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Uterine fibroids treatment: do we have new valid alternative? Experiencing the combination of vitamin D plus epigallocatechin gallate in childbearing age affected women

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Abstract. – OBJECTIVE: Uterine myomas are the most common benign tumors in females, and at least 25% of affected patients experience symptoms severe enough to need treatment, like heavy hemorrhage, pelvic pain, and infertility. Currently, a non-invasive approach is preferred in women of childbearing age who desire pregnancy. The aim of our study was to determine the effect of oral supplementation with a combination of vitamin D plus epigallocatechin gallate (EGCG) and vitamin B6 in women with myomas.

PATIENTS AND METHODS: Between April and December 2020, we enrolled 95 women of childbearing age, afferent to our hospital, displaying at least one myoma with a diameter <4 cm. Patients were divided in two groups: 41 women were treated daily with two tablets of 25 µg vitamin D + 150 mg EGCG + 5 mg vitamin B6 for 4 months; 54 women, representing the control group, received no treatment. Total volume and vascularization of myomas were analyzed ultrasonographically. Bleeding and pelvic pain was also evaluated, as well as patients' quality of life and health through questionnaire Short Form Health Survey (SF-36) and Patient Global Impression of improvement (PGI-I).

RESULTS: After treatment myomas' total volume and peripherical vascularization significantly decreased respectively by 37.9% (p<0.001) and 7.7%. On the other hand, we observed an increase in myomas' volume by 5.5 % and of peripherical vascularization by 5% in the control group. The treated group reported an improvement in SF-36 (p<0.001) and PGI-I (85.4%) questionnaire scores.

CONCLUSIONS: We demonstrated, in young women who want to preserve fertility, that the combined supplementation of vitamin D, EGCG, and vitamin B6 reduced myomas' volume and improved patients' quality of life, without side effects.

Key Words:
Fibroids, Vitamin D, Epigallocatechin gallate, Vitamin B6.

Introduction

Uterine myomas, also known as fibroids, are the most common benign tumors in reproductive women. Their prevalence is reported from puberty and usually decreases with menopause[1]. Uterine fibroids origin from monoclonal growth of smooth muscle cell of the myometrium and are composed of large amounts of extracellular matrix (ECM) containing collagen, fibronectin and proteoglycans[2].

There are several risk factors for uterine fibroids, as race (African-American women have a greater chance of being affected by uterine fibroids rather Caucasian women), age, parity (pregnancy has been found to have a protective effect on the development of uterine fibroids), early menarche, genetic factors, and alcohol and caffeine intake[1-3]. Cigarette smoking does not appear to be related to the overall risk of increased incidence and size of uterine fibroids[4].

Nowadays, the exact pathophysiology of fibroids remains unclear although several mechanisms underlying the pathogenesis of fibroids have been hypothesized. Importantly, sexual hormones, such as estrogens and progesterone, are implicated in growing of fibroids. Estrogen regulates transcription of growth factors and oncogenes, as TGF-β3 and p53, by binding to the nuclear estrogen receptor (ER-α)[5]. Progesterone is also considered a key hormone involved in

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the differentiation and growth of smooth muscle cells of the myometrium. Different pathways and growth factors are involved by progesterone's action[6]. Location and growth of myomas are the main factors that determine symptoms. Leiomyomas are classified according to their position in the myometrium and their relationship to the myometrium and the serous surface. Different locations are classified as follows: submucosal, intramural, and subserosal. In particular, the FIGO classification published by Munro et[7] al in 2011, describes eight types of fibroids (types range from 0 to 8. 0 = Pedunculated, intracavitary; 1 = Submucosal, <50% intramural; 2 = Submucosal, ≥50% ...) as well as hybrid leiomyomas (impact both endometrium and serosa). Small lesions can be symptomatic if located within the uterine cavity or in contact with other organs, while a large lesion on the outside of the uterus may go unnoticed. Although about 50% of women remain asymptomatic, the most commonly occurring symptoms are heavy menstrual bleeding, and subsequent anemia, dysmenorrhea, and pelvic pain[8]. Compression of the surrounding organs like bowel or bladder can lead to urgency, increased daytime urinary frequency, and urinary incontinence[9]. Abdominal distention or distortion, pelvic pressure on the ureters (leading to hydronephrosis) and pelvic blood vessels (especially pelvic veins) can interfere with quality of life (QoL). Moreover, fibroids can affect obstetric outcomes leading to recurrent abortion, preterm deliveries (<37 weeks), primary cesarean section, and lower birth weight infants. Fibroids can impair fertility through several possible mechanisms, mainly in the case of submucous fibroids[10,11]. The mechanisms involved are alteration of the local anatomy with anatomic distortion of the uterine cavity and subsequent alterations to endometrial function. Functional changes, such as impairment of the endometrial and subsequent myometrial blood supply and increased uterine contractility, are involved too in fertility impairment[12].

