INTRODUCTION

Uterine fibroids (UFs), or leiomyomas, are non-malignant uterine tumors. They generally arise from myometrial smooth cells and are biologically characterized by extracellular matrix secretion, steroid hormone responsiveness and increased cell proliferation. UF s are highly sensitive to estrogens and progestins, usually shrinking spontaneously after menopause. Several investigations...
on UF etiology focused on risk and stimulating factors, such as ethnicity and biological factors. Afro-American women are more likely than Caucasian women to develop such a formation, and younger women show higher UF proliferation rates. Other factors associated with UF development include genetics, nulliparity, and early menarche.

During their lifetime, more than 50% of women develop UF, rising to 70% in perimenopausal women. As a result, up to 70% of fertile women can develop UF, even though more than 50% of women affected by UF will never develop symptoms, such as pelvic pain, menorrhagia, dysmenorrhea, anemia, infertility, and troublesome gestation. Due to these severe symptoms, quality of life (QoL) must be considered as an important parameter to assess in women affected by UF, in relation to therapy. The commonest approach in asymptomatic UF management is currently the “wait and see” method, monitoring UF growth and waiting for its spontaneous shrinking after menopause. However, because of the burden of symptoms, symptomatic patients displaying UF are usually scheduled for surgery. The estrogen-responsiveness of UF frequently leads to their recurrence, making hysterectomy the only definitive surgical treatment. Other surgical approaches include myomectomy, uterine artery embolization, and high-frequency magnetic resonance-guided focused ultrasound surgery.

The most expensive and complex pharmaceutical treatments for UF include gonadotropin-releasing hormone agonists and selective progesterone receptor modulators. Ulipristal acetate (UPA), a synthetic selective progesterone receptor modulator, became one of the most widely used drugs in UF treatment. It proved to be useful both in UF management and in pre-surgical treatment, for UF shrinkage and symptom improvement. Nevertheless, important side effects were reported following UPA treatment, the most life-threatening of which was liver failure. Because of these severe adverse effects, on May 13, 2020, the Italian government Pharmaceutical Agency (AIFA) republished the note produced by the European Medicine Agency’s Pharmacovigilance Risk Assessment Committee, recommending immediate suspension of UPA administration.

It therefore became necessary to search for alternative treatments, without the risk of side effects, especially in patients who had previously used UPA. Among these natural treatments, promising data emerged for epigallocatechin gallate (EGCG) and vitamin D3 administration, either alone or in combination. Studies showed that vitamin D3 was able to inhibit cell proliferation, to block growth, while EGCG displayed a UF shrinking activity. Porcaro et al. reported that the combined treatment of EGCG plus vitamin D3 led to a significant reduction in the UF-related symptomatology, with a QoL improvement in patients undergoing this treatment. We, therefore, decided to evaluate the compliance of patients who were forced to stop UPA therapy and switch to another natural therapy such as EGCG plus vitamin D3, analyzing the QoL differences at the end of their 3 months of UPA treatment and after subsequent natural treatment.

2 MATERIALS AND METHODS

A cohort of women undergoing UPA (Esmya®; Gedeon-Richter Company, Milan, Italy) administration for UF symptoms, was contacted by phone by their private gynecologists when the Pharmacovigilance Risk Assessment Committee recommended stopping the use of UPA. Patients were all checked in private clinics by their gynecologists and found to be healthy. Some women asked to switch UPA to other therapies, including natural ones, to continue a treatment against UF, according to common clinical practice. It was proposed to switch from Esmya (stopped after the first cycle of 3 months) to a natural therapy, containing EGCG 150 mg plus vitamin D3 25 µg plus vitamin B6 5 mg (Delphysis®; Farmares Company, Rome, Italy), for 3 months. All patients were asked to anonymously complete the Uterine Fibroids symptoms and Quality of Life Questionnaire (UFS-QOL) after stopping UPA administration (T0) and after 3 months of natural treatment (T1). The UFS-QOL questionnaire aims to evaluate the general health condition of the patient in many areas. The questionnaire comprises 37 questions whose answers are scores from 1 to 5. It included eight questions about symptoms severity (SS), for which the assigned scores are higher in the case of more severe symptoms. The SS value ranged between 8 and 40, 8 being associated with no symptoms and 40 corresponding to severe symptoms. The other 29 questions were about Health-related Quality of Life (HRQL). These questions aimed to verify how the treatment impacted on different aspects of the women’s life. In the HRQL questions, lower scores represented worse life conditions, whereas higher scores were signs of better QoL. The sub-groups of HRQL questions were: Concern, Activities, Energy and Mood, Control, Self-consciousness, and Sexual function. These questions evaluated how the treatment affects respectively: anxiety; daily activities such as sport, travel or work; fatigue, exhaustion and irritability; women’s feeling about their possibilities; women’s perception of their body; sexual desire and activity.

