



Delphys®

For safe and effective treatment of Uterine Fibroids
with Bitartrín D, Epigallocatechin Gallate and Vitamin B6

Women issues

HEAVY BLEEDING

PAIN AND INABILITY TO WORK

**PAIN AND DISCOMFORT
DURING SEX**

CONSTIPATION

PSYCHOLOGICAL DISTRESS

FREQUENT URINATION

HELPLESSNESS

INFERTILITY



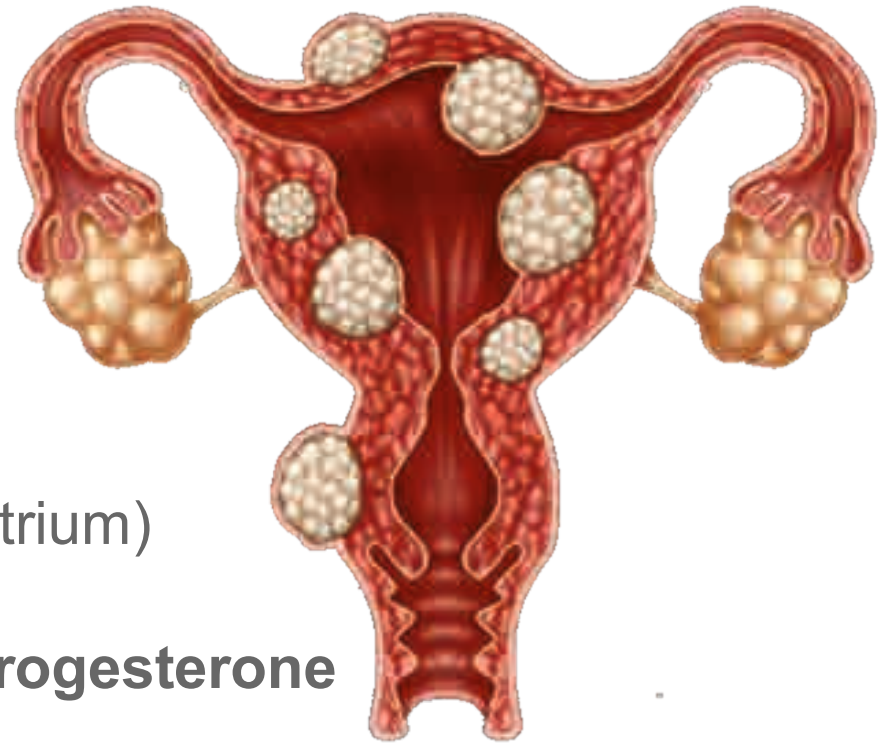
One Woman

BEARING

multiple issues

Uterine fibroids

Uterine Fibroid



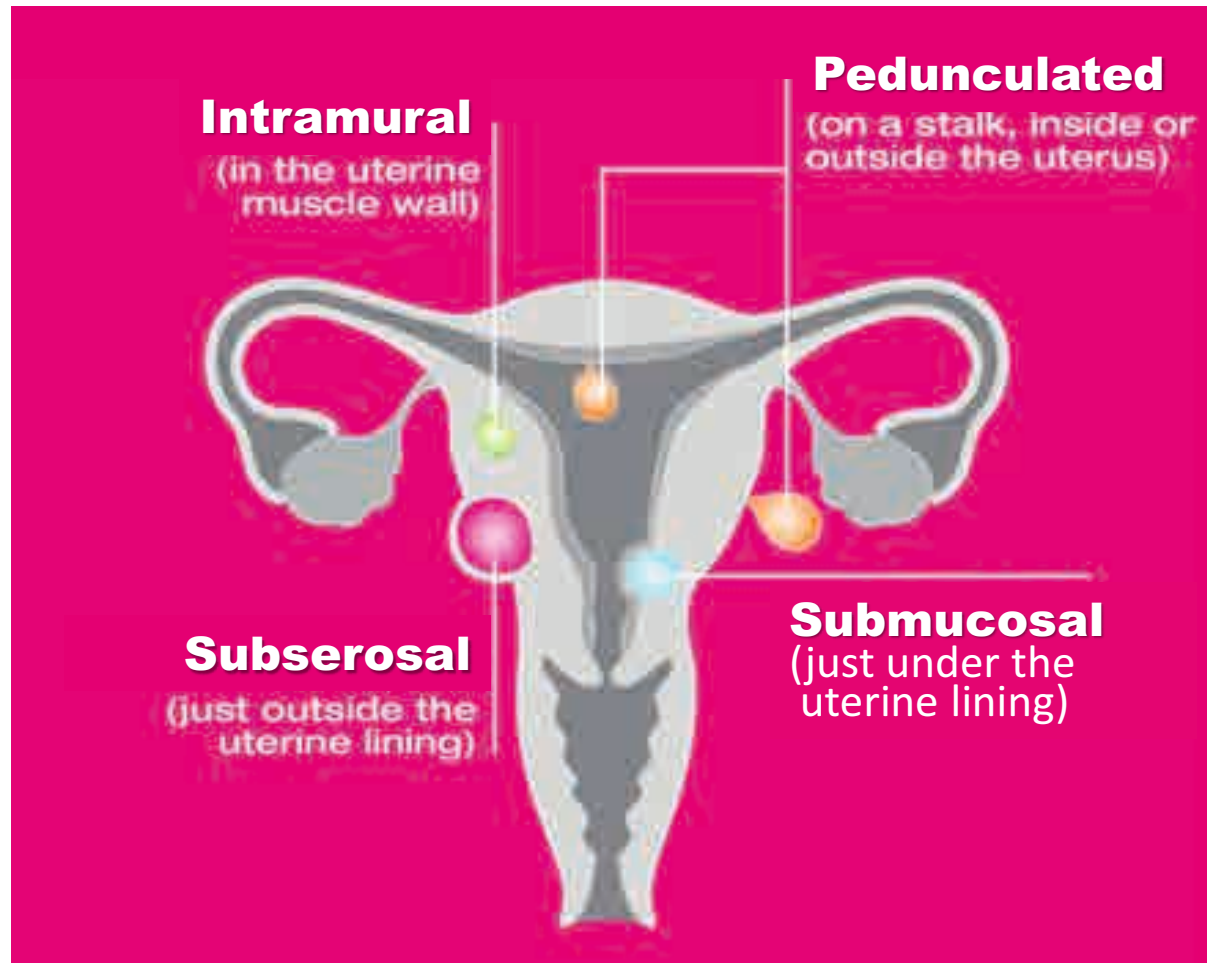
- **Benign tumors**
- Uterine smooth muscle tissue (myometrium)
- Growth dependent on **estrogen** and **progesterone**