Uterine fibroids, therefore, represent a significant burden to the health care system, and at least 25% of affected patients experience symptoms severe enough to need treatment. In women of childbearing age, minimally invasive procedures or alternative medical treatments are preferred, avoiding radical abdominal surgery.

The different clinical approach depends on symptomatology, fibroid size, number, localization and finally on the desire for future pregnancy. Conservative therapy consists of pharmacological treatment with gonadotropin-releasing hormone agonists, estro-progestins or only progesterone for oral route. In recent years, ulipristal acetate (UPA), a selective progesterone receptor modulator (SPRM), was widely discussed in the literature and used in common clinical practice for managing symptomatic fibroids[13]. However, the last safety concerns on the liver injury induced by UPA encouraged new studies to find alternative treatment strategies[14].

The aim of our study was to investigate the efficacy of combined oral supplementation of vitamin D plus epigallocatechin gallate (EGCG) and vitamin B6, in women with myomas, particularly in reducing the size of fibroids and improving the quality of life of women affected.

Vitamin D, which is a common name of group of fat-soluble steroid compounds that present a lot of effects on human body, can be classified as a hormone, with receptors found in various tissues, primarily involved in the regulation of calcium and bone health, and has an anti-proliferative, pro-apoptotic effects and induces cell differentiation[15]. In particular, Corachàn et al[16] demonstrated the decreases of human uterine leiomyoma size in a xenograft animal model, corroborating that long-term vitamin D treatment acts as an anti-proliferative, antifibrotic, and proapoptotic therapy. In addition, a great number of studies have investigated the role of vitamin D also in the growth of myomas and, as demonstrated by Sabry et al[17] and Baird et al[18], women with low vitamin D serum level have an increased risk of uterine fibroid (UF), *vs.* women without UF, with evidence that sufficient vitamin D is associated with a reduced risk of uterine fibroids. Epigallocatechin Gallate (EGCG) is a catechin polyphenol contained in green tea, and different studies have investigated the role of EGCG in the growth of myomas, either *in vitro* or *in vivo* animal models. In the study of Roshdy et al[19], EGCG, given to symptomatic women affected by fibroids, improve women's health globally, reducing human myoma cell proliferation. Furthermore, in different studies[20,21] on UF conducted in an animal model, EGCG showed a reduction in UF cell proliferation while induced cell apoptosis.

Vitamin B6, which is part of the vitamin B group and its active form, pyridoxal 5′-phosphate (PLP), is a coenzyme in at least 100 enzyme reactions in amino acid, glucose, and lipid metabolism, in particular in tryptophan me-

tabolism. Recent studies[22,23] had investigated and opened new scenarios regarding an important role as an antioxidant and anti-inflammatory and as a modulating molecule of immunity and gene expression.

Patients and Methods

Patients and Treatment

Women affected by uterine myomas, referring to the Reproductive Physiopathology and Andrology Unit and to the Department of Obstetrics and Gynecology of Sandro Pertini Hospital of Rome, were enrolled during the period between April and December 2020. All women enrolled gave their written informed consent after the explanation of the study purpose. The study was conducted following the Ethical Principles of the Helsinki Declaration and the national laws and it was approved by our Ethical Committee Protocol No. 0061226/2020 of 08/04/2020.

Inclusion criteria were: women from 18 years of age or older, in childbearing age, with at least one myoma with a diameter <4 cm detected by vaginal (TVU) and abdominal ultrasound, and myoma color score between 1 and 2: Color score 1 means absence of vascularization, color score 2 means a peripherical vascularization of myomas, according to the color power Doppler score classification of Morphological Uterus Sonographic Assessment (MUSA)[24].

