



Review Article

Clinical Verification of the Activity and Tolerability of Fitostimoline Vaginal Pessaries in Women with Hysterectomy: Randomized, Perspective, Monocentric Study

Martina Grandinetti^{1*}, Ludovica Nazzaro¹, Raffaele Izzo², Michele Vignali¹

¹Department of Obstetrics and gynecology, "Statale" University, Milano, Italy

²Department of Advanced Biomedical Sciences, "Federico II" University, Naples, Italy

*Corresponding author: Martina Grandinetti, Department of Obstetrics and gynecology, "Statale" University, Milano, Italy

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Abstract

Objective: To evaluate the activity of Fitostimoline[®] pessaries in comparison to the standard of care in the treatment of women with hysterectomy. **Methods:** An observational, randomized, perspective study performed on 60 women where 30 women were treated with Fitostimoline[®] pessaries for 12 days after surgery and 30 women were treated with the standard of care. A first follow-up visit was performed at 12 +/- 3 days and a final follow-up visit was performed at 40 +/- 3 days. **Results:** At the first control, 45% of patients in the Fitostimoline[®] group reported no evidence of vaginal bleeding after surgery; instead, 41% in the control group reported such result. At the final visit, 79% patients reported no evidence of vaginal bleeding in the Fitostimoline[®] group, while 63% in the control group. The medial duration of minor vaginal bleeding in the Fitostimoline[®] group was 11.8 days, whilst for discrete vaginal bleeding the medial duration was 4 days. In the control group instead it was 12 days, whilst for discrete vaginal bleeding the medial duration was 8 days. **Conclusion:** The use of Fitostimoline[®] ovules after hysterectomy is effective in reducing the quantity of vaginal bleeding, regardless the menopausal status, surgical approach and type of indication to surgery.

Keywords: Hysterectomy; Fitostimoline[®] pessaries; Vaginal bleeding

Introduction

Hysterectomy is the most common gynecologic procedure performed worldwide. Nearly 90% of hysterectomies are performed for benign indications. Among the post-operative complications one of the most common is vaginal bleeding. Bleeding complications are related to several variables, including the type of hysterectomy performed. There are many factors that contribute to increase hysterectomy-related complications, including obesity, poor visual

exposure (attributable to endometriosis, adhesions, large masses), distorted anatomy, uterine fibroids, surgical skill, volume of the surgeon's practice, surgical volume of the hospital, pharmacologic venous thromboembolism prophylaxis, concurrent use of aspirin and other antiplatelet drugs, and over-the-counter preparations [1]. Different kind of bleeding can occur after hysterectomy, from vaginal spotting to massive secondary hemorrhage.

Vaginal bleeding after hysterectomy can also be one of the signs of a more serious post-operative complication: vaginal cuff dehiscence. Vaginal cuff dehiscence is a postoperative complication unique to hysterectomy. Although it is rare, it can

lead to serious morbidity [2]. Total laparoscopic hysterectomy has the highest rate of vaginal cuff dehiscence compared with total abdominal hysterectomy, and total vaginal hysterectomy [3-8]. Vaginal cuff dehiscence usually occurs in the first weeks after surgery but can be delayed up to several years (especially in postmenopausal women). Vaginal cuff dehiscence often presents with postcoital bleeding, other vaginal spotting, or watery vaginal discharge [9].

The manifestation of even a small amount of vaginal bleeding, other than being a sentinel sign of major complications, can be an element of concern for the patient. Hence reducing the incidence of vaginal bleeding after hysterectomy can impact on different aspects of the post-operative management of the patient.

Triticum vulgare has been extensively used in traditional medicine thanks to its properties of accelerating tissue repair. The aqueous extract of *Triticum vulgare* is currently an active component of Fitostimoline-based products and it is used in the presence of problems relating to re-epithelialization or tissue regeneration. *Triticum vulgare* can determine a marked acceleration of tissutal repairing processes by stimulating chemotaxis and the fibroblastic maturation and significantly increasing the fibroblastic index, which are crucial points in the repairing processes.

