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Original Article

Perinatal group A streptococcal infection in vagina and its impact on pregnancy outcomes

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Abstract: Objective: To investigate the prevalence, antimicrobial susceptibility, and the effects on pregnancy and neonatal outcomes of Group A Streptococcal (GAS) infections in the vagina of perinatal women. Methods: From June 2020 to October 2022, 270 perinatal pregnant women underwent vaginal swabs for GAS culture. The antibiotic sensitivity of the positive strains was assessed. Based on GAS detection results, the patients were divided into an observation group (GAS positive) and a control group (GAS negative). Clinical data from both groups were collected to compare the vaginal microecological changes. The adverse outcomes for pregnancy and infants in both groups were retrospectively analyzed. Univariate and multivariate analyses were used to identify the risk factors for adverse outcomes. Results: Among the 270 pregnant women, 30 tested positive for GAS and 240 tested negative, with a colonization rate of 11.1%. No resistance to penicillin, ampicillin, linezolid, vancomycin, or tigecycline was found among the GAS strains. The resistance rates to tetracycline and clindamycin were 73.3% and 70.0%, respectively. Higher vaginal pH (≥4.5), and increased incidences of bacterial vaginitis, aerobic vaginitis, and microecological imbalances were observed in the observation group compared to the control group (all $P<0.05$). The observation group also experienced more adverse pregnancy and infant outcomes, such as chorioamnionitis, postpartum infections, fetal distress, and neonatal pneumonia (all $P<0.05$). Univariate and multivariate analyses indicated that a vaginal pH≥4.5 and microecological imbalance were positively associated with poor maternal and infant outcomes in women with GAS infections (all $P<0.05$). Conclusions: The study found no β-lactam resistant GAS strains. Additionally, a higher vaginal pH (≥4.5) and microecological imbalance were linked to an increased risk of adverse pregnancy and infant outcomes in women with GAS infections.

Keywords: Group A streptococcus, late pregnancy, drug sensitivity, vaginal microecology, adverse maternal and infant outcomes

Introduction

With the widespread use of antibiotics, the incidence of Group A Streptococcus (GAS) infections initially showed a decline. However, due to changes in bacterial drug resistance and virility, the rate of GAS infections has been on the rise in recent years, particularly invasive GAS infections, which have seen an incremental increase. Notably, the mortality rate of such infections can reach as high as 5% to 10% [1]. Recent years have witnessed a surge in reports of adult GAS infections, particularly among pregnant and postpartum women, especially during the perinatal period. The progression of GAS infections in pregnant women is rapid, with a significantly high mortality rate for both mothers and infants, thus becoming a focal point of research in obstetrics and gynecology [2]. Pregnant women and those in the postpartum period are considered high-risk groups for GAS infections. A study showed that, compared to non-pregnant women, the risk of invasive GAS infections is 20 times higher in pregnant and postpartum women [3], with mortality rates being higher for those who contract the infection before, during, or within 12 hours after delivery, compared to those who contract it later. This poses a direct threat to the lives of both mothers and infants and remains a leading cause of maternal deaths [4]. The immune function of pregnant women is compromised, characterized by reduced numbers and activity of lymphocytes, suppressed cellular and