The investigation on QoL after UPA and nutraceutical administration was carried out in private clinics, after informed consent had been signed by all patients spontaneously referred to the proposed study. As a result the study was carried out without Institutional Review Board or Ethics Committee approval.

The collected QoL data were analyzed and transformed into percentage scores as previously described. The scores were then analyzed using paired Student’s t test. A P value less than 0.05 was considered significant. Values are expressed as mean ± standard deviation. In this manuscript, UF are classified with a number ranging from 1 to 3: 1 corresponding to UF in the endometrial cavity; 2 being associated with intramural UF; and 3 belong to serosal UF.

3 RESULTS

Out of 39 patients attending the private clinic, a total of 30 Caucasian women participated in this data collection, with the following
demographic data: mean age 35.9 ± 3.93 years, body mass index (calculated as weight in kilograms divided by the square of height in meters) of 23.63 ± 2.95 on average, mean parity 0.83 ± 0.87 children. The UF parameters were the following: mean number of UFs 1.53 ± 0.68 per woman, and UF diameter 5.65 ± 1.69 cm, with intramural UF as the most frequent type. Their data before starting UPA therapy are reported in Table 1.

At T0, the SS score was 41.46% ±10.28%, but decreased to 29.27% ±4.60% at T1 (P < 0.001). The HRQL mean scores were 70.34% ±10.60% at T0 and 82.13% ±4.91% at T1 (P < 0.001) (Figure 1).

Concerning the sub-group of HRQL questions, the Concern score moved from 71.17% ±12.30% at T0 to 81.33% ±6.94% at T1 (P < 0.001). Activity score at T0 was equal to 66.07% ±14.15%, but at T1 it had increased to 77.62% ±10.01% (P < 0.001). The score of energy and mood sub-group at T0 was equal to 79.52% ±8.12% (P < 0.001). The control sub-group was the most improved, changing from 67.83% ±15.68% at T0 to 84.67% ±7.06% at T1 (P < 0.001). Self-consciousness scores were 77.22% ±12.93% at T0 and 89.72% ±9.71% at T1 (P < 0.001). Sexual function scored 80.00% ±18.74% at T0 and 91.25% ±12.35% (P = 0.0046) (Figure 2). No adverse effects were reported following UPA or EGCG plus vitamin D3 treatments.

