



STUDY REPORT

“SHORT REPORT OF THE MULTI-GYN FLORAPLUS PILOT STUDY”

**A PILOT STUDY OF THE SAFETY AND EFFICACY OF MULTI-GYN FLORAPLUS
IN THE PREVENTION OF THE EXACERBATION OF THE PRESENCE OF CANDIDA ALBICANS
IN THE VAGINAL FLORA**

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1. Introduction

Multi-Gyn FloraPlus is a prebiotic vaginal gel combined with the 2QR-complex that neutralizes pathogenic flora. The product is intended to optimize the vaginal flora by stimulating growth of lactobacilli while suppressing pathogens. Its prebiotic action is particularly focused on the preferred group of lactobacilli - the homofermentative lactobacilli- present in the vagina. Multi-Gyn FloraPlus thereby prevents bacterial infections as well infections with candida as well as recurrent candidosis through competitive growth of lactobacilli. The growth of lactobacilli is stimulated with state-of-the-art prebiotic ingredients that are quickly and selectively metabolized. This selective action is of special importance since it does not favour other microbial species.

Multi-Gyn FloraPlus is packaged in single dose applicators. It is advised to apply the product once per day at bedtime for 5 consecutive days.

2. Rationale of the study

The vaginal ecology consists of a great number of microorganisms living in a community. Ecosystems are always subject to moving boundaries. Problems arise when this movement is disturbed by the dominance of undesired microorganisms, such as by an opportunistic pathogens, for instance candida albicans. The traditional approach of the effort to completely eradicate a microorganism not only has the disadvantage of the side effects of the treatment but also the frustration of the quick re-introduction of the microorganism from the environment. The eradication of a microorganism can in reality only be achieved in vitro.

The principle of Multi-Gyn FloraPlus is that it "moves" the vaginal flora that the lactobacilli-boundary increases versus that of candida. With this principle the exacerbation of candida into a candidiasis as suffered with complaints of itch, burning, pain and excessive cottage cheese-like discharge is prevented.

The rationale for the pilot study is to evaluate the efficacy of Multi-Gyn FloraPlus for the control of the exacerbation of candida.

3. Mode of action of Multi-Gyn FloraPlus

Prebiotics are nutrients for bacilli that are *present* in the host. With a prebiotic product no bacilli are grafted as in a probiotic. A probiotic adds new lactobacilli strains to the flora. A prebiotic stimulates, supports and boosts the desired lactobacilli that are already present in the host. The choice of the nutrients provided in a prebiotic product makes it possible to selectively stimulate the growth of a desired microbial species because certain nutrients are faster and better metabolized one the one species than the other.

Multi-Gyn FloraPlus contains prebiotic ingredients that are *selective* for homofermentative (H₂O₂ producing) lactobacilli and thus gives a growth stimulus to this group of lactobacilli. Multi-Gyn FloraPlus is therefore optimizing the most efficacious vaginal flora as well qualitatively as quantitatively.



This was first shown in in vitro tests. In vitro tests with a mixed culture of lactobacilli and candida showed that Multi-Gyn FloraPlus effectively suppressed growth of candida.

4. Ingredients of Multi-Gyn FloraPlus

The Multi-Gyn FloraPlus formula is comparable to the formulae of Multi-Gyn ActiGel and LiquiGel. Its main active ingredient is the 2QR-complex. The anti-adhesive properties against (opportunistic) pathogens of the 2QR-complex are supported by the growth stimulus of the preferred lactobacilli with selected nutrients.

The bio-adhesive system consists of hydroxymethylethylcellulose and galactoarabinan. A pH stabilizing system controls the pH at around 4.1.

5. Design of the Pilot Study of Multi-Gyn FloraPlus

This Pilot Study evaluated the in vivo effects of the application of this prebiotic vaginal gel.

5.1 Title

A pilot study of the safety and efficacy of Multi-Gyn FloraPlus in the prevention of the exacerbation of the presence of candida albicans in the vaginal flora.