Recent studies have shown that *Triticum vulgare* exerts anti-inflammatory properties since it reduces the release of all the evaluated markers of inflammation, such as NO, IL6, TNF alpha and PGE2 in LPS-activated BV2 microglial cells.

The aim of the study was to evaluate the efficacy and tolerability of vaginal administration of Fitostimoline on the reduction of vaginal bleeding after hysterectomy.

Patients and Methods

Patients

Women aged between 35 and 80 years undergoing hysterectomy were enrolled between October 2020 and July 2021 prospectively; patients entered the study if they could comprehend the procedures and endpoints of the study. Exclusion criteria were the presence of metabolic or endocrine disorders; concomitant treatment with antibiotics, NSAIDs; use of psychoactive

substances; alcohol or smoke abuse; allergy or hypersensitivity to Fitostimoline constituents; treatment with Fitostimoline ovules in the month preceding the surgery.

Study Design, Treatments and Outcome Measures

The study was performed according to an open-label, controlled, randomized NCT04612881, 2-arm (Fitostimoline ovules and control) parallel design. Before surgery the presence of any symptom such as vaginal discharges, itching, vaginal burning, pain during intercourses, signs of infections, stypsis or cystitis were recorded. At the baseline visit, eligible patients were randomly assigned to receive the treatment with Fitostimoline ovules for 12 consecutive days after hospital discharge or were assigned to the control group in which no treatment was performed. Vaginal ovules were given to the patients to be applied in the evenings. A vaginal and speculum exploration was performed at the baseline visit and photos of vaginal cuff were taken. The patients were asked to record any type of symptom occurring in the first 12+/-3 days.

A second visit was performed at 12 +/- 3 days from the baseline visit: vaginal and speculum exploration was performed in order to evaluate the objective presence of vaginal bleeding and the healing of the cuff. Any adverse event or reaction to the product was investigated and recorded. Seven subjective symptoms (vaginal discharges, itching, vaginal burning, pain during intercourses, signs of infections, stypsis or cystitis) were evaluated by a semi quantitative scale (0=absence; 1=mild; 2=moderate; 3=severe). Vaginal bleeding was evaluated by a semi quantitative scale from 0 being absence of blood loss to 10 being severe hemorrhage, for each day.

After 40 +/- 3 days from the baseline visit all the patients were contacted for a telephone interview and the same symptoms were studied with the same scales. Tolerability, practicality and comfort of Fitostimoline ovules were considered. The primary outcome of the study was the efficacy of Fitostimoline ovules on the prevention of vaginal bleeding after hysterectomy compared with no treatment. The secondary outcome of the study was the efficacy of Fitostimoline ovules on symptoms correlated with local inflammation, such as signs of vaginitis, cystitis (Figure 1).