### Table 1: Clinical data of patients

| Patient | Age, years | BMI | Parity | Numbers of fibroids | Fibroid diameter (cm) | Uterine zone |
|---------|------------|-----|--------|---------------------|----------------------|--------------|
| 1       | 32         | 26  | 0      | 2                   | 5-7                  | 2-1          |
| 2       | 38         | 24  | 1      | 1                   | 8                    | 2            |
| 3       | 30         | 21  | 0      | 1                   | 10                   | 1            |
| 4       | 35         | 25  | 0      | 2                   | 6-8                  | 1-2          |
| 5       | 31         | 27  | 1      | 1                   | 7                    | 2            |
| 6       | 33         | 30  | 1      | 2                   | 7-4                  | 1-2          |
| 7       | 41         | 22  | 2      | 1                   | 6                    | 2            |
| 8       | 32         | 24  | 0      | 1                   | 5                    | 1            |
| 9       | 37         | 21  | 2      | 3                   | 5-5-4                | 1-2-2        |
| 10      | 39         | 26  | 1      | 1                   | 9                    | 1            |
| 11      | 36         | 23  | 0      | 2                   | 4-6                  | 2-3          |
| 12      | 31         | 20  | 0      | 3                   | 3-5-7                | 1-1-2        |
| 13      | 34         | 30  | 1      | 1                   | 6                    | 2            |
| 14      | 39         | 22  | 2      | 1                   | 5                    | 3            |
| 15      | 33         | 19  | 0      | 1                   | 7                    | 3            |
| 16      | 35         | 21  | 0      | 1                   | 5                    | 3            |
| 17      | 32         | 23  | 0      | 2                   | 5-4                  | 1-2          |
| 18      | 37         | 22  | 1      | 1                   | 7                    | 2            |
| 19      | 31         | 24  | 0      | 2                   | 7-3                  | 2-3          |
| 20      | 35         | 25  | 1      | 1                   | 7                    | 2            |
| 21      | 40         | 27  | 1      | 1                   | 6                    | 1            |
| 22      | 31         | 20  | 0      | 2                   | 5-6                  | 3-2          |
| 23      | 36         | 21  | 0      | 1                   | 7                    | 1            |
| 24      | 37         | 19  | 1      | 1                   | 5                    | 3            |
| 25      | 42         | 23  | 2      | 2                   | 3-6                  | 1-2          |
| 26      | 34         | 22  | 0      | 1                   | 8                    | 2            |
| 27      | 41         | 24  | 3      | 3                   | 2-4-7                | 1-2-2        |
| 28      | 39         | 28  | 2      | 1                   | 6                    | 2            |
| 29      | 44         | 26  | 2      | 2                   | 3-5                  | 2-3          |
| 30      | 42         | 24  | 1      | 2                   | 4-6                  | 1-2          |
| Mean    | 35.9       | 23.63| 0.83  | 1.53                | 5.65                 | 2            |
| SD      | 3.93       | 2.95 | 0.87  | 0.68                | 1.69                 |              |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); SD, standard deviation.

*Reports mode instead of mean, to evaluate the most affected zone.*
Given the withdrawal of UPA in spring of 2020, during the coronavirus disease 2019 pandemic, gynecologists sought an alternative therapy for UFs with no or few established risks or adverse effects. Patient QoL was already investigated after different cycles of UPA treatment by Lukes et al., showing an important improvement in UF-related symptoms due to the reduction in UF mass. We therefore decided to look for a natural therapeutic alternative to investigate the QoL, achieving comparable results and free from severe adverse effects. Based on the investigation by Porcaro et al., highlighting that an EGCG and vitamin D3 combination reduced UF symptoms and enhanced UF shrinkage, we decided to administer this natural therapy. Evaluation of compliance after stopping UPA therapy showed that natural therapy improved the QoL of women with UFs. As a result, we hypothesize that the positive effects on symptom relief in patients taking UPA for 3 months continued with therapy based on EGCG plus vitamin D3, with a reduction in SS and an improvement in the QoL. In fact, the SS score in these women was 12.19% lower with great significance. We believe that this could be due to three different factors. First, even if UPA administration was suddenly stopped, it caused a long-term improvement, that could be responsible for part of this reduction. Second, EGCG and vitamin D3 administration is known to achieve the same goal, improving general health condition of women with UFs. Third, studies on EGCG and/or vitamin D3 administration in women with UFs have not reported adverse effects, in contrast to UPA, which was withdrawn because of its side effects.

A few days before UPA withdrawal, the Italian government declared a national lockdown to prevent the spread of severe acute respiratory syndrome coronavirus 2, so patients who had to suddenly suspend UPA therapy could not attend routine clinical examinations in hospitals because of the pandemic. Considering patients’ QoL, we decided to recommend a natural treatment based on EGCG and vitamin D3. This treatment, already evaluated in other studies, never reported adverse effects in women with UFs, even if the effects of the shift on QoL were not known. This was also the reason why the study was carried out.

