

## Lactacyd FH as an adjuvant therapy for vulvovaginal infections in Pakistani women: FRESH study, a satisfaction survey

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### Abstract

**Objective:** To demonstrate that adjuvant therapy with lactic acid+lactoserum solution provides satisfactory symptomatic relief and is safe in patients with vulvo-vaginal infections.

**Method:** The open-label survey was conducted at 96 private consultation clinics in 14 cities across Pakistan from May to October 2010, and included consecutive patients >18 years of age with first/recurrent episode of vulvo-vaginal infections, having clinical signs and symptoms of such infections, receiving antibiotics for current infections. Data collected included vulvo-vaginal infection symptoms, baseline history of diabetes and hormone replacement therapy, bimanual examination, and current antibiotic treatment. Follow-up was done at 14 days. Compliance and symptomatic relief, safety (solicited reporting) was noted on day 14 or anytime during the study period.

**Results:** Overall, 919 patients were enrolled. Of these, 842(91.6%) patients completed the study. The mean age was 32.6±8.4 years and 295(35%) were diagnosed to have bacterial vaginosis, 278(33%) vaginal candidiasis, and 126(15%) trichomoniasis. The most commonly used antibiotic was metronidazole in 438(52%) cases. Patients used lactic acid+lactoserum for mean duration of 9.7 4.4 days, twice a day, and reported symptomatic relief by fourth day of application, as assessed by reduction in malodour in 681(80.1%) cases, itching 661(78.5%), burning sensation 652(77.4%), and pain 552(65.6%). Lactic acid+lactoserum was reported to be gentle on skin in 769(91.3%) cases, provide feeling of freshness 727(86.3%), and have mild fragrance 724(85.9%). Overall, 746(88.6%) patients reported satisfaction with lactic acid+lactoserum, and 671(79.7%) patients were willing to use it again. No adverse events were reported.

**Conclusion:** Lactic acid+lactoserum as an adjuvant treatment of vulvo-vaginal infections demonstrated high percentage of satisfaction and safety in Pakistani women.

**Keywords:** Adjuvant, Lactic acid, Lactoserum, Vaginal diseases, Pakistan. (JPMA 66: 521; 2016)

### Introduction

Reproductive tract infections (RTIs), including sexually transmitted infections (STIs), are common and contribute to a large portion of global healthcare burden.<sup>1</sup> The consequences of RTIs/STIs for reproductive health in women can be severe and life-threatening.<sup>1</sup> Vulvovaginal infections (VVI), such as bacterial vaginosis (BV) and trichomoniasis, have been shown to be associated with adverse outcomes of pregnancy, maternal mortality and morbidity, and increased risk of human immunodeficiency virus (HIV) infection.<sup>2,3</sup> Also, women suffering from recurrent episodes of RTIs have significantly lower quality of life and sexual health.<sup>4</sup>

According to a recent study in Pakistan, the total population is approximately 160 million, and 21.6% of this population are women in reproductive age.<sup>5</sup> Earlier studies showed high prevalence of RTIs in Pakistani

women. A study in 300 Pakistani women showed that the prevalence of Chlamydia trichomonitis ranged from 2% in asymptomatic antenatal women to 12% in women attending family planning clinics.<sup>6</sup> As per a community-based study in Pakistan, 23.8% women had VVIs (n=237) by laboratory investigations, including 10.3% BV, 6.8% candidiasis, and 0.6% trichomoniasis.<sup>7</sup>

Vaginal bacterial flora, predominantly Lactobacilli, produces lactic acid, hydrogen peroxide, and bacteriocin which form a thin acid mantle of pH 4-6. It inhibits invasion of other pathogens, thus protecting vagina from irritation or infection.<sup>8-10</sup> The measures to reduce VVIs include keeping the vulva clean by gentle cleansing, maintaining the acid mantle, and wearing loose, absorbent clothing.<sup>10</sup> However, previous episodes of RTIs, lack of awareness of perineal hygiene, and aggressive hygiene practices disrupt the protective barrier of acid mantle, increasing the risk of colonisation by pathogens. Soaps with high pH can cause loss of the acid mantle, and dryness in vaginal surface resulting in itching and irritation. Increase in vaginal pH is detrimental to the survival of Lactobacilli, and favourable for replication of