Exclusion criteria were: pregnant women or intended to become pregnant during the following six months, currently breastfeeding, in menopause, with severe anemia or other medical morbidities, such as hypertension, diabetes, obesity (patient BMI > 30 kg/m^2), more than 5 fibroids for patient, history of myomectomy, endometrial lesions (polyps, endometrial hyperplasia, and intrauterine adhesions), uterine malformations eligible to surgery, treatment with corticosteroids or hormones (oral contraceptives, estrogenic, progestin), elevated liver enzymes, use of GnRH analogues or SPRM within the past six months.

We enrolled 102 women coming to our hospital's divisions, fulfilling inclusion/exclusion criteria. 7 of them left the study and the remaining 95 women were divided in two groups.

The first group (study group) of 41 women received by oral route one tablet of 25 μg vitamin D + 150 mg EGCG + 5 mg vitamin B6 (Delphys, Farmares S.r.l., Rome, Italy), twice a day for 4 months. The second group of 54 women (control group), who did not accept to follow a therapy during the same period of 4 months, preferred to be only monitored and received no treatment.

Study Outcomes

The primary outcome was the change of myoma volume assessed by transvaginal ultrasonography (TVU), and/or transabdominal ultrasonography.

Secondary outcomes were the variation of myomas color score, distress by heavy bleeding during the menstrual period (we decide to consider only the heavy subjective experience of bleeding through a self-administered bleeding assessment), pelvic pain, measured thanks VAS scale, and health of the women measured through questionnaires: PGI-I and SF-36.

An instrumental evaluation was performed at baseline (T0) and after 4 months of therapy (T1). All vaginal/abdominal ultrasounds were performed by an expert operator, using the same ultrasounds machine (Samsung WS80A). The volume of myomas (expressed in cm^3) was calculated as $1/6\ \pi \times D1 \times D2 \times D3$, where D1, D2, and D3 are the three diameters of the nodule that are at right angles to each other. Vascularization was assessed by color Doppler of the ultrasound machine.

To evaluate women's pain experience, we administered to both groups the visual analogue scale (VAS), which is a psychometric response scale that can be used in questionnaires, namely a measurement instrument for subjective characteristics or attitudes that cannot be directly measured. When responding to a VAS item, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two endpoints. To calculate women's health and quality of life, we asked both groups to fill in the Short Form Health Survey (SF-36) at (T0) and after 4 months (T1), and we administered the Patient Global Impression of Improvement questionnaire (PGI-I) only to those patients underwent the 4 months treatment. The SF-36 is a measure of health status and is commonly used in health economics as a variable in the quality-adjusted life year calculation to determine the cost-effectiveness of a health treatment[25]. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. The lower the score (minimum score 0) the more disability and the higher the score (maximum score 100) the less disability. The Patient Global Impression of Improvement

(PGI-I) is a global index used to rate the response of a condition to therapy, with scores from 1 (very much better) to 7 (very much worse). Regarding gynecological disease, until now, PGI-I has only been validated for urinary incontinence, and other recent studies are trying to validate this test for other diseases, like prolapse[26]. We used this scale because it is simple, direct, and easy intuitively understandable to clinicians.

Statistical Analysis

Statistical analysis was performed using unpaired test when comparing two groups, with the results expressed as mean ± standard deviation (SD). Wilcoxon-Mann-Whitney test was used for VAS scale, SF-36, and PGI-I and other clinical results; values are indicated as sum, median, percentage. A p-value ≤0.05 is considered statistically significant.

Results

In this study, 95 women with myomas were enrolled and divided into two groups. The study group was orally supplemented for 4 months with one tablet containing an association of 25 µg vitamin D + 150 mg EGCG + 5 mg vitamin B6 twice a day. The control group received no treatment.

Regarding demographics characteristics of our sample, both two groups were comparable for all parameters. The baseline clinical features of the patients from both groups are reported in Table I.

After 4 months of daily treatment with vitamin D, EGCG and vitamin B6, though the ultrasonography exam, we observed that myomas' total volume significantly decreased by 37.9% in the study group (from a mean value of 20.55 cm³ at T0 to 12.65 cm³ at T1, p-value <0.001) (Table II) whereas we observed an increase by 5.5% of the total fibroid volume in the control group.

With respect to myoma's vascularization, we observed a decrease of the peripherical vascularization (color score 2) in the 7.7% of treated patients (36.3% pre-treatment *vs.* 28.6% after treatment), whereas in the control group, we found an increase of 5.5% of color score 2 (38.8% pre-treatment *vs.* 41.1% after treatment). Neither the number of myomas (91 pre-treatment *vs.* 99 after treatment), nor their localization, changed after 4 months of therapy in both groups (Table II).

