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Short Communication

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A New Strategy for Chronic Endometritis Treatment Using Fermented Soy Product (ImmuBalance™)

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Abstract

Background: Chronic endometritis (CE) significantly contributes to repeated implantation failure (RIF). Although antibiotics are common treatments for CE, some patients do not achieve resolution. Therefore, the use of an alternative method involving the administration of ImmuBalance™ (IMB), a combination of pre- and probiotics, was explored in the current study.

Methods: This retrospective study was conducted between April 2021 and August 2022. A total of 819 women with CE were treated with antibiotics-1 (doxycycline, n=809) or IMB (n=10, Group 1). Following endometrial biopsies, CE was not resolved in 209 out of 819 women. Subsequently, 194 patients were treated with antibiotics-1 (n=4) or -2 (amoxicillin, azithromycin, and metronidazole, n=190), whereas 15 were treated with IMB (n=15, Group 2). After the treatment with antibiotics-2, four women underwent IMB (Group 3). Statistical analysis of the number of plasma cells with CD138 before and after treatment was conducted using Fisher's exact test and p-values <0.05 were considered statistically significant.

Results: CE was treated in 60% of patients (6/10) in Group 1; however, the reduction in CD138 count was not statistically significant (p=0.13). In Groups 2 and 3, CE was treated with a significantly reduced CD138 count (Group 2, p<0.01; Group 3, p=0.04). CE was treated in 100% of cases in Group 2 and 3 (15/15 and 4/4, respectively).

Conclusion: Based on the findings of this study, administration of IMB may be effective in treating CE, especially following antibiotic treatment.

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Introduction

Chronic endometritis (CE) is a persistent inflammatory condition characterized by the infiltration of plasma cells into the uterine endometrial stroma (1). Particularly, it is believed that CE is a contributing factor to repeated implantation failure (RIF) or recurrent pregnancy loss (RPL) in women undergoing assisted reproductive technology treatments. It is anticipated that successful treatment of CE could lead to improved implantation rates in RIF patients and increased ongoing pregnancy rates in RPL patients (2-6). Regarding the treatment of CE, the standard approach has traditionally involved the administration of oral antibiotics (3, 4, 6, 7). Doxycycline, a broad-spectrum antibiotic, is the standard first-line treatment for CE (3, 6, 7). In cases where doxycycline treatment fails, a combination of metronidazole along with either ciprofloxacin or of-

loxacin is often selected (2, 8). This second-line regimen resulted in a cure rate of 95% among women with CE (2). Despite the well-discussed and established treatment protocols for CE, it remains uncertain how the inflammatory condition in the uterine cavity arises.

A recent report indicated that peritoneal microorganisms originating from the gastrointestinal tract could potentially traverse the fallopian tubes and reach the uterine endometrium in humans, leading to endometritis (9). Additionally, recent research has demonstrated that regulating intestinal flora can reduce endometritis in mice (10). These findings collectively suggest that medical interventions aimed at maintaining a healthy intestinal environment could potentially serve as an efficient strategy for CE treatment. ImmuBalance™ (IMB) (Nichimo Biotics, Japan) is a fermentation product derived from defatted soybeans using Aspergillus oryzae and lactic acid bacteria through proprietary fermentation technology (11, 12). A previous study demonstrated that IMB could improve chronic kidney disease by exerting anti-inflammatory effects and modulating gut microbiota (13). Based on this evidence, oral supplementation of IMB is anticipated to positively influence gut microbiota, thereby potentially improving the uterine endometrial environment. Consequently, daily intake of IMB could emerge as a promising treatment approach for CE. In the present study, the effectiveness of oral administration of IMB in improving CE was evaluated.

Methods

Study population: This retrospective observational study was conducted at Sugiyama Clinic Shinjuku between April 2021 and August 2022. The study received ethical approval from the Ethics Committee of Sugiyama Clinic (Approval No. 22-010). During the study period, a total of 819 women were diagnosed with CE.