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pathogenic microorganisms.<sup>11</sup> Therefore, local acidification with lactic acid or Lactobacilli is useful for the restoration of biological and chemical characteristics of vaginal ecosystem.<sup>11</sup>

Lactic acid has a low pH which acts against the growth of many microorganisms in the vaginal fluid.<sup>12</sup> Lactoserum also has low pH (~ 5.2) and is derived from cow's milk. It is very rich in mineral salts, metals, and vitamins B and C.<sup>13</sup> Lactacyd® FH, the combination of lactic acid and lactoserum, for feminine hygiene, is a liquid soap for daily perineal wash. It has been used by many women all over the world as a feminine wash for external use and as an adjuvant to the standard antimicrobial regimen for treating VVIs. Earlier studies in patients from various countries demonstrated high percentage of satisfaction and safety of lactic acid+lactoserum, and established it as a suitable option for prevention of recurrence of VVIs.<sup>13-18</sup> However, to the best of our knowledge, the effectiveness of lactic acid+lactoserum as an adjuvant therapy has not been evaluated in Pakistani women having VVIs.

The current SatisFaction suRvEy on the use of Lactacyd® FH in Pakistani women presenting with (FRESH) symptoms suggestive of vulvovaginal infections in gynaecological patients aimed at documenting the satisfaction of Pakistani women using lactic acid+lactoserum and thus investigating the effectiveness of topical application of this combination as an adjunct for symptomatic relief from pruritus, burning, and malodour often associated with VVIs. The secondary objective was to evaluate safety of topical application of lactic acid+lactoserum in achieving personal hygiene in women with RTIs.

## Patients and Methods

The national, open-label, multi-centre, prospective survey was conducted at private consultation clinics in 14 cities across Pakistan from May to October 2010, and comprised women having VVIs. Administrative approval was taken from each participating investigator/clinic, and all the enrolled patients signed informed consent forms.

Investigators representing all the four provinces in Pakistan were selected from the most exhaustive list of practising gynaecologists providing care to ambulatory patients at the community level across the country. The list was available with Sanofi Pakistan Limited.

For sample size calculation, we considered the fact that Pakistan has a population of 160 million, one-fourth of which consists of women of reproductive age.<sup>5</sup> The

prevalence of RTIs is estimated to be 24% in this population.<sup>7</sup> In an earlier study conducted in 835 Indian women with RTIs, 88% reported satisfaction following application of lactic acid+lactoserum.<sup>16</sup> To demonstrate similar results, and considering 20% loss to follow-up, it was planned to recruit 1000 patients from 100 sites across Pakistan.

The study included married women aged  $\geq 18$  years presenting with clinical signs and symptoms of VVIs (e.g., BV, candidiasis, and trichomoniasis) such as pruritus, tenderness, erythema, malodour, and abnormal white or gray vaginal discharge; first and recurrent VVIs; and patients who were treated with antibiotics for current VVI.

The exclusion criteria comprised age  $< 18$  years, pregnancy, mental illness, atopy, use of other topical medication in the perineal region, local ulcers and lacerations on perineum, and use of lactic acid+lactoserum as monotherapy at the time of enrolment.

At each study site, 10 consecutive eligible patients were enrolled. The gynaecologists examined the patients and prescribed lactic acid+lactoserum as adjuvant therapy in addition to routine treatment of vulvovaginitis. Lactacyd® FH was provided by Sanofi, Pakistan as the part of investigator's resource kit. Each investigator was provided 10 bottles of 60 ml Lactacyd® FH, for distribution among 10 patients (1 bottle per patient). This therapy was sufficient for 15 days per patient.

At baseline visit (visit 1), data on the eligibility criteria, anthropometric characteristics, medical history, including history of diabetes, parity status and dysuria, along with symptoms of current VVIs, and findings of bimanual examinations were recorded on data collection forms (DCFs).