Moreover, after treatment, we recorded a statistically significant improvement of symptoms, like pelvic pain: in the study group VAS scale median value was 4 at T0 and 2 at T1 (p-value: 0.03), while the control group showed a value of 4 both at baseline and after treatment.

Also, heavy bleeding, reported from patients of both groups, decreased in the treated group even if this reduction was not statistically significant (p-value 0.09) compared to the control group.

Table I. Baseline characteristics of patients in study and control group.

Variables	Study group (n° 41) mean ± SD	Control group (n° 54) mean ± SD	*p*-value
Age (years)	37.78 ± 2.1	38.96 ± 2.4	0.56
BMI (kg/m^2)	23.58 ± 2.9	24.98 ± 1.8	0.74
Caucasians (n°) (%)	32 (78)	41 (76)	0.32
African Americans (n°) (%)	9 (22)	13 (24)	0.21
Nulliparous (n°) (%)	27 (65.8)	30 (55.6)	0.45
Multiparous (n°) (%)	14 (34.2)	24 (44.4)	0.15
Cigarette smokers (n°) (%)	9 (21.9)	11 (20.3)	0.34
Patients with one fibroid (n°) (%)	13 (31.7)	16 (29.6)	0.34
Patients with two or more fibroids (n°) (%)	28 (68.3)	38 (70.3)	0.12
Myoma's localization according FIGO classification 7 (n°) (%):			
0 (Pedunculated intracavitary)	5 (5.55)	6 (6.66)	0.72
1 (< 50% intramural)	6 (6.59)	4 (4.04)	0.75
2 (> 50% intramural)	5 (5.55)	8 (8.08)	0.58
3 (100% intramural)	6 (6.59)	8 (8.08)	0.65
4 Intramural	20 (22)	19 (19.9)	0.92
5 Subserosal > 50%	18 (19.78)	23 (23.23)	0.42
6 Subserosal < 50%	22 (24.17)	21 (21.21)	0.66
7 (Subserosal pedunculated)	8 (8.79)	7 (7)	0.74
8 (Other)	1 (1.09)	3 (3.03)	0.64

Table II. Clinical evaluation of myomas' volume, color score, pelvic pain and quality of life.

Variables	Study group T0	Study group T1	*p*-value	Control group T0	Control group T1	*p*-value
Myomas' volume (mean/SD) cm³	20.55 ± 1.16	12.75 ± 1.16	< 0.001	21.31 ± 1.91	22.5 ± 2.11	0.83
Color score 1 (n°- %)	58 (63.7)	65 (71.4)	0.06	60 (61.2)	57 (58.1)	0.55
Color score 2 (n°- %)	33 (36.3)	26 (28.6)	0.09	38 (38.8)	41 (41.9)	0.11
Number of total myomas (n°)	91	99	0.88	91	99	0.88
Heavy bleeding (n°- %)	23 (56%)	17 (41%)	0,09	27 (50%)	26(48.1%)	0.9
Pelvic pain: VAS scale (median)	4 (4-5)	2 (1-3)	0.03	4 (4-6)	4(4-5)	0.28
SF-36 (mean/SD)	61.86 ± 9.21	80.77 ± 10.71	< 0.001	59.45 ± 8.98	67.41 ± 9.11	0.21

Abbreviation: T0: Before treatment, T1: After 4 months of therapy with vitamin D, EGCG and vitamin B6. Color Score 1: Absence of vascularization, 2: Peripherical vascularization. Vas scale: Visual analogue scale. SF-36: Short Form Health Survey 36.

In addition, we reported a significant improvement in SF-36 questionnaire with a mean score pre-treatment of 61.86 *vs.* 80.77 post-treatment in the group of treated women (*p*-value <0.001) (Table II).

In addition, in PGI-I questionnaire, that was filled out at the end of supplementation given, we had a successful result in 85.4% of treated women, given from points 1 + 2 of the questionnaire: 1 – "very much better" (73.2%) and 2 – "much better" (12.2%) (Table III). Notably, the treated patient reported no side effects during the 4 months of evaluation, and the supplementation resulted well-tolerated from all the treated patients.