Up-regulation of **ER** and **PR**



Uterine Fibroid classification

Uterine fibroids are classified based on location



Uterine Fibroid **size**



Watermelon
40 cm



Mango
15 cm



Limon
8.5 cm



Peach
7.5 cm



Lime
5 cm



Cranberry
2 cm



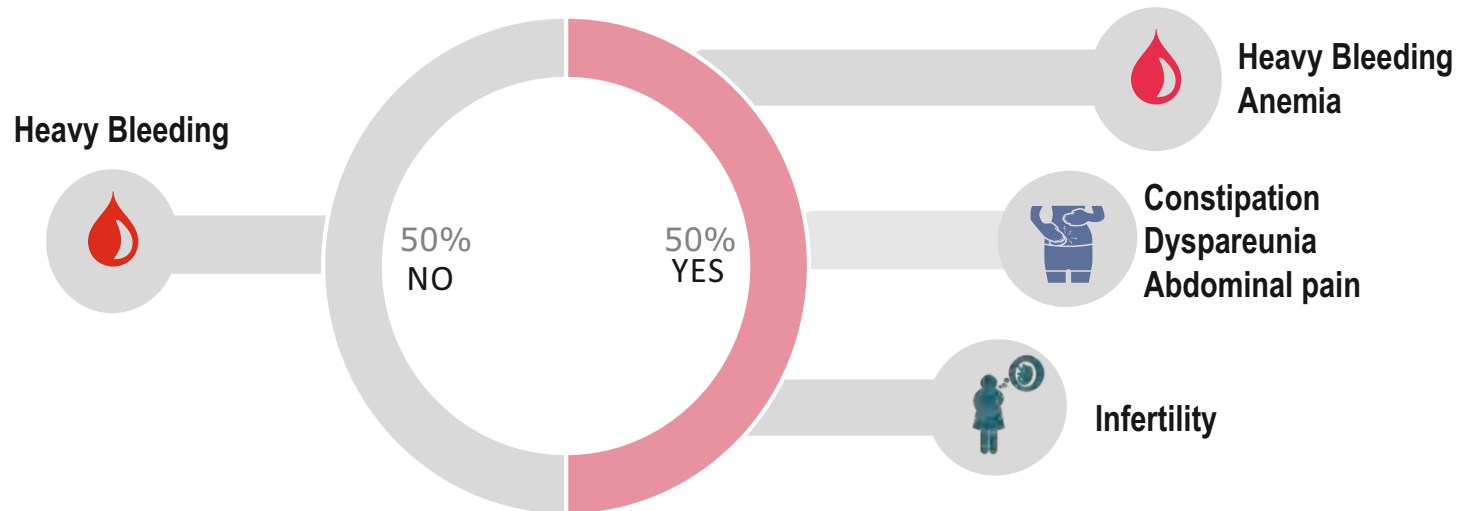
Cheerio
1 cm



Apple seed
0.5 cm

Uterine Fibroid symptoms

The symptoms and treatment options are affected by the size, number, and location of the tumors





Afro-American women
have 2-3 fold higher
incidence



UFs worse
with age



Genes alteration: ex.
The collagen formation
increment



Some diet and lifestyle
conditions can affect the
development of UTs

Uterine Fibroid risk factors

Current therapeutic approaches



SURGERY

**INTERVENTIONAL
RADIOLOGY**

DRUGS

WAIT & SEE

Each one with limitation!



Main Surgery Approaches

Myomectomy



The most frequent gynecological surgery technique.

High Relapse risk

Hysterectomy



The unique resolutive surgery technique.

No preservation of the uterus

Embolization



The most frequent gynecological surgery technique.

High risk Re-intervention
Low data on fertility preservation

WOMAN FEAR



Only for symptoms management

Contraceptives

Used for pain, not effective for size reduction!

IUD

Not indicated when the morphology of the uterus is modified; it does not act on fibroids size.

GnRh

Pharmacological Menopause and related side effects! Off-Label use

Tranexamic acid

Oral nonhormonal antifibrinolytic agent for menstrual blood reduction.

Ulipristal Acetate (UPA)

It works on fibroids

BUT



Pharmacovigilance Risk Assessment Committee (PRAC)

NO FDA approved

SEVER LIVER INJURY



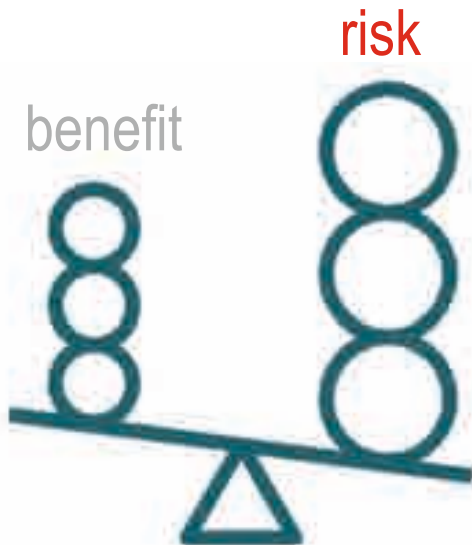
Suspension of ulipristal acetate for uterine fibroids during ongoing EMA review of liver injury risk

On 12 March 2020, EMA's safety committee (PRAC) recommended women to stop taking 5-mg ulipristal acetate (Esmya and generic medicines) for uterine fibroids while a safety review is ongoing. No new patients should start treatment with the medicines, which will be temporarily suspended throughout the EU during the review.



