.7)	10 (2.4)		
No	24 (92.3)	402 (97.6)		
Neonatal asphyxia			–	0.059[a]
Yes	2 (7.7)	5 (1.2)		
No	24 (92.3)	407 (98.8)		
Stillbirth			–	1.000[a]
Yes	0 (0.0)	1 (0.2)		
No	26 (100.0)	411 (99.8)		
Delivery mode			0.111	0.740
Vaginal delivery	12 (46.2)	204 (49.5)		
Cesarean section	14 (53.8)	208 (50.5)		

Italicized values indicate statistical significance; a indicates Fisher exact test; b indicates adjusted chi-square analysis

the uterus increases as gestation progresses, compressing the digestive tract. Increased rectal venous pressure and the presence of food residues in the digestive tract for a longer time may lead to constipation, new onset of external hemorrhoids, or aggravation of existing external hemorrhoids. Hemorrhoids in pregnancy are very common [15]. Meanwhile, the microorganisms colonizing the digestive tract may spread locally and cross-colonize the vagina when the rectal mucosa is exposed to the perineum in women with external hemorrhoids.

As the most dominant cause of neonatal morbidity and mortality worldwide, PTB is still a great challenge for obstetricians [16, 17]. According to the latest statistics on Chinese national and subnational all-cause and cause-specific child mortality, PTB was the second leading cause of mortality [18]. Infection commonly accounts for 40–50% of PTBs [19]. In 2009, Donders et al. showed that AV was associated with PTB [20]. The presence of AV during the first trimester was associated with a shorter cervix at 20–24 weeks and 30–34 weeks and may be a risk factor for PTB [21]. Furthermore, AV has been shown to be involved in the pathogenesis of chorioamnionitis and fetal funisitis by elevating vaginal interleukin-1, interleukin-6, and interleukin-8 levels and by activating other unknown complicated pathways [20, 22].

The most frequently isolated pathogenic bacteria in AV include *Enterococcus faecalis*, *Streptococcus agalactiae*, *Escherichia coli*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* [3,]. In our study, *Enterococcus faecalis* and *Staphylococcus epidermidis* are commonly isolated in AV patients, though cases are limited.

Streptococcus agalactiae and *Escherichia coli*, which are common pathogens isolated in AV [23], are also commonly found in subclinical intrauterine infections associated with PTB [24]. The observed rate of PROM in pregnant women with AV in our study was higher than that in control participants. Ascending infection caused by vaginal pathogens might explain the mechanism of AV-related adverse pregnancy outcomes. Lower genital tract infections can spread into the upper genital tract through the vagina and cervical canal. Although the cervical mucus plug can inhibit the passage of ascending pathogens from the vagina during pregnancy, it cannot entirely prevent this process [25]. Maternal and fetal responses to intrauterine infections include immune reactions in the fetal membranes, synthesis of prostaglandins, and release of metalloproteases. Ultimately, weakened chorionic amniotic membranes induce cervical ripening and uterine contractions may promote premature birth and result in preterm delivery [19].

To date, though AV is notorious, no consensus on the optimal treatment for AV in pregnant or nonpregnant women has been published. Clindamycin, which is a broad-spectrum antibiotic, may be a treatment option for preventing infection-associated PTB [26, 27]. Topical formulations of kanamycin, which have good intestinal activity against Gram-negative bacteria and natural inactivity against lactobacilli, have been confirmed to have therapeutic efficacy for AV [28, 29]. Our previous case-control study showed that moxifloxacin may be a potential first-line treatment for AV in nonpregnant women [30]. Safe and sensitive antibiotics selected by bacterial culture and drug susceptibility testing should be included in targeted and individualized AV treatment. Recently, the role of probiotics in maintaining vaginal health has been widely investigated. Women with abnormal vaginal flora may benefit from either oral or vaginal use of probiotics [31–33]. Further investigation of the management and treatment of AV is warranted.

In conclusion, vaginal infections are more common during pregnancy than nonpregnancy period. AV, which is a common form of vaginal infection during pregnancy, is associated with a high incidence of PROM. Personal hygiene habits may play a vital role in the pathogenesis of AV. Vaginal microbiota screening may potentially contribute to the improvement of pregnancy outcomes and reduction in PTB, PROM and other adverse pregnancy outcomes.

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Compliance with ethical standards

All authors have read and have abided by the statement of ethical standards for manuscripts submitted to "European Journal of Clinical Microbiology & Infectious Diseases". The study was reviewed and approved by the ethical committee of Tianjin Medical University General Hospital, and the participants were enrolled into the study after obtaining their written informed consent.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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