The flowchart of the classification of the partici-

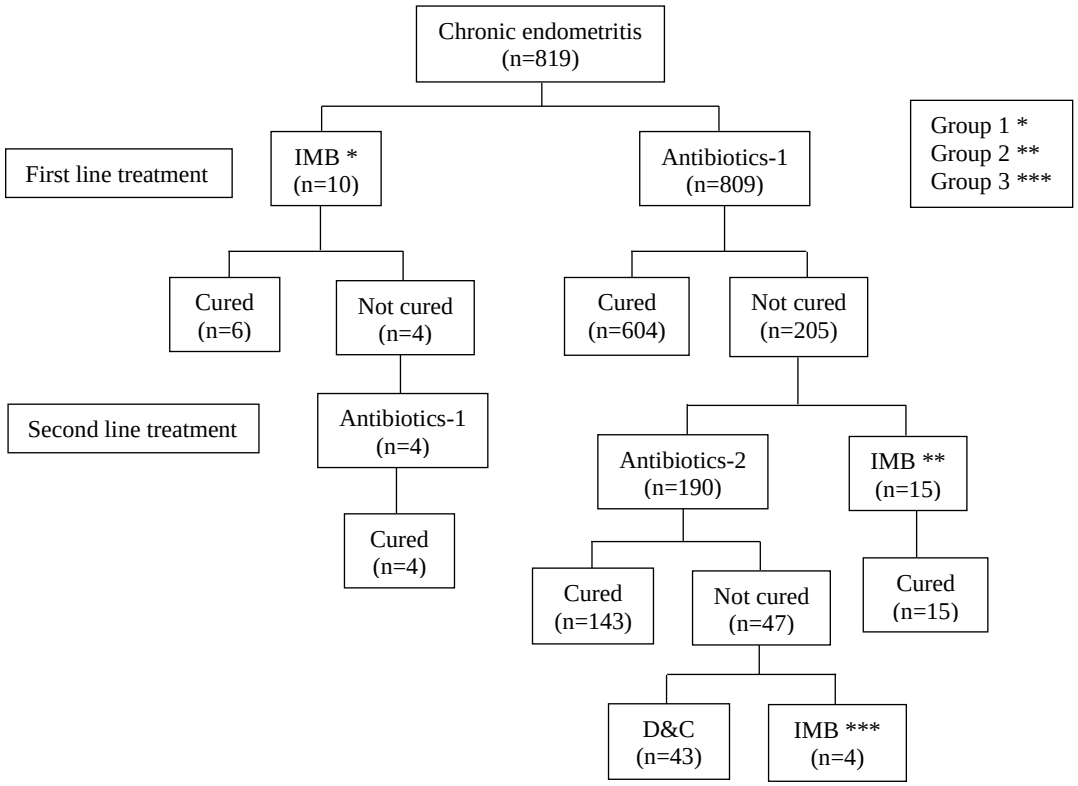

Figure 1. Flowchart of participant classification for this study
Among 819 women who were diagnosed as CE, 809 women were treated by antibiotics (doxycycline, antibiotics-1) and the others (n=10) received IMB as the first-line treatment. One or two weeks following the first-line treatment, all women were evaluated for treatment effect via endometrial biopsy to count the number of CD138-positive plasma cells. A total of 610 women were cured, and the remaining 209 women were treated with either antibiotics-1 (n=4), a combination of amoxicillin, azithromycin, and metronidazole (antobiotics-2, n=190), or IMB (n=15) regarding second-line treatment. One or two weeks following the second- line treatment, a total of 209 women were evaluated for the treatment effect again by endometrial biopsy to count the number of CD138-positive plasma cells, 162 women were judged as cured, and the remaining 47 women were treated by either IMB or curettage.
CE: chronic endometritis, IMB: ImmuBalance™

pants is shown in figure 1. Among the 819 women diagnosed with CE, 809 received treatment with antibiotics (doxycycline, antibiotics-1), while the remaining 10 women received IMB (Group 1). One or two weeks following the first-line treatment, all women underwent evaluation of treatment effectiveness through endometrial biopsy. Out of the 819 women, 610 were determined to be cured after the initial treatment, while the remaining 209 women required further intervention. Of the 209 women, four received doxycycline, 190 received a combination of amoxicillin, azithromycin, and metronidazole (antobiotics-2), and 15 received IMB (Group 2). After one or two weeks from the second-line treatment, the treatment effectiveness was reassessed through endometrial biopsy. Out of the 209 women, 162 were determined to be cured, while the remaining 47 women underwent additional treatment with either IMB (n=4, Group 3) or curettage (14). Overall, 29 women received IMB as the treatment for CE.