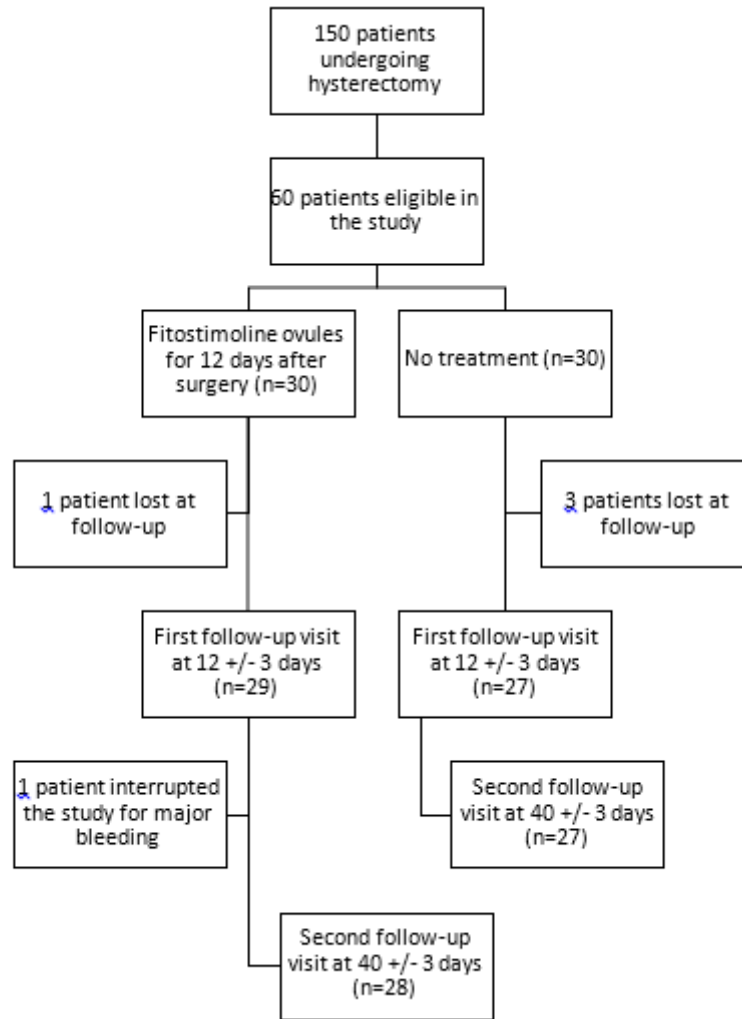


Figure 1: Study design and patients.

Ethics

The study was conducted according to the criteria set by the declaration of Helsinki and each subject signed an informed consent before participating to the study.

Statistics

Data were analyzed using IBM SPSS statistics (version 27.0; SPSS, Chicago, IL, USA) and expressed as means \pm SD. All variables deviating from normal distribution were log transformed before parametric statistics. Descriptive statistics were performed using the analysis of variance (ANOVA) test or χ^2 distribution, with Monte Carlo simulation to generate exact p-value. Significance was set at $p < 0.05$.

Results

A population of 150 women underwent hysterectomy at Macedonio Melloni Hospital between October 2020 and July 2021. Among these, 60 women fulfilled the inclusion criteria and were enrolled in the study. Four patients were lost during the follow up. Thirty-four women underwent surgery due to uterine fibroids, 4 were treated for endometriosis, 2 for adnexal masses, 3 patients had endometrial hyperplasia, 3 uterine prolapse, 14 for neoplastic diseases. Median age of all population was 50 years (IQR 47-55); 18 out of 60 patients were already in menopause. Laparoscopy hysterectomy was performed in 41 patients, laparotomic hysterectomy in 14 patients and vaginal hysterectomy in 5 patients. Where laparoscopic surgery was performed, vaginal

cuff was always closed laparoscopically (Table 1). The patients were randomized into the Fitostimoline ovules group and control group.

Fitostimoline ovules group

Thirty patients were enrolled in the Fitostimoline group. Twenty-four (80%) out of 30 patients underwent laparoscopic hysterectomy, 3 (10%) laparotomic hysterectomy whilst vaginal hysterectomy was performed in 3 (10%) patients. Median age was 50,5 years.

Indication to hysterectomy was fibroid in 18 (60%) women, endometriosis in 1 (3%), adnexal masses in 2 (7%) uterine prolapse in 2 (7%) and neoplastic diseases in 7 (23%) (Table 1). One of the patients in this group was lost at follow-up because she didn't show up at the post-operative controls.