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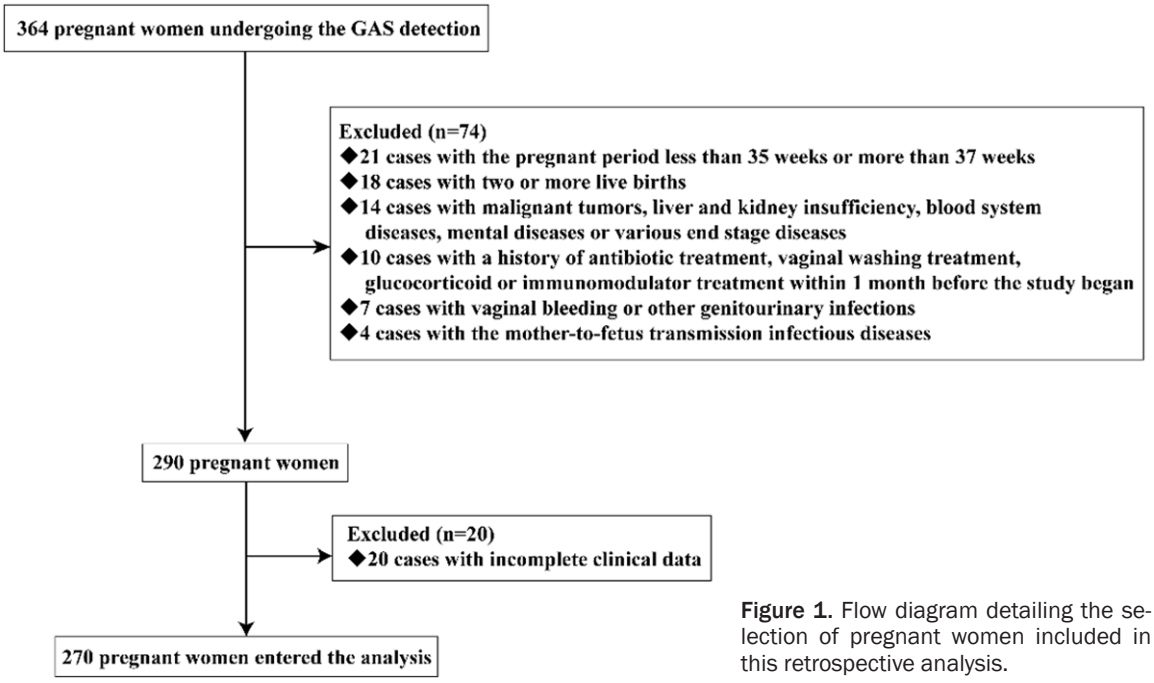

Figure 1. Flow diagram detailing the selection of pregnant women included in this retrospective analysis.

humoral immunity, and increased uterine blood flow in late pregnancy, all of which provide an ideal environment for GAS growth and reproduction. The condition of mothers and infants suffering from streptococcal toxic shock syndrome (STSS) in the third trimester is notably more severe than in earlier stages of pregnancy or the postpartum period [5]. Therefore, early identification, diagnosis, and treatment of GAS infection are crucial to reduce maternal and fetal mortality and improve outcomes.

To date, there is a lack of effective clinical evidence regarding vaginal GAS infections in pregnant women, with few studies exploring the impact of such infections on pregnancy outcomes. Based on this context, this clinical research was designed to explore the prevalence, antimicrobial susceptibility, and the effects on pregnancy and neonatal outcomes of GAS infections in the vaginas of perinatal women. This study is of significance to provide references for the prevention and treatment of vaginal GAS infections in pregnant women within China.

Materials and methods

Study design and subjects

This research had been approved by the Ethics Committee of Jinan Maternal and Child Health Hospital (Approval No. 2020-018) and was structured as a retrospective cohort study. As illustrated in **Figure 1**, through the electronic medical record system, 270 perinatal pregnant patients admitted to the Department of Obstetrics and Gynecology at Jinan Maternal and Child Health Hospital between June 2020 and October 2022 were selected according to the following inclusion criteria: (1) Gestational age between 35 and 37 weeks. (2) Singleton live birth. (3) Complete medical records, including current and past medical history, laboratory and imaging results. Exclusion criteria: (1) Patients with malignant tumors, liver and kidney failure, hematologic disorders, psychiatric disorders, or various terminal illnesses. (2) Patients who had received antibiotics, vaginal douching treatments, glucocorticoids, or immunomodulators within one month prior to admission. (3) Patients presenting with vaginal bleeding or other genitourinary infections. (4) Patients with infectious diseases transmissible from mother to fetus, such as syphilis, human immunodeficiency virus, and hepatitis B virus. All the procedures were conducted by the same medical team. Based on the results of perinatal GAS screening, included patients were divided into two groups: the control group, comprising pregnant women with negative GAS results, and the observation group, consisting of pregnant women who tested positive for GAS.