Endometrial biopsies for CD138 immunohistochemistry: To evaluate the intrauterine environment and diagnose CE, endometrial sampling was performed between the late follicular and luteal phases of the menstrual cycle using an endometrial suction curette. The specimens collected were fixed in 10% formaldehyde. Pathologists stained the specimens using an anti-CD138 antibody and counted CD138-positive plasma cells in 10 non-overlapping random stromal areas visualized at 400-fold magnification. CE was diagnosed in cases where five or more CD138-positive cells were present (2).

Treatment of chronic endometritis: The first-line antibiotic treatment included the administration of 100 *mg* of oral doxycycline (Vibramycin®), twice a day for 14 days (2). The second-line antibiotic treatment consisted of a combination of 250 *mg* of amoxicillin (Sawacillin®), 250 *mg* of azithromycin (Azithromycin®), and 250 *mg* of metronidazole (Flagyl®), along with 6 *mg* of antibiotic-resistant lactic acid bacteria (Biofermin-R®), administrated twice a day for 14 days. For the treatment of CE with IMB, supplementation involved the administration of IMB (ImmuBalance™) at a dose of 9 tablets daily for 14 days.

The definitions of the variables and the statistical analysis: The following data were extracted from medical records: age, pregnancy history, treatment for CE, and the number of CD138-positive cells before and after treatment. Statistical analysis of the number of CD138-positive cells before and after the treatment was conducted using Fisher's exact test.

All the statistical analyses were conducted using EZR software. The $p<0.05$ were considered statistically significant.

Results

A total of 29 women received IMB as the treatment for CE. The median age of the participants was 36 years, with an age range between 31 and 41 years. Among them, 21 women had a history of pregnancy, 11 had a history of labor, and 17 had a history of miscarriage.

In Group 1, consisting of women who received IMB as the first-line treatment, six out of ten participants (60%) achieved a clinical cure with IMB alone. The remaining four women, who were not treated with IMB, attained a successful outcome following the administration of oral doxycycline (antibiotics-1). The median CD138-positive plasma cell counts before and after taking IMB were 9.5 (range: 6-19) and 3.5 (range: 0-20) per 10 high power fields (HPF), respectively. However, this reduction was not statistically significant (p=0.13, table 1). In Group 2, consisting of 15 women who were not treated by antibiotics-1, only IMB was administered as the second-line treatment. All participants in this group achieved clinical cure following the administration of IMB. The median CD138-positive plasma cell count was 15 (range: 5-89) per 10 HPF before CE treatment. After the

Table 1. The changes of CD138-positive plasma cells before and after treatment in Group1

	Before taking IMB	After taking IMB
CD138-positive plasma cell count per 10 HPF	9.5 (6-19)	3.5 (0-20)
	p=0.13	
IMB		
HPF		
Continuous variables are reported as the median (range)		

IMB: ImmuBalance™, HPF: High Power Field

Table 2. The changes of CD138-positive plasma cells in Group 2

	Before treatment	After taking antibiotics-1	After IMB
CD138-positive plasma cell count per 10 HPF	15 (5-89)	16 (6-94)	1 (0-7)
	p=1.0	p<0.01	
IMB			
HPF			
Antibiotics-1: doxycycline			
Continuous variables are reported as the median (range)			

IMB: ImmuBalance™, HPF: High Power Field
In Group 2, 15 participants who were deemed untreated by antibiotics-1 received only IMB as the second-line treatment. All 15 participants were cured after this treatment. The median count of CD138-positive plasma cell count was 15 (range: 5-89) per 10 HPF before CE treatment. This was similar to the count after the first-line treatment with antibiotics-1, which was 16 (range: 6-94) per 10 HPF, showing no statistically significant difference (p=1.0). However, after IMB administration as a second-line treatment, there was a significant decrease in CD138-positive plasma cell count, which was 1 (range: 0-7) per 10 HPF, (p<0.01) compared to that after administration of antibiotics-1

Table 3. The change of CD138-positive plasma cells in Group3

	Before treatment	After antibiotics-1	After antibiotics-2	After IMB
CD138-positive plasma cell count per 10 HPF	7 (5-13)	10 (8-13)	9 (7-15)	1 (0-3)
	p=1.0	p=1.0	p=0.04	
IMB				
HPF				
Antibiotics-1: doxycycline				
Antibiotics-2: a combination of amoxicillin, azithromycin, and metronidazole				
Continuous variables are reported as the median (range)				