5.2 Primary Objectives

To assess the efficacy of a five days application Multi-Gyn FloraPlus for the prevention of the exacerbation of the presence of candida albicans in the vaginal flora.

5.3 Secondary Objective:

To assess the safety of the 5 days application of Multi-Gyn FloraPlus.

5.4 Tertiary Objective

To assess the effect of Multi-Gyn FloraPlus on the candida- related vaginal complaints.

5.5 Study Design

Evidence based study.

5.6 Sample Size

A minimum of 20 evaluable patients was required for this Pilot Study.

5.7 Study locations

Gynaecological practice of dr. Bojovic, Belgrade, Serbia.

5.8 Study Population

Women to whom the investigator would routinely prescribe a topical anti-mycotic cream.

5.9 Inclusion criteria

1. Vulvovaginitis
2. Complaints of the patient
3. A topical antimycotic treatment is indicated
4. Diagnosis of candida by wet mount +/- (very mild), + (mild). ++ (moderate), +++ (severe)
5. Negative amine odor test ("whiff test")

5.10 Exclusion Criteria

Patients to whom the investigator would routinely prescribe a systemic antimycotic because of the extreme severity of the candida infection (candidiasis).

6 Study Results

The number of evaluable patients in this pilot study was 26.

The study results were evaluated with the following parameters:

1. Vulvovaginitis as diagnosed by the investigator
2. Candida as diagnosed by the LCPL
3. Abnormal discharge
4. Itch as perceived by the patient
5. Pain as perceived by the patient
6. Burning as perceived by the patient
7. Treatment results as judged by the investigator
8. Treatment satisfaction as judged by the patient for the relief of symptoms

Additionally the patients were asked for their opinion of Multi-Gyn FloraPlus with respect to the consistency and application of the product.

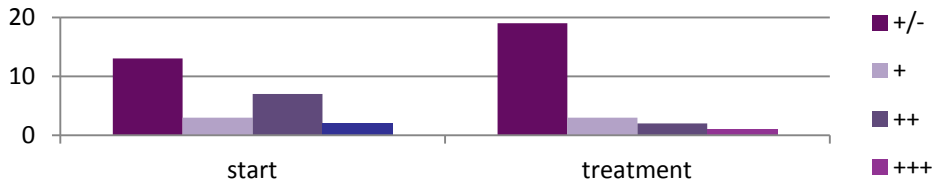
6.1 Cytological valuation of smears

6.1.1 Candida

The main inclusion criteria in this pilot study were the presence of candida and candida-related complaints. In the study report only patients with a cytological confirmed diagnosis were evaluated.

Cytological analyses were conducted by the LCPL. The severity of candida is expressed with +/-, +, ++, +++.

Candida (Icpl)



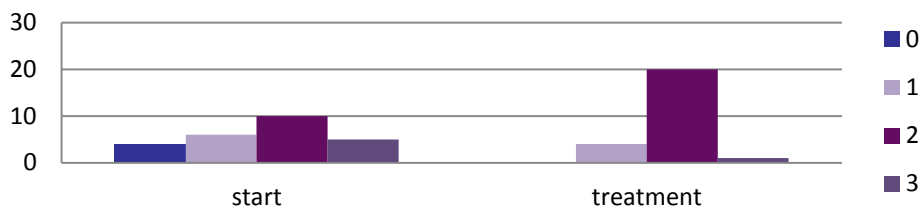
Discussion on the results of FloraPlus on candida

It is shown that FloraPlus is not candidacidal. This is no surprise because the mode of action of FloraPlus in candida is based on competitive growth and competition for adhesion sites of the mucous tissues. Candida is therefore still present in the smears but has lost its virulence after 5 days course of application of FloraPlus. This is clearly shown in the results on the relief of the complaints of the patients.