Clinical Surveillance

- Asymptomatic women
- Unbalance



**9% AVERAGE
GROWTH RATE
of UTERINE
FIBROIDS
OVER 6
MONTHS**

** Dolmans_et_al-2019-Journal_of_Obstetrics_and_Gynaecology_Research*

Delphys[®]

Gives the solution to UF



Delphys®



- ✓ Clinically tested product: **EFFECTIVE**
- ✓ Widely **accepted** or even **requested** by clinicians
- ✓ The only **SAFE** alternative for fibroids

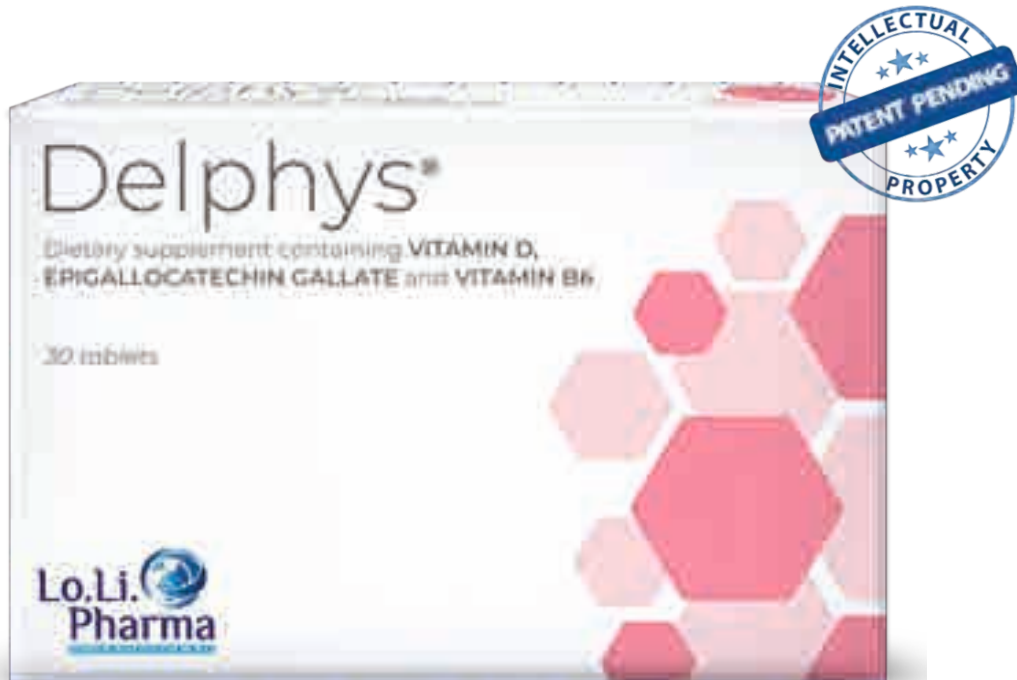


Delphys®

This is it.

We have all the ingredients for success
we could ask for.

The Solution



COMPOSITION FOR 1 TAB	
Green tea extract	333.35 mg
Titered 45% in Epigallocatechin gallate (EGCG)	150 mg
Vitamin B6	5 mg
Vitamin D	25 mcg



S

STOP

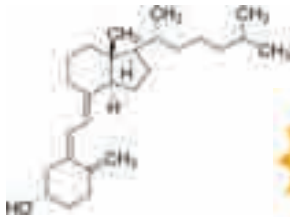
R

REVERT

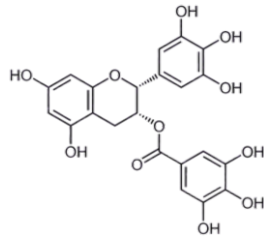
B

BALANCE

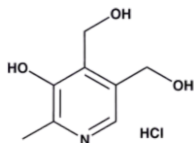
Composition in brief



Anti-proliferative (Stop)



Pro-apoptotic (Revert)



Hormonal balance – EFSA (Balance)