Data collection

The primary outcomes included GAS prevalence and adverse maternal and neonatal outcomes, while the secondary outcomes included general information of the pregnant women and vaginal microbiota imbalance.

The general data of eligible pregnant women, including age, gestation, gravida, body mass index (BMI), parity, history of miscarriages, gestational diabetes mellitus, and gestational hypertension were collected from the patient records.

Information regarding vaginal GAS infection was also extracted from the medical records, including GAS detection outcomes and the antimicrobial susceptibility of GAS. In additional, conditions indicative of vaginal microbiota imbalance, such as vaginal pH of 4.5 or higher, vulvovaginal candidiasis, bacterial vaginosis, aerobic vaginitis, and vaginal microecology imbalance, along with adverse maternal and infant outcomes (e.g., neonatal pneumonia, postpartum infection, fetal distress, and chorioamnionitis), were documented. For patients diagnosed with vaginal microbiota imbalance or experiencing adverse maternal and infant outcomes, two experienced obstetrician & gynecologists further checked the medical records to confirm the accuracy of the diagnosis following the aforementioned validated criteria.

Methods for GAS detection

The pregnant women were positioned supine for the procedure. Following the cleaning of vulvar secretions, a sterile swab was rotated once in the lower third of the vagina to collect a sample of vaginal secretion. The swab was then placed in a sterile test tube for storage and immediately transported to the microbiological laboratory for analysis. The collected samples were inoculated onto GAS-specific color plates and incubated in a constant temperature incubator with 5% CO_2 at 37°C for 24-48 hours. Subsequently, colonies suspected of being GAS were transferred to the target plate of a mass spectrometer. After treatment with formic acid and matrix solution, the TSQ Fortis type mass spectrometer (Thermo Fisher Scientific, Germany) was utilized for mass spectral identification. Colonies positively identified by mass spectrometry were further cultured on Colombian blood agar plates within the constant temperature incubator with 5% CO_2 at 37°C for 24-48 hours for purification. A single purified colony was selected and adjusted to a concentration of 0.5-0.62 McFarland units. Antimicrobial susceptibility testing of the isolated and identified GAS strains was conducted using the Kirby-Bauer disk diffusion method. The quality control strain used was Staphylococcus aureus ATCC 25923. Interpretation of the antimicrobial susceptibility test results was based on the Chinese Expert Consensus on the Specification of Antimicrobial Susceptibility Testing Reports for Common Bacteria. The diagnostic criteria for genital tract GAS infection adhered to the Expert Consensus on the Prevention of Perinatal Group A Streptococcosis (China), as established by the Perinatal Medicine Branch of the Chinese Medical Association and the Obstetrics Group of the Gynecology and Obstetrics Branch of the Chinese Medical Association [6].

Examination of vaginal microbiota

The conditions of vaginal microbiota imbalance were compared between the two groups. The assessment of vaginal microbiota was categorized into three sections as follows [7]: (1) Dry chemistry analysis involved the measurement of pH value, catalase presence, leukocyte esterase, and sialidase activity; (2) Wet mount microscopy was utilized to inspect the samples for Trichomonas, Candida, spores, white blood cells, epithelial cells, and to assess aerobic vaginitis; (3) Following the drying and fixation of vaginal discharge smears, the bacterial community characteristics of the specimens, including the proportion of lactobacilli, bacterial density, microbial diversity, and Nugent scores, were evaluated under an oil immersion microscope after Gram staining. Moreover, the microecological status of the specimen was examined. The evaluation criteria for vaginal microbiota were based on the Expert Consensus on Clinical Application of Vaginal Microecology Evaluation (2016 edition) and the Diagnosis and Treatment Guidelines for Bacterial Vaginitis (2021 revised edition) issued by the Obstetrics and Gynecology Branch of the Chinese Medical Association [8]. A balanced vaginal microbiota was characterized by a Lactobacillus proportion of ≥70%, other miscellaneous bacteria

<30%; microbial intensity at levels II-III; microbial diversity at levels II-III; white blood cells ranging from 0 to 10, with no pus cells or other specific pathogens per high power field. Vaginal microbiota imbalance was defined as any deviation or presence of pathogens regarding the intensity, diversity, predominant bacteria, white blood cell count, and pH value in vaginal secretions.