On the second visit, 14 days after enrolment (visit 2), compliance with the use of lactic acid+lactoserum, patient satisfaction questionnaire, and time taken for symptomatic relief of VVIs were noted on the DCFs. The patient satisfaction questionnaire included satisfaction parameters to measure reduction in symptoms, such as itching, burning, pain, and malodour; and product-related characteristics such as prolonged feeling of freshness, gentleness on skin, mild scent, and value for money. These criteria were measured on a scale of 1-5 (1-strongly disagree, 2-disagree, 3-uncertain, 4-agree, 5-strongly agree).

At visit 2, other evaluating parameters such as overall satisfaction with the use of lactic acid+lactoserum and

willingness to use it again were noted on the same 1-5 scale. Also, the results on overall satisfaction assessed by patients and physicians were noted using the Likert scale with categorical headings as excellent, good, satisfactory, and poor. The gradation was based on subjective opinion of patients and physicians in terms of satisfaction with lactic acid+lactoserum in symptomatic relief.

Safety (solicited reporting) was noted on day 14 or anytime during the study period.

All statistical analyses were performed using SPSS 18. Continuous data was expressed as mean  $\pm$  standard deviation (SD), and categorical data was described as frequencies and percentages.

## Results

Overall, 919 patients were enrolled. Of these, 842(91.6%) patients completed the study, while 77(8.2%) patients did not undergo bimanual examination and their responses were not recorded. Between May 2010 and October 2010, the study was conducted at 96 centres in 14 cities across Pakistan. The study enrolled 919 patients with signs and symptoms of VVI. Data analysis was performed for 842

**Table-1:** Patient characteristics (n = 842).

Parameters	Values
<b>Characteristics, mean Standard Deviation</b>	
Age (years)	32.6 8.4
Weight (kg)	63.7 11.6
Height (cm)	155.8 8.8
Body temperature ( F)	98.2 0.7
Abdominal girth (cm)	90.9 24.2
<b>Medical history, n (%)</b>	
Diabetes	92 (10.9)
Parity status	473 (56.2)
Complain of dysuria	373 (44.3)
<b>Symptoms, n (%)</b>	
Abnormal vaginal discharge	767 (91.1)
Perineal itching	661 (78.5)
Irritation of perineal site	641 (76.1)
Malodour	634 (75.3)
Burning sensation	532 (63.2)
Pain in the perineal region	455 (54.0)
Vaginal bleeding	73 (8.7)
<b>Findings on bimanual examination, n (%)</b>	
Abnormal vaginal discharge	777 (92.3)
Inflammation on vulvular skin	357 (42.4)
Vaginal tenderness	230 (27.3)
Flaccid vaginal tone	172 (20.4)
Erosion on vulvular skin	98 (11.6)
Foreign body in uterus	78 (9.3)
Vaginal bleeding	56 (6.7)
Prolapse of uterus	50 (5.9)

**Table-2:** Summary of antibiotics prescribed.

Antibiotics	Patients, n (%)	Dosage (mg), Mean SD	Duration (days), Mean SD
Metronidazole	438 (52.0)	370.9 $\pm$ 81.1	7.5 $\pm$ 2.4
Fluconazole	94 (11.2)	156.9 $\pm$ 64.7	2.6 $\pm$ 2.4
Ciprofloxacin	72 (8.6)	461.6 $\pm$ 90.8	8.4 $\pm$ 5.5
Azithromycine	65 (7.7)	268.9 $\pm$ 107.9	4.5 $\pm$ 2.6
Clotrimazole	36 (4.3)	377.3 $\pm$ 342.7	4.4 $\pm$ 2.5

SD: Standard deviation.

patients, as 77 patients did not undergo bimanual examination and their responses were not recorded. All the patients had given written informed consent prior to inclusion in the survey.

Anthropometric characteristics, medical history, and symptoms of VVIs as assessed at visit 1 were noted (Table-1).

Median duration of the current episode of VVIs was 7 days (range: 1-150 days), while the mean number of episodes of VVIs in the previous year was 3.4  $\pm$  2.6. The most common symptom in the analysis population was abnormal vaginal discharge in 767(91.1%) cases, followed by perineal itching 661(78.5%), irritation of local perineal site 641(76.1%), and malodour 634(75.3%). As per bimanual examinations, abnormal vaginal discharge 777 (92.3%), inflammation on vulvular skin 357(42.4%), and vaginal tenderness 230(27.3%) were the most common findings.