As previously reported, the baseline features, such as age, numbers of fibroids, and smoking activity, were similar between the study and control groups. Moreover, we examined the impact of treatment with vitamin D, EGCG, and vitamin B6 in a subgroup of smoker patients. As reported in Table IV, the percentage of myomas' volume significantly (*p*-value <0.001) decreased by 38.49% in the smokers treated patients, similarly to what was observed for the whole sample of treated women (37.9%). On the contrary, the fibroid volume slightly increased (5%) in the smoker women of the control group.

Table III. Patient global impression of improvement (PGI-I) after 4 months of treatment with vitamin D, EGCG and vitamin B6. 35 Women (85.4%) reported positive results after treatment.

Variables	Number of patients (%)
1: very much better (%)	30 (73.2)
2: much better (%)	5 (12.2)
3: a little better (%)	4 (9.7)
4: no improvement (%)	2 (4.9)
5: a little worse (%)	0
6: much worse (%)	0
7: very much worse (%)	0
Success (1+2) (%)	35 (85.4)

Discussion

Compelling evidence in the literature reported that natural molecules, such as vitamin D, EGCG, and vitamin B6, are effective in the management of benign tumors, like uterine fibroids. A recent and complete review from Cibiera et al[27] summarized all the currently available data about natural compounds helpful to treat myomas and relieve their related symptoms, especially with a focus on those women who want to preserve their future fertility. Among the examined molecules, vitamin D and epigallocatechin gallate (EGCG) represent alternative treatments for uterine myomas.

Regarding Vitamin D, Sharan et al[28] reported that it inhibits fibroid cell growth through the suppression of catechol-O-methyltransferase (COMT), an enzyme-linked to the pathogenesis of UFs. In this study, authors demonstrated that vitamin D suppressed the expression and activity of COMT and downregulating kinases and Bcl2 involving in the growth of myoma's cell. Therefore, Halder et al[29] showed that vitamin D consistently reduced TGF-β3 effects that are involved in the process of fibrosis in human leiomyoma cells. TGF-β3 upregulates the synthesis of many of extracellular matrix proteins, like fibronectin and collagen type 1 expression, that are associated with tissue fibrosis.

Table IV. Clinical evaluation of myomas' volume in two subgroups of smokers, treated and no-treated patients.

Variables	Study group smokers (n° 9) T0	Study group smokers (n° 9) T1	*p*-value	Control group smokers (n° 11) T0	Control group smokers (n° 11) T1	*p*-value
Myomas' volume (mean/SD) cm^3	19.69. ± 1.32	12.11 ± 1.76	< 0.001	20.37 ± 1.87	21.5 ± 0.98	0.93

Also, Cibiera et al[30], in a study of 2016, found that higher TGF-b3 serum concentration, higher BMI, and positive family history increases the probability of developing uterine fibroids, instead higher vitamin D serum concentrations decrease the risk for UF. Al-Hendy et al[31] demonstrated that decreased estrogen induced UF cell proliferation following vitamin D treatment. Indeed, compared to normal myometrium, the expression of ER-α and progesterone receptors (PR-A and PR-B) inversely correlated with vitamin D receptor expression in fibroid tissue. These effects demonstrate that vitamin D antagonizes sex hormones in fibroid cells and, therefore, may have a role as anti-fibroid treatment. In 2016, Ciavattini et al[32] demonstrated that vitamin D-treated women displayed a reduced disease progression in relation to small UF. Collectively, considering the effectiveness for myomas reduction and its safety profile, vitamin D has emerged as a notable candidate for fibroid treatment and, possibly, for their prevention.

EGCG, belonging to the group of bioflavonoids, has attracted a lot of attention for fibroids' management in the last years. Literature data report that EGCG may prove beneficial outcome in preventing myoma cell proliferation since it effectively downregulates cyclin-dependent kinases involved in human cell growth (CDKs), induces apoptosis, and inhibits mitogenesis and angiogenesis, and blocks metalloproteases enzymes (MMPs) activation[33-35]. Therefore, Lu et al[36] provided basic information on the methylation of EGCG and suggested that EGCG may inhibit COMT-catalyzed methylation of endogenous and exogenous compounds. Zhang et al[37], in 2014, demonstrated that the antiproliferative and gene-modulating effects of EGCG on human myoma cells are mediated, at least partially, by the effect on COMT expression and enzyme activity.