Adverse maternal and infant outcomes

According to previous reports [9], the adverse maternal and infant outcomes were evaluated. The diagnostic criteria for chorioamnionitis, puerperal infection, fetal distress, and neonatal pneumonia are detailed as follows: (1) Diagnosis of chorioamnionitis was considered when pregnant women exhibited a body temperature of ≥37.8°C, pulse rate of ≥100 beats/min, fetal heart rate of ≥160 beats/min, tenderness in the uterine fundus, odor in vaginal secretions, and a peripheral white blood cell count of ≥15 × 10^9/L, especially when an increase in body temperature was accompanied by two or more of these symptoms. (2) Puerperal infection was diagnosed when, 12 hours postpartum, the average body temperature of increased to ≥38°C, accompanied by swelling and pain in the surgical wound or perineum, odor in vaginal secretions, the detection of pathogenic bacteria in blood or secretion cultures, and tenderness in the uterine fundus. (3) Fetal distress is identified by late-phase fetal heart rate deceleration, variable deceleration, or lack of variation in the baseline. (4) Neonatal pneumonia was considered when newborns exhibited symptoms within 24 hours after birth, accompanied with a history of asphyxia. After resuscitation, the patients may experience shortness of breath, grunting, breathing difficulties, unstable body temperature, poor responsiveness, coarse and moist lung sounds, and in severe cases, respiratory failure, heart failure, disseminated intravascular coagulation, or shock.

Statistical analysis

Data analysis in this research were conducted using SPSS software, version 23.0 and GraphPad Prism version 8.0.1. Measurement data were expressed as Mean ± Standard deviation. The independent t-tests were used for intergroup comparison. Count data were expressed in percentages or cases, and χ^2 tests were used for intergroup comparisons. Both univariate and multivariate analyses were conducted to evaluate risk factors for adverse maternal and infant outcomes in perinatal pregnancy patients with GAS infections. Univariate analysis covered factors such as vaginal pH, bacterial vaginosis, aerobic vaginitis, and microecological imbalance. Variables that show a significant difference association with prognosis were further analyzed in multivariate logistic regression models using the forward LR method to identify significant risk factors for adverse maternal and infant outcomes in perinatal pregnancy patients with GAS infections. P<0.05 indicated a statistically significant difference.

Results

General data

The general information of the 270 eligible patients in this study are presented in **Table 1**. Out of the 270 pregnant women, 30 tested positive for GAS and 240 negative, resulting in a colonization rate of 11.1%. According to the GAS results, the patients were divided into an observation group (GAS positive) and a control group (GAS negative). No significant differences were observed in age, gestational age, gravidity, body mass index (BMI), parity, history of abortion, gestational diabetes mellitus, and gestational hypertension between the two groups (all P>0.05), ensuring comparability between the two groups.

Antimicrobial sensitivity

The antimicrobial sensitivity testing in **Table 2** revealed 100% sensitivity of the GAS strains to penicillin, ampicillin, linezolid, vancomycin, and tigecycline, indicating no resistance to these antibiotics within the GAS strains. Resistance rates to tetracycline and clindamycin were notably high, at 73.3% and 70.0%, respectively. Sensitivity to Macrodantin exceeded 85%, while sensitivities to ciprofloxacin, levofloxacin, and moxifloxacin stood at 50%.

Vaginal microbiota imbalance

As show in **Table 3**, in the control group, there were 60 (25.0%) cases with a vaginal pH≥4.5, 9 (3.8%) cases of vulvovaginal candidiasis, 10

Table 1. General information of the pregnant women included in this study

Parameters		Control group (N=240)	Observation group (N=30)	χ^2/t value	*P* value
Age (years)		28.7±2.6	28.4±2.9	0.588	0.557
Gestation weeks		36.7±0.9	36.9±0.8	1.161	0.247
Gravidity (Times)		1.8±1.0	1.9±1.0	0.516	0.606
BMI (kg/m^2)		26.5±2.9	26.7±3.0	0.355	0.723
Parity (Cases)	Primiparity	198	25	0.013	0.910
	Multiparity	42	5		
History of misccarige (Cases)		34	4	0.508	0.476
Gestational diabetes mellitus (Cases)		25	3	0.324	0.569
Gestational hypertension (Cases)		22	3	0.117	0.732

BMI: body mass index.