Vitamin D



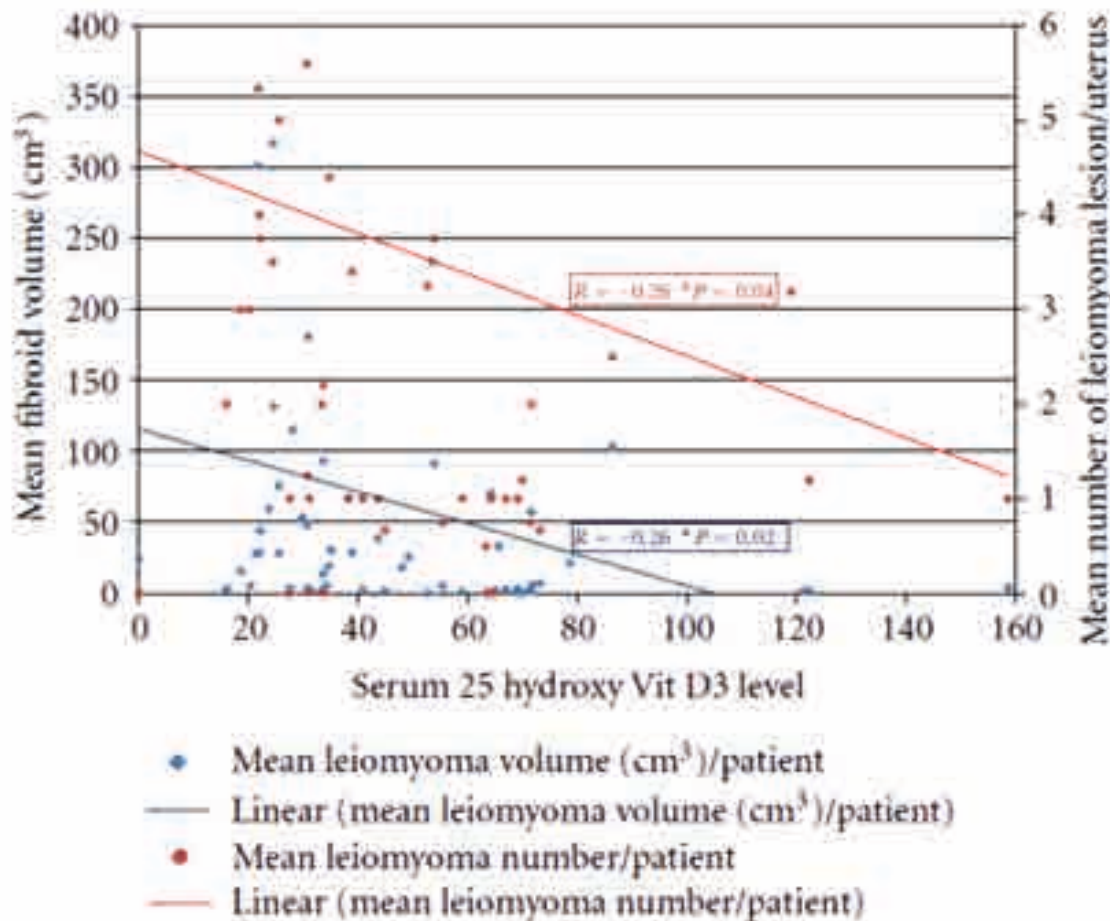


Vitamin D: to keep in mind

- The synthesis is mostly in the skin, activated by sun
- Liver and kidneys process the molecule after
- **VDR are present in all tissues**
- **Vitamin D = Hormone**