| | Fitostimoline group (n=30) | Control group (n=30) | Population (n=60) |
|--------------------------------|----------------------------|----------------------|-------------------|
| Age | | | |
| 35-44 | 3 (10%) | 4 (13%) | 7 |
| 45-54 | 22 (73%) | 15 (50%) | 37 |
| 55-64 | 2 (7%) | 6 (20%) | 8 |
| 65-80 | 3 (10%) | 5 (17%) | 8 |
| Menopause | | | |
| Yes | 9 (30%) | 9 (30%) | 18 |
| No | 21 (70%) | 21 (70%) | 42 |
| Type of hysterectomy | | | |
| Laparoscopic | 24 (80%) | 17 (56%) | 41 |
| Laparotomic | 3 (10%) | 11 (37%) | 14 |
| Vaginal | 3 (10%) | 2 (7%) | 5 |
| Reason for hysterectomy | | | |
| Fibroids | 18 (60%) | 16 (54%) | 34 |
| Endometriosis | 1 (3%) | 3 (10%) | 4 |
| Adnexal mass | 2 (7%) | 0 | 2 |
| Uterine prolapse | 2 (7%) | 1 (3%) | 3 |
| Endometrial hyperplasia | 0 | 3 (10%) | 3 |
| Neoplastic disease | 7 (23%) | 7 (23%) | 14 |

Table 1: Patient characteristics.

At the first control at 12 +/- 3 days after hospital discharge, 13 out of 29 (45%) of patients in the Fitostimoline group reported no evidence of vaginal bleeding after surgery. Thirteen patients (45%) reported minor vaginal bleeding, 2 (7%) discrete vaginal bleeding and 1 (3%) had a major vaginal bleeding that required interruption of the treatment and the exclusion from the study.

At the second control at 40 +/- 3 days after hospital discharge, 22 out of 28 (79%) patients reported no evidence of vaginal bleeding, 5 patients (18%) reported minor vaginal bleeding and one (3%) had discrete vaginal bleeding (Table 2).

The medial duration of minor vaginal bleeding in the Fitostimoline group was 11.8 days (IQR 6.5-11.5), whilst for discrete vaginal bleeding the medial duration was 4 days (IQR 3.5-4.5).

Control group

Thirty patients were enrolled in the control group. Seventeen (56%) out of 30 patients underwent laparoscopic hysterectomy, eleven (37%) laparotomic hysterectomy whilst vaginal hysterectomy was performed in two (7%) patients. Median age was 51 years.

Indication to hysterectomy was fibroid in 16 (54%) women, endometriosis in 3 (10%), uterine prolapse in 1 (3%), endometrial hyperplasia in 3 (10%) and neoplastic diseases in 7 (23%) (Table 1).

Three of the patients in this group were lost at follow-up because they didn't show up at the post-operative controls. At the first control at 12 +/- 3 days after hospital discharge, 11 out of 27 (41%) of patients in the control group reported no evidence of vaginal bleeding after surgery. Five patients (18%) reported minor vaginal bleeding and eleven (41%) discrete vaginal bleeding. At the second control at 40 +/- 3 days after hospital discharge, 17 out of 27 (63%) patients reported no evidence of vaginal bleeding, 6 patients (22%) reported minor vaginal bleeding and 4 (15%) had discrete vaginal bleeding. (Table 2).

| | Fitostimoline group 12 +/- 3 days | Fitostimoline group 40 +/- 3 days | Control group 12 +/- 3 days | Control group 40 +/- 3 days |
|---------------------------|--------------------------------------|--------------------------------------|--------------------------------|--------------------------------|
| No vaginal bleeding | 13/29 (45%) | 22/28 (79%) | 11/27 (41%) | 17/27 (63%) |
| Minor vaginal bleeding | 13/29 (45%) | 5/28 (18%) | 5/27 (18%) | 6/27 (22%) |
| Discrete vaginal bleeding | 2/29 (7%) | 1/28 (3%) | 11/27 (41%) | 4/27 (15%) |
| Major vaginal bleeding | 1/29 (3%) | 0 | 0 | 0 |

Table 2: Results.

The medial duration of minor vaginal bleeding in the control group was 12 days (IQR 6.5-16.5), whilst for discrete vaginal bleeding the medial duration was 8 days (IQR 5-10).