Table 2. Antimicrobial sensitivity (%)

Antibacterial agents	Effects		
	Sensitivity	Intermediate	Resistance
Penicillin	100.0	0.0	0.0
Linezolid	100.0	0.0	0.0
Ampicillin	100.0	0.0	0.0
Vancomycin	100.0	0.0	0.0
Tetracycline	26.7	0.0	73.3
Tigecycline	100.0	0.0	0.0
Clindamycin	30.0	0.0	70.0
Ciprofloxacin	50.0	20.0	30.0
Moxifloxacin	56.7	20.0	23.3
Macrodantin	86.7	10.0	3.3
Levofloxacin	50.0	23.3	26.7

(4.2%) cases of bacterial vaginosis, 70 (29.2%) cases of aerobic vaginitis, and 136 (56.7%) cases of vaginal microecology imbalance. In contrast, the observation group had 15 (50.0%) cases with a vaginal pH≥4.5, 3 (10.0%) cases of vulvovaginal candidiasis, 4 (13.3%) cases of bacterial vaginosis, 3 (10.0%) cases of aerobic vaginitis, and 9 (30.0%) cases of vaginal microecology imbalance. No differences were found in the occurrence of vulvovaginal candidiasis between the two groups. However, the occurrences of bacterial vaginitis (P=0.033), aerobic vaginitis (P=0.026), and microecological imbalance (P=0.006) were significantly higher in the observation group than those in the control group.

Adverse maternal and infant outcomes

As depicted in **Table 4**, in the control group, there were 9 (3.8%) cases of neonatal pneumonia, 14 (5.8%) cases of puerperal infection, 4 (1.7%) cases of fetal distress, and 5 (2.1%) cases of chorioamnionitis, while in the observation group, there were 4 (13.3%) cases of neonatal pneumonia, 7 (23.3%) cases of puerperal infection, 6 (20.0%) cases of fetal distress, and 3 (10.0%) cases of chorioamnionitis. The incidence rates of neonatal pneumonia (P=0.021), puerperal infection (P=0.010), fetal distress (P<0.001), chorioamnionitis (P=0.041) and total adverse maternal and infant outcomes (P<0.001) in the observation group were significantly higher than those in observation group (all P<0.05).

Univariate and multivariate analyses factors affecting the prognosis

In the observation group, there were 10 patients with a good prognosis and 20 with a poor prognosis. **Table 5** shows the results of the univariate analysis, indicating that a vaginal pH≥4.5 and vaginal microecology imbalance were associated with adverse maternal and infant outcomes. Further, as detailed in **Table 6**, a vaginal pH≥4.5 (P=0.006) and vaginal microecology imbalance (P=0.002) were identified as independent risk factors for adverse maternal and infant outcomes in perinatal pregnancy patients with GAS infections.

Discussion

The vaginal microbiota is a complex system. The normal vaginal microbiota is dominated by lactobacilli, which could compete with other pathogenic bacteria for nutrients and space to dynamically maintain the balance of the vaginal microbiota. However, in the late stages of preg-

Table 3. Comparison of vaginal microbiota imbalance between two groups [n (%)]

Groups	PH≥4.5	Vulvovaginal candidiasis	Bacterial vaginosis	Aerobic vaginitis	Vaginal microecology imbalance
Control group (N=240)	60 (25.0)	9 (3.8)	10 (4.2)	70 (29.2)	136 (56.7)
Observation group (N=30)	15 (50.0)	3 (10.0)	4 (13.3)	3 (10.0)	9 (30.0)
χ^2 value	8.308	2.453	4.558	4.966	7.627
P value	0.004	0.117	0.033	0.026	0.006

Table 4. Comparison of adverse maternal and infant outcomes between two groups [n (%)]