Considering HRQL parameters, these natural molecules showed important benefit in all the life-related parameters analyzed. The control sub-group was the most improved by EGCG and vitamin D3 treatment, rising significantly by 16.84%. The other sub-groups were also significantly improved. Concern improvement was equal to 10.16%, activity score rose by 11.55%, energy and mood rose by 9.4%, self-consciousness growth was 12.5%, and sexual function increased by 11.25%. These data show that EGCG plus vitamin D3 could represent a therapeutic opportunity, in terms of compliance and QoL, for patients forced to stop taking UPA.

Moreover, besides the positive effects of EGCG and vitamin D3 on the QoL, these molecules have already proved to be efficient against UFs. EGCG reported significant antiproliferative effects in human UF cells, even after transplantation in nude mice, reducing tumor progression. EGCG was confirmed to modulate the cell cycle in different cancer types, inhibiting cyclin-dependent kinases 1 and 2. EGCG also has antioxidant and anti-inflammatory activities, scavenging free oxygen radicals and interfering with pro-inflammatory signaling cascades. It also has the ability to induce

**FIGURE 1** Symptom severity and health-related quality of life (HRQL) after ulipristal acetate (UPA) and after epigallocatechin gallate plus vitamin D3 (EGCG+Vit D3) treatments; ***P < 0.001

**FIGURE 2** Health-related quality of life (HRQL) subgroups after ulipristal acetate (UPA) and after epigallocatechin gallate (EGCG+Vit D3) treatments; **P < 0.01; ***P < 0.001
apoptosis in cancerous cell lines and in tumor-transplanted nude mice.29

Vitamin D3 is an indispensable molecule, exerting its activities on the whole body. Researchers found out that in UF-affected women, vitamin D3 serum level was inversely correlated with UF volume. This molecule also regulates the cell cycle, blocking cells in G phase,30 and inhibiting proliferation of UFs.19 In addition to all these effects against UFs and tumors, the combination of these molecules proved to reduce UF size and SS, so improving QoL.20

Considering that Lukes et al.,23 reported a significant improvement in all the UFS-QOL parameters after 3 months of 5 mg of UPA per day, authors can deduce that EGCG and Vitamin D3 combined treatment confirmed and maintained UPA compliance, even with better results. Finally, Lukes et al.,23 also highlighted that women who continued on the therapy after the first cycle showed slight or absent improvement in QoL, so we can hypothesize that natural therapy could improve the QoL of these patients.

The strength of the study is that it was conducted in a period of pandemic, when physicians were unable to select a clinical alternative without side effects for a cohort of women left temporarily without therapy by the sudden withdrawal of their treatment from the market. These women all needed harmless therapeutic alternatives because of the lack of appropriate clinical controls. We believe that the present investigation could represent an intriguing therapeutic opportunity for patients forced to suddenly suspend UF treatment with UPA, as the natural treatment for UFs, based on EGCG and vitamin D3, was safe and improved their QoL after a single UPA cycle of 3 months. The sudden withdrawal of UPA from the drug market left an important bias in the therapeutic management of UFs and natural treatment replaced hormonal treatment, with a positive impact on QoL.

The limits of the study are that it is observational, conducted over a short period of time and on a small sample size. Therefore, we would encourage further placebo-controlled, randomized, and double-blind studies on this subject, comparing UPA directly with the EGCG plus vitamin D3 combination, to validate these preliminary data.

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CONFLICTS OF INTEREST
The authors declare that they have no conflicts of interest and nothing to disclose. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

AUTHOR CONTRIBUTIONS
AT and SG contributed to the concept and design. All authors contributed to the acquisition of data. AT, OD’O and ML drafted the article, and AT and SG provided critical revision for important intellectual content.

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