6.1.2 Lactobacilli

Cytological analyses were conducted by the LCPL. The amount of Lactobacilli was noted in the Nugent Score and is expressed with 0, 1, 2 and 3.

Lactobacillae



Discussion on the results of FloraPlus on lactobacilli

The number of lactobacilli was boosted by a 5 days course of application of FloraPlus. This result supports the intended effect of the formula on “moving the boundaries” of the microbial community into a flora consisting of beneficial commensal flora.

6.1.3 Gardnerella

Cytological analyses were conducted by the LCPL. The amount of Gardnerella (BV flora) was noted in the Nugent Score.

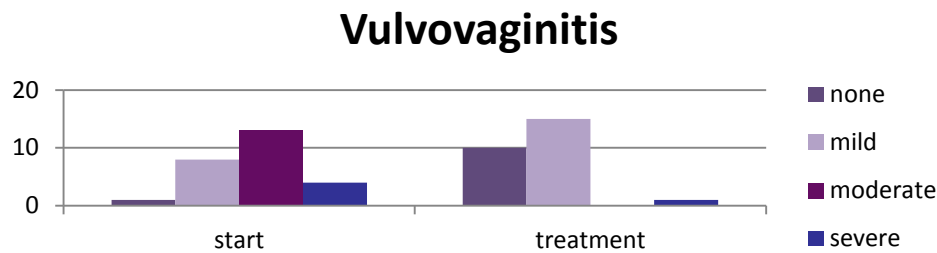
Discussion on the results of FloraPlus on Gardnerella (BV flora)

As could be expected in this pilot study that focuses on candida, only 6 patients had Gardnerella. After the 5 days course of application of FloraPlus no gardnerella was found.

7 Evaluation of the complaints related to Candidiasis

7.1 Vulvovaginitis

The number of patients with any degree of complaints of vulvovaginitis decreased from 26 to 17 after treatment.

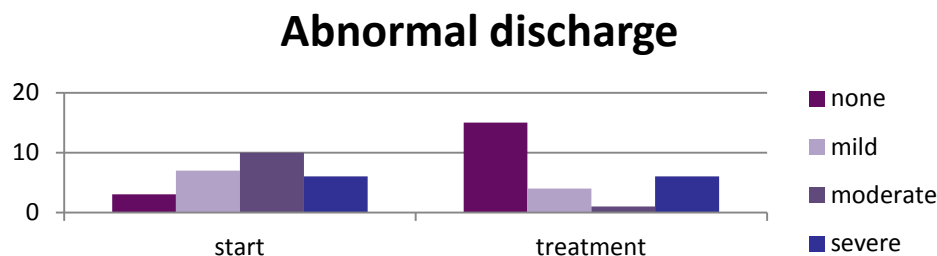


Discussion on the results of FloraPlus on vulvovaginitis

Vulvovaginitis decreased considerably after the 5 days course of application of FloraPlus as well in number of patients as in severity.

7.2 Abnormal discharge

The number of patients with any degree of complaints of discharge decreased from 24 to 12 after treatment.

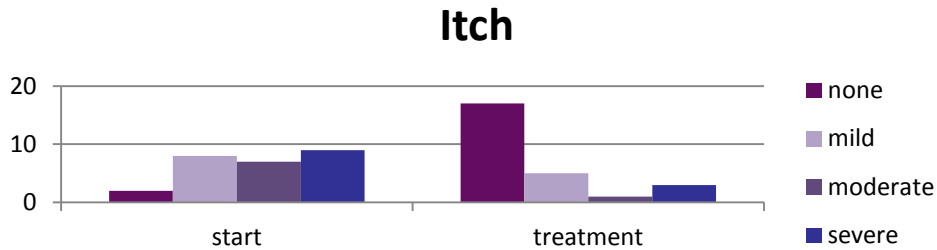


Discussion on the results of FloraPlus on discharge

The abnormal discharge decreased considerably after the 5 days course of application of FloraPlus as well in number of patients as in severity. When before treatment 3 patients had no complaints on their discharge, this number increased to 15 after treatment with FloraPlus. It can't be explained why the 7 patients that complained about severe abnormal discharge showed no improvement. The parameter is subjective and it is possible that these patients have generally a lot of discharge without an underlying cause of infection.