Groups	Neonatal pneumonia	Puerperal infection	Fetal distress	Chorioamnionitis	Total adverse outcomes
Control group (N=240)	9 (3.8)	14 (5.8)	4 (1.7)	5 (2.1)	32 (13.3)
Observation group (N=30)	4 (13.3)	7 (23.3)	6 (20.0)	3 (10.0)	20 (66.7)
χ^2 value	5.344	6.727	17.700	3.738	48.780
P value	0.021	0.010	<0.001	0.041	<0.001

Table 5. Univariate analysis of adverse maternal and infant outcomes in pregnant women [n (%)]

Parameters	Good prognosis (N=10)	Poor prognosis (N=20)	χ^2 value	*P* value
Vaginal pH			6.696	0.010
<4.5	8 (80.0)	6 (30.0)		
≥4.5	2 (20.0)	14 (70.0)		
Bacterial vaginosis			0.480	0.488
Yes	1 (10.0)	4 (20.0)		
No	9 (90.0)	16 (80.0)		
Aerobic vaginitis			0.085	0.770
Yes	3 (30.0)	5 (25.0)		
No	7 (70.0)	15 (75.0)		
Microecological imbalance			18.370	<0.001
Yes	1 (10.0)	18 (90.0)		
No	9 (90.0)	2 (10.0)		

Table 6. Multivariate analysis of adverse maternal and infant outcomes in pregnant women [n (%)]

Parameters	Coefficients	Standard error	Wald	*P* value	OR (95% CI)
Vaginal pH≥4.5	2.204	0.687	7.911	0.006	5.385 (2.128-10.057)
Microecological imbalance	3.896	0.754	12.687	0.002	7.310 (4.629-15.127)

nancy, hormonal fluctuations, diminished immune function, and increased vaginal discharge and moisture can foster pathogen proliferation, resulting in the changes of vaginal flora. The dynamic balance and interaction of vaginal microbiota are crucial for maintaining vaginal health. It was reported that vaginal mucosal edema and congestion in late pregnancy may increase the risk of GAS infection in the reproductive tract [10]. Previous research has indicated that the GAS infection rate among perinatal pregnant women in China varies from 3.5% to 9.7% [11]. This study found a GAS infection rate of 11.1% in the reproductive tract of perinatal pregnant women in our hospital, which is different from the results from other centers. It may be due to differences in specimen collection, detective methods, subject selection, etc. Many studies have revealed that GAS's potent adhesion and penetration capabilities on fetal membranes, leading not only to inflammation, but also to the downregulation of

keratin expression, which is vital for maintaining the cytoskeleton [12]. Recently, there is an increasing awareness of pregnancy related diseases caused by GAS. Investigating the colonization rate of GAS in the vaginas of late-term pregnant women in late pregnancy, the current resistance profile of GAS-positive strains, and the pregnancy outcomes can provide evidence for antibiotic application in clinical practice, promoting their rational use and preventing adverse pregnancy outcomes.

In this study, antimicrobial susceptibility testing revealed that GAS strains showed no resistance to penicillin and ampicillin, which remain the drugs of choice for the treatment of GAS-related pregnancy diseases. Although no resistance was observed for linezolid, vancomycin, and tigecycline, their use as first-line prophylactic agents is discouraged due to potential adverse drug reactions, toxic side effects, and risks to maternal and neonatal safety. Some research supports the effectiveness of penicillin and ampicillin in the prevention and treatment of GAS-related conditions. Others studies also demonstrated that the use of these drugs was effective in preventing GAS-related diseases, particularly noting a significant impact on preterm birth, with patients in the GAS-positive group experiencing improved maternal and neonatal outcomes following antimicrobial intervention [13].