IMB: ImmuBalance™, HPF: High Power Field
In Group 3, four participants who were deemed untreated by both antibiotics-1 and antibiotics-2 received only IMB. All four participants were confirmed to be cured after treatment. The median of CD138-positive plasma cell count before CE treatment was 6.5 (range: 5-13) per 10 HPF, and after first- and second-line treatments with antibiotics-1 and antibiotics-2, these values increased to 9.5 (range: 8-13) per 10 HPF and 10.5 (range: 7-15) per 10 HPF, respectively. However, the median of CD138-positive plasma cell count after receiving IMB was 1 (range: 0-3) per 10 HPF, which is a significant decrease compared to the previous treatments with antibiotics (p=0.04)

first-line treatment with antibiotics-1, this count slightly increased to 16 (range: 6-94) per 10 HPF, with no statistically significant difference (p=1.0). However, there was a significant decrease in CD138-positive plasma cell counts to a median of 1 (range: 0–7) per 10 HPF after IMB treatment compared to the counts following antibiotics-1 administration (p<0.01) (Table 2). In Group 3, four women who were not treated by both antibiotics-1 and antibiotics-2 received IMB, and all four were confirmed to have attained clinical cure. The median of CD138-positive plasma cell count before CE treatment was 6.5 (range of 5-13) per 10 HPF. After the first- and second-line treatments with antibiotics-1 and antibiotics-2, these values increased to 9.5 (range: 8-13) per 10 HPF and 10.5 (range: 7-15) per 10 HPF, respectively. The median of CD138-positive plasma cell counts after receiving IMB decreased to 1 (range: 0-3) per 10 HPF, representing a significant decrease compared to that after the second-line treatment (p= 0.04, table 3).

Discussion

CE is widely believed to be potentially caused by microorganisms in the uterine cavity, although its exact origin remains unclear and not fully understood. Recent research has suggested that microorganisms from the gastrointestinal tract can migrate to the uterine cavity via the fallopian tube (9). Moreover, another study indicated that regulating intestinal flora can improve the condition of uterine tissues and reduce the prevalence of CE (10). Based on these findings, it is plausible to

speculate that the improvement of CE following the administration of oral antibiotics may be attributed to the destruction of intestinal microflora, which could lead to a reduction in the presence of microorganisms associated with the condition. Moreover, these two studies strongly suggest that the dysbiosis of the intestinal microflora may contribute to the development of CE. Considering our hypothesis and the aforementioned research findings, it can be concluded that administering a product capable of improving intestinal microflora could be a viable treatment option for CE. Therefore, the effectiveness of administering IMB, a product that aligns with our hypothesis, was investigated as a potential treatment for CE.

ImmuBalance™ contains koji polysaccharide as its main ingredient, which is derived from fermenting defatted soybeans with Aspergillus oryzae and lactic acid bacteria (11). This fermentation process results in a product rich in both probiotics (lactic acid bacteria) and prebiotics (dietary fiber and soybean oligosaccharides). The synergistic action of these probiotics and prebiotics is believed to improve intestinal microflora. To the best of our knowledge, this is the first study to demonstrate that IMB can serve as a viable treatment option for CE. In this study, the administration of IMB led to a significant decrease in the CD138-positive plasma cells in CE cases, particularly for the patients who experienced antibiotic-resistant CE (Tables 1-3). Kadogami et al. suggested that a combination of prebiotics and probiotics, administered after antibiotic treatment, can improve the intrauterine microbiome (15). This finding aligns closely with the results of our study. Our overall hypothesis posits that while antibiotics create a bacteriostatic environment in the intestinal tract, subsequent administration of IMB helps normalize gut microbiota. This normalization process may explain why CE was effectively treated with IMB, especially after antibiotic administration.

The present study has limitations that warrant consideration. The retrospective nature of our study and the relatively small study population may introduce inherent biases. Future studies with larger sample sizes are needed to validate our results.

Conclusion

Based on the findings of the study, it can be concluded that IMB can emerge as a promising supplementation material for treatment of CE. Moreover, IMB may represent a viable treatment option for cases of antibiotic resistance in CE.