7.3 Itch

The number of patients with any degree of complaints of itch decreased for 24 to 9 after treatment.

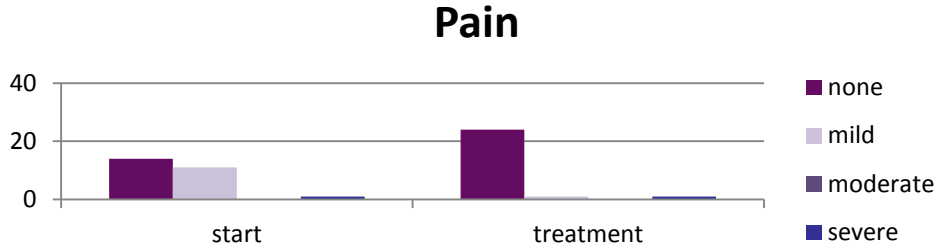


Discussion on the results of FloraPlus on itch

The 5 days treatment course with FloraPlus had a great effect on itch, as seen in the decrease of the number of patients with any degree of a complaint of itch as in the decrease of the severity of the itch.

7.4 Pain

The total number of patients with any degree of complaints of pain decreased from 12 to 3 after treatment.



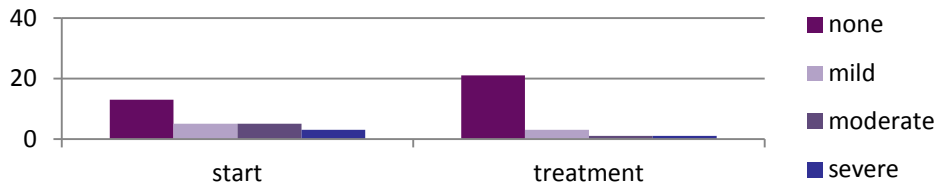
Discussion on the results of FloraPlus on pain

The 5 days treatment course with FloraPlus had a beneficial effect on pain, as seen in the decrease of the number of patients with any degree of a complaint of pain. There is no explanation for the fact that one more patient complaint of severe pain. As pain is also related to various sexual activities it is difficult to trace the very cause.

7.5 Burning

The total number of patients complaining of any degree of burning decreased from 13 to 5 patients after treatment.