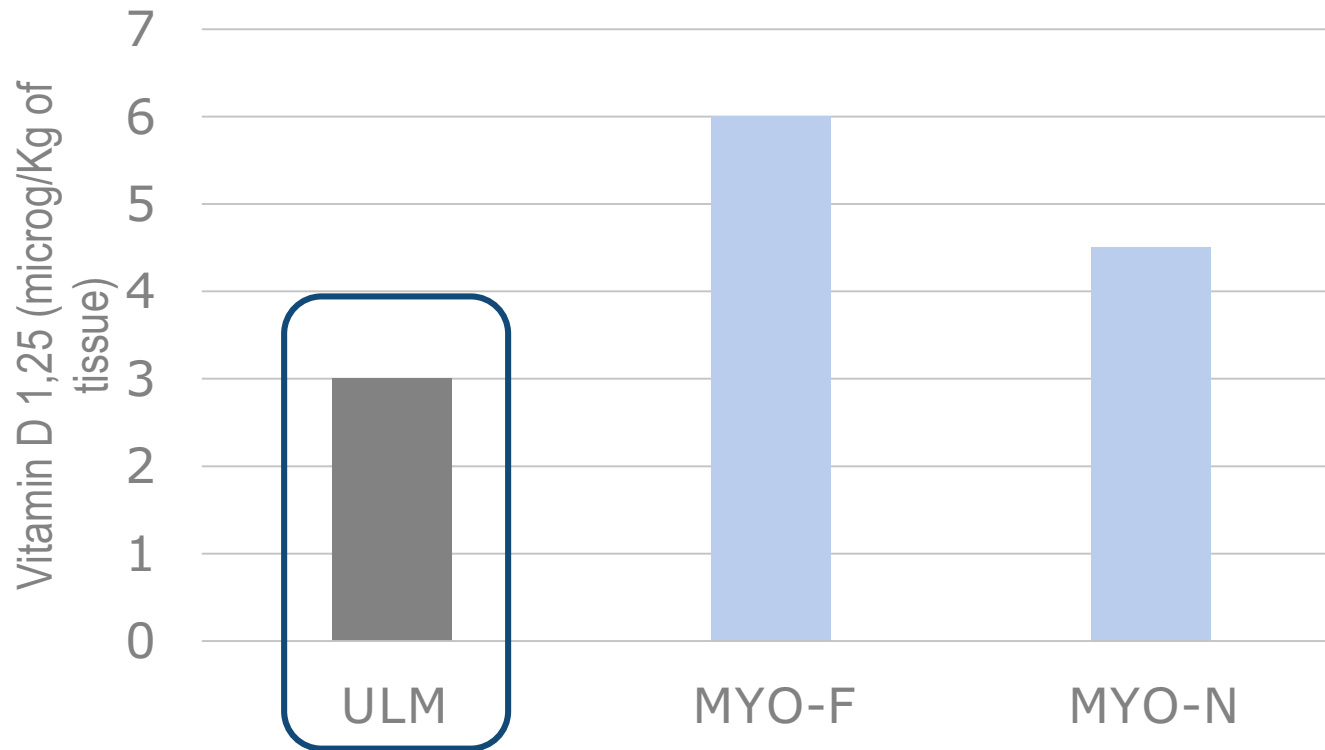
Deficit of Vitamin D & fibroids



Vitamin D levels are **inversely correlated** to fibroids volume and number



