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Original Article

Metronidazole plus lacidophilin vaginal capsules for vaginitis and its effects on pregnancy outcomes in pregnant women

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Abstract: Objective: To explore the therapeutic effects of metronidazole in combination with lacidophilin vaginal capsules in pregnant women with vaginitis and its impacts on pregnancy outcomes in these women. Methods: Pregnant women who had been treated for vaginitis (n=110) in the outpatient department of Obstetrics and Gynecology were recruited into the study and randomly assigned to the observation group or the control group. Pregnant women in the control group received the clinically common metronidazole treatment, while those in the observation group were given lacidophilin vaginal capsules combined with metronidazole. The treatment effects on vaginitis and pregnancy outcomes in the pregnant women were observed and assessed at 7 days. Results: Compared with the control group, the observation group had significantly lower scores for increased leucorrhea, vaginal pruritus and urinary frequency and urgency; greater improvements in vaginal lavage fluid IL-2 (Interleukin-2), IL-8 (Interleukin-8) and IL-13 (Interleukin-13) expression, and vaginal pH values; a higher response rate of treatment, a lower recurrence rate; a lower incidence of adverse pregnant outcomes and a higher satisfaction rate from pregnant women (all $P<0.05$). Conclusion: The results showed that metronidazole in combination with lacidophilin vaginal capsules was effective in treating vaginitis. The regimen maintained the acid-base balance in the vagina, and improved pregnancy outcomes.

Keywords: Metronidazole, lacidophilin vaginal capsule, vaginitis, pregnancy outcome

Introduction

Vaginitis, a common gynecological disease, may induce abnormal secretions, pruritus and pain in the vagina of pregnant women. A small number of pregnant women with vaginitis develop symptoms of urinary tract infections, and even premature delivery in a severe conditions [1]. Metronidazole is the primary medication for vaginitis. However, metronidazole not only kills bacteria, but also prevents the normal vaginal flora from reproducing normally in pregnant women, thereby reducing the inherent resistance of the vagina itself [2]. Additionally, this conventional medication has potential adverse effects on both pregnant women and their fetuses. Hence, a major concern for medical staff is to find a high-quality method as quickly as possible for treatment of vaginitis in pregnant women.

The addition of lacidophilin vaginal capsules to metronidazole has been shown to have a better therapeutic effects. Metronidazole is a representative agent for the treatment of trichomonas vaginitis. It does inhibit the propagation of normal flora in the vagina. However, it also kills trichomonas and reduces the number of lactobacilli in the vagina, leading to a weak vaginal defense ability, poor long-term efficacy, and recurrence of the disease [3].

In the treatment of vaginitis during pregnancy, we need to not only consider the effectiveness of drugs, but also try to prevent any adverse effect of the drugs on the fetus. Metronidazole is a class B drug for women in pregnancy. There is no evidence that metronidazole has a teratogenic or mutagenic effect on early the embryo, but metronidazole is not recommended for use in women in the first trimester of pregnancy [4].

Recent studies have demonstrated that the use of low-dose metronidazole is safe in women in the second and third trimesters of pregnancy [5]. The live lactobacillus capsule is a new formulation of live lactobacilli. After administration, the live lactobacillus capsule is attached to the vagina where the lactobacilli rapidly propagate untill they restore a dominant ratio in the vagina and the microbial barrier of the vagina is reestablished. In this way, a great number of organic acids including lactic acid and acetic acid are produced to maintain an acidic microenvironment and improve the colonization resistance of the vaginal epithelium in the vagina, inhibit trichomonas from attaching to vaginal mucosa, improve cleanness and self-purification of the vagina and restore the microecological balance in the vagina [6]. Meanwhile, lactobacilli activate the local immune function of the vaginal mucosa and inhibit bacteria and trichomonas vaginalis infections [7]. Li and colleagues found that the combination of lacidophilin vaginal capsules and metronidazole was effective in the treatment of pregnant women with BV (bacterial vaginosis) and resulted in a lower rate of recurrence, but they did not observe and evaluate the impact of the regimen on pregnancy outcomes and its safety profile in the study [8]. Therefore, this study was designed to further explore the effects of the regimen in the treatment of vaginitis, and the details are described as below.

Materials and methods

General data

Pregnant women who had received treatment for vaginitis (n=110) in the outpatient department of Obstetrics and Gynecology in Yuncheng Central Hospital from November 2018 to November 2019 were enrolled in this study. Pregnant women were randomly assigned to the observation group or the control group. After a one-week treatment, the pregnant women in both groups were evaluated for the treatment effects. This study was approved by the Ethics Committee of Yuncheng Central Hospital, and written informed consent was obtained from all pregnant women or their families.