Burning

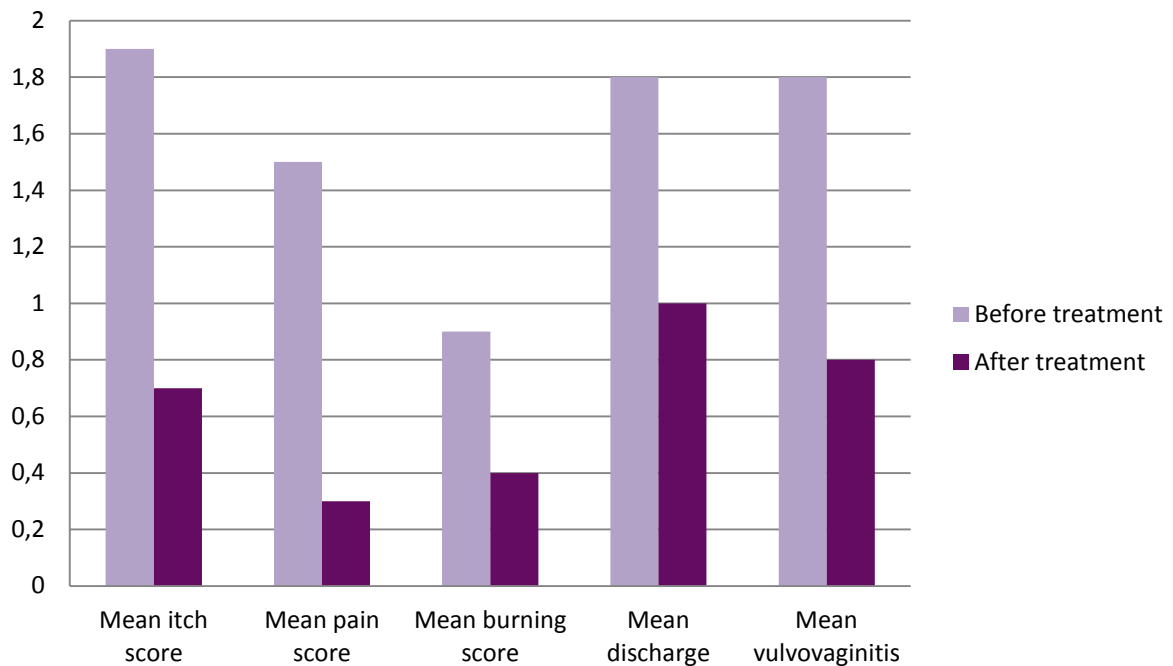


Discussion on the results of FloraPlus on burning

The 5 days treatment course with FloraPlus had a great effect on burning, as seen in the decrease of the number of patients with any degree of a complaint of burning as in the decrease of the severity of the burning.

7.6 Mean values of all complaints

Mean values of all complaints



- Mean average score of itch**
 (0=0, mild=1, moderate=2, severe=3)
 Start: 1.9 After treatment: 0.7
- Mean average score of pain**
 (0=0, mild=1, moderate=2, severe=3)
 Start: 0.5 After treatment: 0.3

- **Mean average score of burning**
(0=0, mild=1, moderate=2, severe=3)
Start 0.9 After treatment: 0.4
- **Mean average score of discharge**
(0=0, mild=1, moderate=2, severe=3)
Start = 1.8 After treatment: 1.0
- **Mean average score of vulvovaginitis**
(0=0, mild=1, moderate=2, severe=3)
Start = 1.8 After treatment: 0.8

7.7 General questions on the use of Multi-Gyn FloraPlus

Treatment result (investigator):

good: 16 not sufficient:8 none: 2 worse: 1

Was other medication prescribed?

Yes: 4 no: 23

7.8 Patient's satisfaction with Multi-Gyn FloraPlus

Relief of complaints:

good: 17 not sufficient: 8 none: 0 worse: 1

Was the patient satisfied with the treatment:

yes: 18 no: 9

Would you use the product again?

yes: 19 no: 8

Was the treatment product?

- easy to apply? yes: 20 no: 7
- pleasant? yes: 21 no: 6
- well lubricating? yes: 25 no: 2
- leaking? no: 13 a little: 10 a lot: 3
- itchy? no: 19 a little: 5 a lot: 3
- burning? no: 20 a little: 6 a lot: 0

7.9 Discussion of the comments on the use of FloraPlus

In view of the broad range of complaints related to vulvovaginitis caused by candida the the general treatment results of this pilot study and the satisfaction of patient are promising. No adverse effects have been noticed. As an gel with a low pH some remarks on itchiness and burning are to be expected.

It is very promising that only 4 patients needed further medication for candidiasis and that the investigator concluded that in 16 patients the treatment with FloraPlus was “good”. Also two thirds of the patients in the study would use the product again and were satisfied with the treatment results.

8 Conclusion

It is clearly shown that the approach of competitive growth with the stimulation of the beneficial commensal flora of lactobacilli is efficacious in a great number of patients with diagnosed candidiasis. The relief of candidiasis-related complaints is very good.

In view of the non-antimycotic, non candidal mode of action of FloraPlus the results of this pilot study warrant a study with a larger number of patients.

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