In this study, no significant differences were observed in general data, such as age, gestation period, gravidity, BMI, parity, history of miscarriage, gestational diabetes mellitus, and gestational hypertension. However, the rates of vaginal pH≥4.5, bacterial vaginosis, aerobic vaginitis, and vaginal microbiota imbalance in GAS-positive patients (observation group) were significantly higher than those in the control group. This finding suggests a positive correlation between GAS infections in the vagina and the occurrence of the disorders and imbalances within the vaginal microbiota. Lactobacillus, as a dominant bacterium in vagina, could protect the host from reproductive tract infections. A decrease in lactobacilli can lead to rapid growth of other bacterial communities [14]. Aerobic vaginitis, caused by aerobic bacteria, could lead to miscarriage, premature rupture of membranes, chorioamnionitis, and premature birth [15]. Bacterial vaginosis is a mixed infection caused by dysbiosis of the normal vaginal flora, which could reduce lactobacilli, causing an imbalance in the vaginal microenvironment and increasing the proliferation of microorganisms [16]. Some scholars revealed that GAS reproduction increased the permeability of vaginal epithelium, making it more susceptible to damage and infection in the uterus [17].

Antibiotics have commonly been used for treating and managing imbalances in the vaginal microbiota during pregnancy. Ventimiglia et al. [18] found that probiotics could be used to restore balance to the vaginal microbiota of pregnant women and improve pregnancy outcomes when the imbalance was caused by lactobacilli deficiency and bacterial vaginosis. Another study indicated that administering lactobacilli to pregnant women effectively eliminated GAS colonization in the vagina [19]. Therefore, intervening in case of ecological imbalance during pregnancy is crucial for reducing the risk of adverse maternal and infant outcomes.

Adverse pregnancy outcomes in GAS-positive perinatal women include premature rupture of membranes, premature birth, chorioamnionitis, postpartum hemorrhage, puerperal infections, etc. These conditions may also lead to a series of GAS-related complications, such as urinary tract infections, nephritis, postpartum intrauterine inflammation, mastitis, and even osteomyelitis. The pathogenic mechanism of GAS infections in perinatal pregnant women involves the direct invasion of fetal membranes by producing a significant quantity of metabolites and enhancing the phagocytic activity of inflammatory cells, coupled with the physiological characteristics of pregnancy. This process can weaken the local integrity of the membrane, causing severe damage to fetal membrane tissues. Consequently, it leads to the premature rupture of membranes, ascending infections, and adverse outcomes, including infections within the amniotic cavity, preterm birth, and potentially miscarriage or stillbirth [20]. GAS infection in perinatal pregnant women poses a significant risk to neonatal health, capable of causing intrauterine and neonatal infections that lead to adverse pregnancy outcomes, and in the most severe cases, threatening the lives of newborns. GAS strains with strong virulence could attack vascular endothe-

lium, vaginal wall tissue, and chorionic villi. In vitro studies have confirmed that GAS strains exhibit stronger adsorption and penetration capabilities on chorionic villi compared to Escherichia coli and Neisseria gonorrhoeae. These strains can breach the fetal membrane, invade the uterine cavity, infect the fetus, and ultimately lead to miscarriage or stillbirth [21]. The results of this study showed that the overall incidence of adverse pregnancy outcomes was significantly higher in the observation group at 66.7% compared to 13.3% in the control group. Specifically, the incidence rates of puerperal infection and fetal distress were elevated in the observation group, at 23.3% and 20.0%, respectively. Univariate and multivariate analyses found that the pH value and imbalance of vaginal microbiota were risk factors that caused adverse pregnancy outcomes in late pregnancy in pregnant women with GAS infections, thereby threatening maternal and neonatal health. These findings align with those of previous study [22].

This study acknowledges several limitations. Firstly, the small sample size suggests potential underpowering of the research. Secondly, being a retrospective study, the scope of available information was limited. Thirdly, the absence of subgroup analysis and mechanistic studies constrains the comprehensiveness of the findings. To achieve more scientifically robust results, future research should adopt a multi-center, randomized controlled study design.

In summary, there was a notable incidence rate of GAS infection in the vagina of pregnant women, which is linked to an increased risk of adverse pregnancy outcomes. This risk is associated with the vagina pH value and imbalance of vaginal microbiota. Timely intervention targeting these risk factors is essential for minimizing the occurrence of adverse maternal and infant outcomes.

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Disclosure of conflict of interest

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