Pregnant women in the control group ranged in age from 22 to 38 years old, with a mean age of 30.2±3.5 years; they had a gestational age of 21 to 33 weeks (mean, 27.0±3.0 weeks), and a disease course of 5 days to 2 months (mean, 1.1±0.3 months). Pregnant women in the observation group had an age of 22 to 38 years (mean, 30.2±4.0 years), a gestational age of 20 to 32 weeks (mean, 27.0±3.2 weeks), and a course of disease of 4 days to 2 months (mean, 1.0±0.3 months).

Methods

Each pregnant woman in the control group placed one pill of metronidazole (Zhejiang DND Pharmaceutical Co., Ltd., specification: 0.2 g per pill) into the vagina before going to bed each night, and continued the regimen for one week.

In contrast, pregnant women in the observation group were required to take metronidazole plus live lactobacillus capsules. Each woman placed one pill of metronidazole and two live lactobacillus capsules (Inner Mongolia Shuangqi Pharmaceutical Co., Ltd., specification: 0.25 g per pill) into the vagina before going to bed each night for one consecutive week.

Outcome measures

Eligible pregnant women were evaluated for the changes in the levels of inflammatory cytokines and pH values in vaginal lavage fluid. First, vaginal lavage fluid was collected from each pregnant woman before and after treatment. After that, the levels of IL-2 (Interleukin-2), IL-8 (Interleukin-8) and IL-13 (Interleukin-13) in the vaginal lavage fluid were tested by radioimmunoassay, while pH values were measured using vaginal pH test paper [9].

The treatment effects of pregnant women were evaluated according to the following criteria: cured (disappearance of such symptoms as increased leucorrhea, pruritus and malodor in the vagina, and a negative result of the trichomonas vaginalis test), significantly effective (substantial improvement of clinical symptoms, and a weak positive result of the trichomonas vaginalis test) and ineffective (insignificant improvement or even aggravation of symptoms and signs, and a positive result of the trichomonas vaginalis test). The overall response rate of treatment was equal to the sum of cured rate and effective rate [10].

Table 1. Major symptom scores of pregnant women ($\bar{x}$ ± sd)

Project	Observation group (n=55)	Control group (n=55)	t	P
Increased leucorrhea	0.61±0.14	1.34±0.31	8.452	0.000
Vaginal pruritus	0.45±0.56	1.24±0.37	7.891	0.000
Urinary frequency and urgency	0.43±0.13	1.15±0.38	8.014	0.000

Table 2. Inflammatory cytokines and pH in vaginal lavage fluid of pregnant women ($\bar{x}$ ± sd)

Group	Observation group	Control group	t	P
IL-2 (pg/ml)				
Before treatment	10.49±5.19	10.45±5.02	0.04	0.971
After treatment	9.03±2.56*	9.85±2.49*	2.56	0.010
IL-8 (pg/ml)				
Before treatment	4256.29±334.99	4231.42±351.99	0.26	0.800
After treatment	1752.29±156.32*	2635.09±202.25*	17.27	0.000
IL-13 (pg/ml)				
Before treatment	48.10±12.29	46.20±14.34	0.50	0.622
After treatment	14.40±5.21*	18.29±5.49*	2.51	0.020
PH				
Before treatment	5.59±0.15	5.65±0.13	0.92	0.370
After treatment	4.49±0.55*	5.10±0.52*	4.62	0.000

Note: IL-2: Interleukin-2; IL-8: Interleukin-8; IL-13: Interleukin-13. Compared with before treatment, *P<0.05.

Table 3. Treatment effects of pregnant women (n (%))

Group	Observation group (n=55)	Control group (n=55)	t	P
Cured	32 (58.18)	20 (36.36)		
Significantly effective	21 (38.18)	22 (40.00)		
Ineffective	2 (3.64)	13 (23.64)		
Overall efficiency	53 (96.36)	42 (76.36)	16.978	0.000

Adverse pregnancy outcomes included preterm delivery, premature rupture of fetal membranes and puerperal infection [11].

A self-designed questionnaire (with a total score of 100) was used to investigate the satisfaction degree of pregnant women in the control group and the observation group [12].

Statistical analysis

All the data were analyzed with the use of SPSS statistical software (IBM, USA), version 22.0. Measurement data were tested for normality. Measurement data with normal distribution were represented by mean ± standard deviation ($\bar{x}$ ± sd) and between-group comparisons were performed by the t test. Count data were expressed as cases/percentage (n/%). A *P* value of <0.05 indicated a statistically significant difference.

Results

Major symptom scores of pregnant women

The scores for increased leucorrhea, vaginal pruritus, urinary frequency and urgency of pregnant women in the observation group were significantly lower than those of pregnant women in the control group (P<0.05, **Table 1**).

Inflammatory cytokines and pH in the vaginal lavage fluid of pregnant women

Greater improvement in IL-2, IL-8, and IL-13 expression and pH values in the vagina of pregnant women were observed in the observation group than in the control group (all P<0.05, **Table 2**).