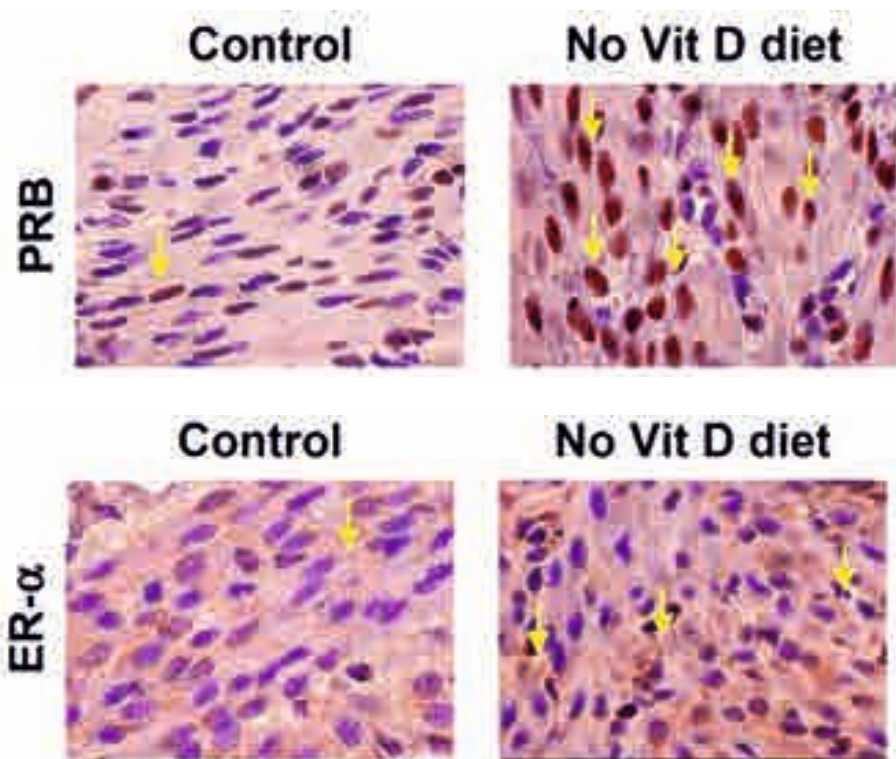
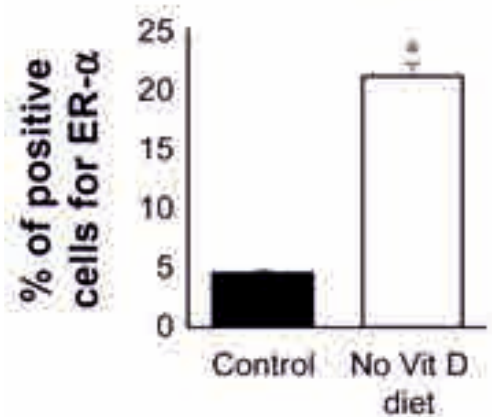
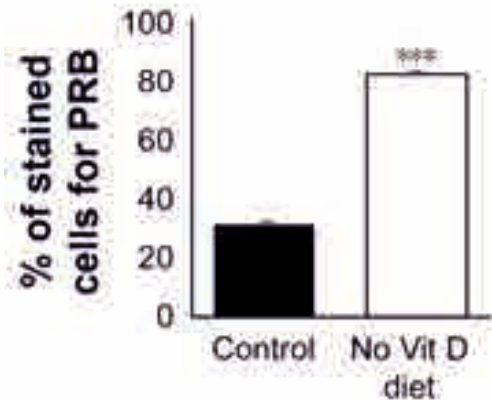
Deficit of Vitamin D in fibroids