Notably, Zhang et al[38] showed that *in vitro* ECGC inhibits the proliferation and induces apoptosis of human uterine leiomyoma cells. In this study we demonstrated *in vitro* that EGCG significantly inhibited cell growth after 5 days of exposure, and a higher dose of ECGC reached a significant result within 3 days. This study also demonstrated that EGCG induced apoptosis in a dose-dependent manner, downregulating the anti-apoptotic protein Bcl2, as well as upregulating pro-apoptotic factors. These results suggest that EGCG may be a potential anti-uterine fibroid agent acting through multiple signal transduction pathways.

Moreover, Roshdy et al[19], in a pilot randomized controlled study, investigated safety and efficacy of EGCG as anti-fibroid treatment. 33 women with symptomatic myomas were enrolled to receive daily 800 mg of EGCG for 4 months. The authors noted a significant decrease in fibroid volume, an improvement in symptoms, such as anemia, and increased health-related quality of life scores when compared to controls, who reported a worsening of symptoms over the same period. From recent studies in the literature, EGCG appears to be a well-tolerated, readily available natural compound that presents promising results for fibroid treatment. Studies with larger randomized cohorts are essential to validate the clinical effect of EGCG, alone or in combination.

Regarding vitamin B6, some studies investigated the relationship between vitamin B6 and hormones. Rose et al[39] and Bender et al[40] demonstrated that vitamin B6 interacts with both endogenous and exogenous hormones and the use of estrogen-containing oral contraceptives was associated with an abnormality of tryptophan metabolism, like that seen in dietary vitamin-B6 deficiency. The authors demonstrated that the deficiency was corrected by pyridoxine administration. Therefore, regarding the gynecological disease, there is evidence in the literature that vitamin B6 is useful in the treatment of premenstrual syndrome (PMS). In a recent study of 2020 of Retallick-Brown et al[41] vitamin B6, at high dosage of 80 mg daily, confronted with broad-spectrum micronutrient

formula (consisting mainly of minerals and vitamin) showed specific advantages for those whose symptoms are more severe. Until now, there aren't studies that investigate the use and the effect of vitamin B6, singularly administered, in the treatment of UF.

Finally, we demonstrated that the combination of vitamin D, EGCG and vitamin B6 provided a synergistic positive effective on uterine fibroids' management. Indeed, this association showed significant results in terms of reducing myomas' volume and vascularization; meanwhile, in the untreated group, an increase of volume and vascularization was observed.

Interestingly, as another important goal achieved in treated women, patients' quality of life resulted highly improved, like evidenced by SF-36 questionnaire. Different factors may have contributed to this result, including clinical and psychological aspects correlated to the supplementation, even if the reduction of the heavy bleeding and pelvic pain during the menstrual period are probably the most relevant.

Our clinical results, in terms of mean myoma volume reduction, and in terms of increasing of quality of life of patients treated, are in line with the encouraging results of a recent study conducted by Porcaro et al[42], and they are extremely relevant considering the last restrictions on the use of UPA.

We also evaluated the impact of smoking on myomas. We identified two sub-groups of smokers, with similar features, as numbers of fibroids, and smoking activity. We observed the same trend in terms of fibroid volume reduction. In comparison with the sub-group of no-treated smokers, we noticed a lightly increase of uterine volume after 4 months, similarly to the whole group of no-treated patients. We want to underline that, till now, the relationship between smoking habits and uterine fibroids in the literature is not yet elucidated and represents a controversial issue. Recently, a systematic review and a meta-analysis of Chiaffarino et al[43], included all identified studies on the association between smoking and uterine myoma. This meta-analysis found no significant relationship between smoking and risk of uterine myoma, and our study seems to confirm that result.

Overall, we observed that the oral supplementation of vitamin D and EGCG has a positive impact on the general health status of women with myomas, preventing a possible increase of their size[27,42].

Conclusions

This manuscript showed the effectiveness and safety of a 4-month oral supplementation with a combination of vitamin D, EGCG and vitamin B6 in reducing uterine fibroids' volume and improving the quality of life of childbearing women. Thus, this supplementation may represent a valid alternative to the classic "wait and see" approach and, at the same time, an adjuvant treatment that could be administered along with pharmacological therapies, even before surgery to reduce the occurrence of possible complications. Certainly, the next step will be to better clarify how these three natural compounds synergistically work together against uterine fibroids. Therefore, future randomized double blinded controlled studies with larger groups of women affected by fibroids are needed to validate these encouraging results, also on different ethnic groups.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

All authors contributed substantially to the work reported, have read and agreed to the published version of the manuscript.

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