Discussion

Triticum vulgare, belonging to the family of Gramineae, is the selected source used by Farmaceutici Damor to prepare Fitostimoline ovules. It has been extensively used in traditional medicine thanks to its properties of accelerating tissue repair by stimulating chemotaxis and the fibroblastic maturation and significantly increasing the fibroblastic index, which are crucial points in the repairing processes [10,11,13]. Furthermore, TVE is able to stimulate the polymerization of actin, the motor of cell contractility and movement. An increase of actin polymerization has been linked to an increase in cell migration on wound edge and an improvement of wound contraction. By increasing the level of polymerized actin in fibroblasts, TVE could regulate the proliferative and remodeling phases of wound healing, accelerating the ability of fibroblasts to repair the damage [9]. In 2018, Sanguigno, et al. demonstrated that TVE also exerts anti-inflammatory properties since it reduces the release of the well-known agents triggering the inflammatory process, such as IL-6, TNF α , prostaglandin E2 and nitric oxide in LPS-stimulated BV2 microglial cells and in primary rat microglia, thus exerting an anti-inflammatory activity and favoring the transition from the inflammatory to regenerative process [12].

Surgical traumas can activate several biological pathways among which an increased production of reactive species causing the state known as oxidative stress [15,16]. As a surgical procedure, hysterectomy triggers detectable changes of oxidative stress status and different studies identified several factors that contribute to the production of free oxygen radicals during and after the intervention (e.g. peritoneal closure, retention of ovaries, hormonal changes) [17-19]. TVE is utilized to produce different pharmaceutical products that are commonly used for the treatment of decubitus ulcers, burn lesions, scarring, and sores. All these injuries are associated with increased free radical production, which might delay the wound healing process [9].

Thus, we supposed that the application of *Triticum vulgare* ovules in patients undergoing hysterectomy could reduce the oxidative stress linked to the surgical procedure and facilitate the local healing process, stimulating the reparative process of the vaginal cuff, therefore reducing the vaginal bleeding.

In this randomized clinical trial, treatment with Fitostimoline ovules was more effective than no treatment in reducing the quantity of postoperative vaginal bleeding in women after hysterectomy. Our study showed that patients that used Fitostimoline after surgery had a median duration of discrete vaginal bleeding of 4 days, compared with 8 days without the treatment, this being statistically significant with a p-value of 0.015. If we consider minor vaginal bleeding there is no statistical significance in the duration between the two groups.

As previously stated, vaginal bleeding after hysterectomy can be one of the signs of vaginal cuff dehiscence. By now, only two effective strategies have been identified in reducing the risk for this complication: the use of barbed sutures and the adoption of a laparoscopic approach to close the vaginal cuff [20].

The decreasing of the duration of post-operative vaginal bleeding is an indirect sign of a better tissutal regeneration for the already cited biological reasons of the TVE, and we can speculatively affirm that the application of Fitostimoline ovules may be useful in the prevention of more serious complications such as vagina cuff dehiscence.

Investigating the number of patients with vaginal bleeding, with and without Fitostimoline ovules, we observed that there was no statistical difference between the two groups, considering either minor or discrete blood loss. All the patients treated with Fitostimoline ovules had a good compliance (>95%) to the therapy. None interrupted the study due to discomfort or side effects. All patients, when asked, reported a good tolerance to the product. When stratifying the patients in the two groups by menopausal status, surgical approach and the reason why the patient was undergoing the surgery, no difference emerged between the two groups.

Conclusions

Our study showed that the use of Fitostimoline ovules after hysterectomy is effective in reducing the quantity of vaginal bleeding, regardless the menopausal status, surgical approach and type of indication to surgery. Considering the risk of major complications related to post-hysterectomy vaginal bleeding, such as vaginal cuff dehiscence, Fitostimoline ovules could be considered a valid option in order to prevent the occurrence of this complication.

Author Contributions

MG, LN and MV were responsible for data collection and manuscript writing. MV was responsible for project development and manuscript writing. RI contributed to statistical analysis and manuscript revision.

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