On the basis of symptoms and bimanual clinical examination used for making provisional diagnosis, gynaecologists suspected that around 295(35%) patients had BV, 278(33%) had vaginal candidiasis, and 126(15%) had trichomoniasis. In 151(18%) patients, investigators suspected multiple infections.

The patients were prescribed lactic acid+lactoserum as an adjuvant treatment to prescribed antibiotics. The most commonly used antibiotic was metronidazole in 438(52%) cases, followed by fluconazole 94(11.2%) and ciprofloxacin 72(8.6%) (Table-2).

The patients used lactic acid+lactoserum for a mean period of 9.7 $\pm$ 4.4) days twice a day (mean number of uses/day: 2.6 $\pm$ 1.3).

On visit 2, 681(80.1%) patients reported reduction in malodour and gave the rating of agree and strongly agree. Reduction in itching was reported in 661 (78.5%), reduction in burning sensation 652 (77.4%), and the reduction in pain 552 (65.6%) (Table-3). Lactic acid+lactoserum was reported to be gentle on skin in

**Table-3:** Patient satisfaction following topical application of lactic acid+lactoserum.

Parameters	Patient satisfaction scale, n (%)					
	Strongly disagree	Disagree	Uncertain	Agree	Strongly agree	Satisfied (agree + strongly agree)
<b>Parameters of symptomatic reduction</b>						
Malodour	3 (0.4)	6 (0.7)	114 (13.5)	409 (48.6)	272 (32.3)	681 (80.1)
Itching	5 (0.6)	25 (3.0)	119 (14.1)	469 (55.7)	192 (22.8)	661 (78.5)
Burning sensation	5 (0.6)	18 (2.1)	137 (16.3)	432 (51.3)	220 (26.1)	652 (77.4)
Pain	10 (1.2)	46 (5.5)	196 (23.3)	409 (48.6)	143 (17.0)	552 (65.6)
<b>Characteristics related to lactic acid+lactoserum</b>						
Gentle on skin	4 (0.5)	12 (1.4)	43 (5.1)	433 (52.4)	336 (39.9)	769 (91.3)
Gives prolonged feeling of freshness	2 (0.2)	6 (0.7)	91 (10.8)	387 (46.0)	340 (40.4)	727 (86.3)
Has a smell of mild scent	0 (0.0)	5 (1.8)	76 (9.0)	419 (49.8)	305 (36.2)	724 (85.9)
Satisfied with the use	4 (0.5)	13 (1.5)	73 (8.7)	434 (51.5)	308 (36.6)	746 (88.6)
Provides values for money	6 (0.7)	24 (2.9)	107 (12.7)	391 (46.4)	292 (34.7)	683 (81.1)

**Figure:** Overall assessment of satisfaction.

769(91.3%) cases, provided feeling of freshness 727(86.3%), and had mild fragrance 724(85.9%). Overall, 746(88.6%) patients reported satisfaction with lactic acid+lactoserum, and 671(79.7%) patients were willing to use it again.

According to patients' assessment of satisfaction, 252(30%) reported satisfaction as excellent, while 379(45%) rated it as good, 194(23%) as satisfactory and 25(3%) poor. When physicians' satisfaction levels were assessed, 29(30%) found it excellent, 43(45%) good, 22(23%) satisfactory and 3(3%) poor (Figure).

Regarding the safety analysis of lactic acid+lactoserum, no adverse events (AEs) were reported.

## Discussion

In this nationwide patient satisfaction survey among women using lactic acid+lactoserum as an adjuvant

therapy for treating VVIs, 88.6% were satisfied with the topical use, and 79.7% agreed that they would routinely use lactic acid+lactoserum for personal hygiene. Also, no AEs were reported during the study period, following the topical use.