Treatment effects of pregnant women

The response rate of treatment in the observation group was higher than that in the control group (P<0.05, **Table 3**).

Recurrence of pregnant women

Recurrence was observed in fewer pregnant women in the observation group than in the control group (P<0.05, **Table 4**).

Pregnancy outcomes of pregnant women

A lower incidence of adverse pregnancy outcomes was seen in pregnant women in the observation group than those in the control group (P<0.05, **Table 5**).

Table 4. Recurrence of pregnant women (n (%))

Group	Three months	Six months
Observation group (n=55)	2 (3.64)	3 (5.45)
Control group (n=55)	10 (18.18)	15 (27.27)
t	10.875	17.397
P	0.000	0.000

Table 5. Pregnancy outcome of pregnant women (n (%))

Group	Premature	Premature rupture of membranes	Puerperal infection
Observation group (n=55)	1 (1.82)	2 (3.64)	2 (3.64)
Control group (n=55)	8 (14.55)	9 (16.36)	8 (14.55)
t	5.929	4.949	3.960
P	0.014	0.026	0.046

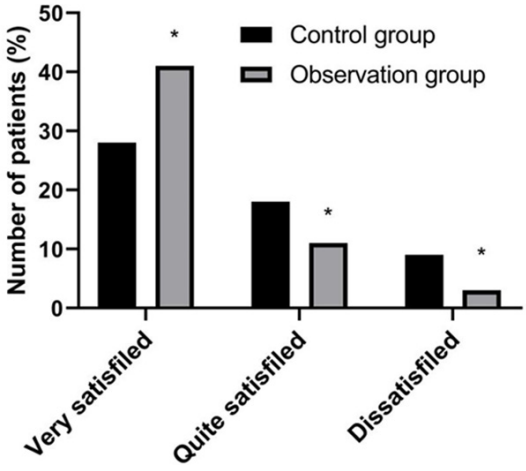

Figure 1. Comparison of patient satisfaction. Compared with the control group, *P<0.05.

Treatment satisfaction of pregnant women

A higher satisfaction rate was seen in pregnant women in the observation group than those in the control group (P<0.05, **Figure 1**).

Discussion

Vaginitis is a common gynecological disease. It occurs more frequently in women during pregnancy. Although vaginitis does not do great harm to pregnant women, it is associated with abnormal secretion, vaginal pruritus and pain. Symptoms of urinary tract infection may occur in some pregnant women with vaginitis, and if the condition is severe enough, premature delivery may also occur. Currently, metronidazole is used as a standard method for treatment of vaginitis. However, a study suggested that metronidazole killed bacteria and prevented normal flora from reproducing in the vagina of pregnant women, which diminished the resistance of the vagina itself [13]. Moreover, this conventional method may cause adverse effects on both pregnant women and their fetus [14, 15].

Previous studies have indicated that live lactobacillus capsules contribute to re-establishment of the microbial barrier in the vagina of pregnant women, inhibiting the onset of vaginitis [16, 17]. In the current study, the symptoms of vaginitis in pregnant women were significantly relieved in the observation group, which were consistent with the results of the study conducted by Chen et al [18].

In the past, metronidazole was primarily used in the treatment of trichomonal vaginitis. Metronidazole prevents systemic or local infection induced by anaerobic bacteria and inhibits the propagation of pathogenic bacteria in the vagina; nevertheless, metronidazole cannot improve the internal environment of the vagina, so it cannot achieve the effect of eradication [19]. Multiple clinical trials have proved that metronidazole has certain therapeutic effect on vaginitis, and the addition of lacidophilin vaginal capsules to metronidazole further significantly decreases the level of inflammatory cytokines in the vagina of pregnant women, and regulates the pH values in the vagina [20, 21]. In this study, the levels of IL-2, IL-8, IL-13 and pH values in the vagina of pregnant women in the observation group were better improved than those of pregnant women in the control group. The overall response rate of the observation group (96.36%) was higher than that of the control group (76.36%).

In this study, 8 cases of preterm delivery, 9 cases of premature rupture of fetal membranes and 8 cases of puerperal infection were observed in the control group; while 1 case of preterm delivery, 2 cases of premature rupture of fetal membranes and 2 cases of puerperal infection occurred in the observation group. The difference between the two groups was statistically significant, suggesting that metro-

nidazole in combination with lacidophilin vaginal capsules resulted in improved pregnancy outcomes in pregnant women with vaginitis compared with metronidazole alone. Moreover, a higher rate of satisfaction was found in pregnant women in the observation group than those in the control group.

In conclusion, the combination of metronidazole and lacidophilin vaginal capsules for the treatment of vaginitis in pregnant women improved the therapeutic effects and pregnancy outcomes compared with metronidazole alone. Thus, metronidazole combined with lacidophilin vaginal capsules is worthy of extensive application.

Disclosure of conflict of interest

None.

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