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Conflict of Interest

Fumio Suyama, Koji Nakagawa, Keisuke Shiobara, Takashi Horikawa, Keiji Kuroda, Hisayo Kataoka, Yuko Ojiro, Satoru Takamizawa, and Rikikazu Sugiyama declared no conflicts of interest that could appear to influence the results from this study.

References

1. Kitaya K, Yasuo T. Immunohistochemistrical and clinicopathological characterization of chronic endometritis. Am J Reprod Immnol. 2011;66(5):410-5.
2. Kuroda K, Matsumura Y, Ikemoto Y, Segawa T, Hashimoto t, Fukuda J, et al. Analysis of the risk factors and treatment for repeated implantation failure: optimizing of thyroid function, IMmumnity, and uterine milieu (OPTIMUM) treatment strategy. Am J Reprod Immunol. 2021;85(5):e13376.
3. Kitaya K, Matsubayashi H, Takaya Y, Nishimura R, Yamaguchi K, Takeuchi T, et al. Live birth rate following oral antibiotic treatment for chronic endometritis in infertile women with repeated implantation failure. Am J Reprod Immunol. 2017;78(5).
4. McQueen DB, Bernardi LA, Stephenson MD. Chronic endometritis in women with recurrent early pregnancy loss and/or fetal demise. Fertil Steril. 2014;101(4):1026-30.
5. Cicinelli E, Matteo M, Tinelli R, Pinto V, Marinaccio M, Indraccolo U, et al. Chronic endometritis due to common bacteria is prevalent in women with recurrent miscarriage as confirmed by improved pregnancy outcome after antibiotic treatment. Reprod Sci. 2014;21(5):640-7.
6. Kuroda K, Ikemoto Y, Horikawa T, Moriyama A, Ojiro Y, Takamizawa S, et al. Novel approaches to the management of recurrent pregnancy loss: the OPTIMUM (optimization of thyroid function, thrombophilia, immunity, and uterine milieu) treatment strategy. Reprod Med Biol. 2021;20(4):524-36.
7. Johnston-MacAnanny EB, Hartnett J, Engmann LL, Nulsen JC, Sanders MM, Benadiva CA. Chronic endometritis is a frequent finding in women with recurrent implantation failure after in vitro fertilization. Fertil Steril. 2010;93(2):437-41.

8. Kimura F, Takebayashi A, Ishida M, Nakamura A, Kitazawa J, Morimune, et al. Review: chronic endometritis and its effect on reproduction. J Obstet Gynaecol Res. 2019;45(5):951-60.
9. Chen C, Song X, Wei W, Zhong H, Dai J, Lan Z, et al. The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases. Nat Commun. 2017;8(1):875.
10. Hu B, Dong Y, Zhou W, Ma Y, Li L, Fu X, et al. Effect of Inonotus obliquus polysaccharide on composition of the intestinal flora in mice with acute endometritis. PLoS One. 2021;16(11): e0259570.
11. Kadotani H, Asai K, Miyamoto A, Iwasaki K, Kawai T, Nishimura M, et al. The fermented soy product immuBalance™ suppresses airway inflammation in a murine model of asthma. Nutrients. 2021;13(10):3380.
12. Matsuda A, Tanaka A, Pan W, Okamoto N, Oida K, Kingyo N, et al. Supplementation of the fermented soy product ImmuBalance™ effectively reduces itching behavior of atopic NC/Tnd mice. J Dermatol Sci. 2012;67(2):130-9.
13. He LX, Abdolmaleky HM, Yin S, Wang Y, Zhou JR. Dietary fermented soy extract and oligo-lactic acid alleviate chronic kidney disease in mice via inhibition of inflammation and modulation of gut microbiota. Nutrients. 2020;12(8):2376.
14. Kuroda K, Ishiyama S, Shiobara S, Nakao K, Moriyama A, Kataoka H, et al. Therapeutic efficacy of genetle endometrial curettage on antibiotic-resistant chronic endometritis in infertile women. Reprod Med Biol. 2023;22(1):e12525.
15. Kadogami D, Nakaoka Y, Morimoto Y. Use of a vaginal probiotic suppository and antibiotics to influence the composition of the endometrial microbiota. Reprod Biol. 2020;20(3):307-14.