Some species of Lactobacilli are known to be main sources of lactic acid and hydrogen peroxide in vagina, and help in reducing the risk of colonisation by pathogens.<sup>9</sup> An earlier randomised controlled study showed higher cure rates with adjunctive oral probiotic Lactobacilli therapy in patients having BV compared to placebo.<sup>20</sup> There are many probiotic products available which can be vaginally administered for the prevention of urogenital infections in women. In an open-label pilot study in women having BV, 6-day treatment using vaginal douche containing a strain of *L. acidophilus* contributed to high cure rate, along with lowering pH and reducing malodour.<sup>21</sup> An earlier study showed that adjuvant therapy with Lactobacilli contributed significantly to avoidance of relapse of BV.<sup>22,23</sup> However, some studies showed that short term and extended treatment of adjuvant vaginal Lactobacilli did not reduce BV recurrence.<sup>24,25</sup>

Adjuvant treatment with lactic acid and lactoserum with oral metronidazole demonstrated increased Lactobacilli colonisation and prevented recurrent BV.<sup>15</sup> Another study showed that the combination lactic acid and lactoserum prevented recurrence BV after treatment and cure with oral metronidazole.<sup>18</sup> Other studies reported symptomatic relief in patients having VVIs who used adjunctive treatment with combination of lactic acid and lactoserum.<sup>16,17</sup> In a study in Indian women with VVIs, majority of patients who used lactic acid+lactoserum as an adjuvant treatment to antibiotics, reported reduction in itching (83.6%), burning/pain sensation (83.6%), and



malodour (91.3%). The feeling of cleanliness was noted in 89.60% patients.<sup>16</sup> In an earlier study in Mexican women having VVIs who used the combination of lactic acid and lactoserum, majority of patients reported feeling of cleanliness (92.2%), feeling of freshness (91.7%), and general feeling of wellbeing (93.9%). The combination of lactic acid and lactoserum was regarded as user-friendly (97.2%), gentle on skin (94.9%), and having pleasing aroma (95.2%).<sup>17</sup> In line with these studies, our study showed that lactic acid+lactoserum demonstrated symptomatic relief in almost three-fourth of the patients having VVIs. It reduced malodour (80.1%), itching (78.5%), burning sensation (77.4%), and pain (65.6%) in almost 4 days of treatment.

Majority of patients also reported satisfaction regarding various aspects of lactic acid+lactoserum such as being gentle on skin (91.3%), giving feeling of freshness (86.3%), and having mild fragrance (85.9%). Similar results regarding the satisfaction parameters have been reported in earlier studies.<sup>13,14</sup> Overall, 88.6% patients were satisfied in our study compared to 88.9% in India.<sup>16</sup>

In the present study, lactic acid+lactoserum was shown to be safe in Pakistani women, with no reports of AEs. Earlier studies also demonstrated lactic acid+lactoserum to be safe and tolerable, with very few patients experiencing AEs.<sup>14,15,18</sup> In a study in Thai women, 6(2%) patients experienced itching, abnormal vaginal discharge, burning sensation, and itching with fungal vaginosis, due to the use of combination of lactic acid and lactoserum.<sup>14</sup> In a study in Philippines, 1(1.7%) patient receiving lactic acid+lactoserum vaginal gel reported presence of curd-like vaginal discharge, while in patients receiving metronidazole and lactic acid+lactoserum gel, there were 5 AEs, including dizziness, epigastric pain and dyspnoea, mild epigastric discomfort, flatulence and loose stool.<sup>15</sup> Another study in Brazil reported that 9(9.8%) patients experienced 11 AEs associated with the combination of lactic acid and lactoserum, which included vaginal candidiasis, erythema, hyperaemia, irritation and itching.<sup>18</sup>

To the best of our knowledge, this is the first multi-centre, open-label nationwide survey carried out in women with VVIs in Pakistan, which evaluated effectiveness and safety of lactic acid+lactoserum when used as an adjuvant therapy to routine treatment of VVIs. It is a clinic-based study conducted in patients visiting gynaecologists, and does not represent the general population. Moreover, the study is non-blinded as we did not have any control or placebo group, which could provide a comparison about the satisfaction profile of lactic acid+lactoserum. The

follow-up was done only up to 14 days. Future randomised comparative studies with long-term follow-up could be designed to study the long-term use of lactic acid+lactoserum in the local population.

## Conclusion

Lactic acid+lactoserum demonstrated high percentage of satisfaction in Pakistani women with VVIs. The combination was apparently effective and safe when used as an adjunctive treatment of VVIs and offered symptomatic relief.

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