Uterine fibroid cells
contain **lower**
Vitamin D levels



Deficit of Vitamin D

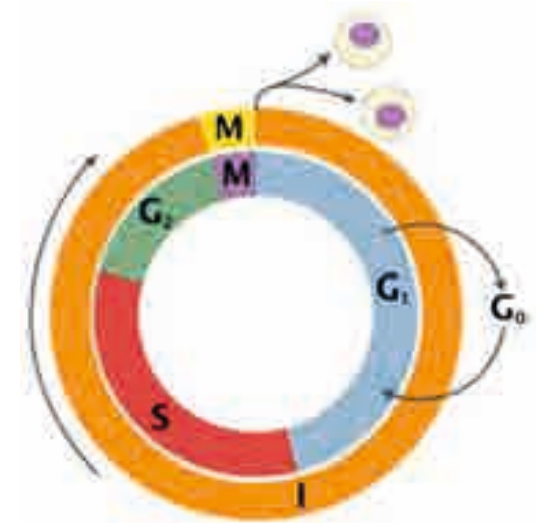
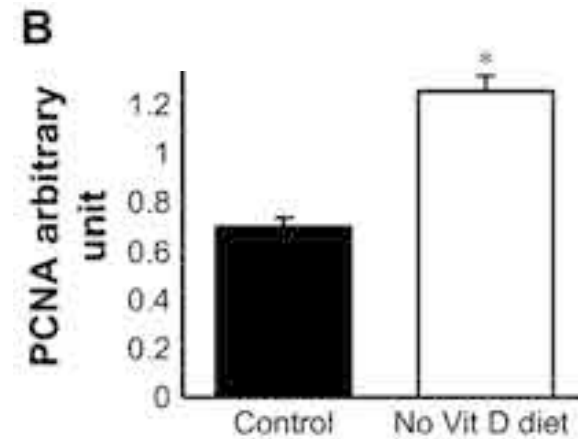
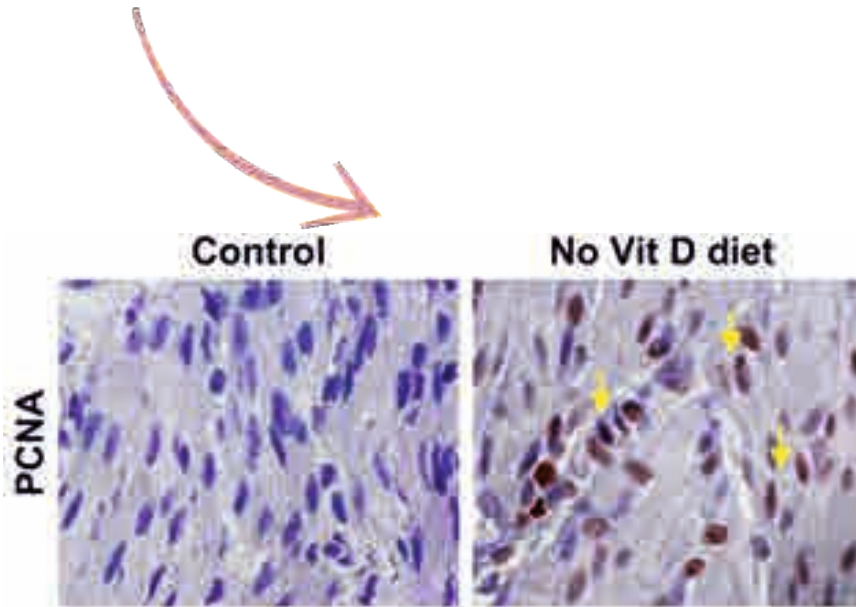


Hormone receptors expression in myometrial tissue increases in the absence of Vitamin D



Vitamin D & cell cycle

PCNA: Proliferating Cell Nuclear Antigen

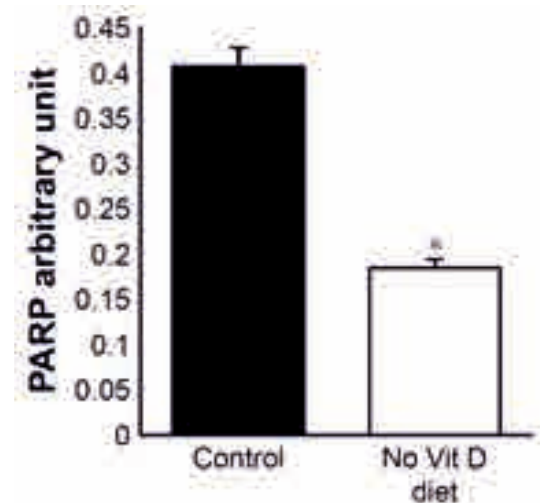
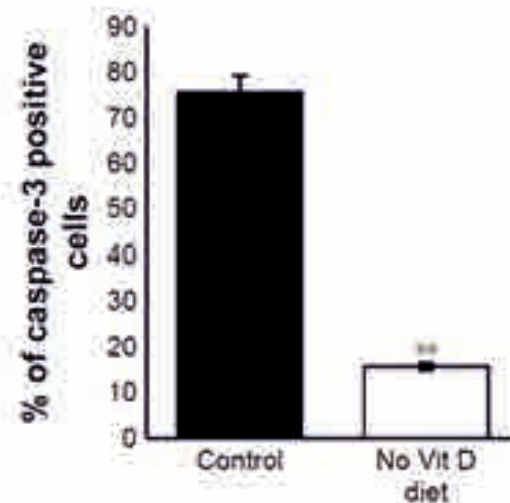
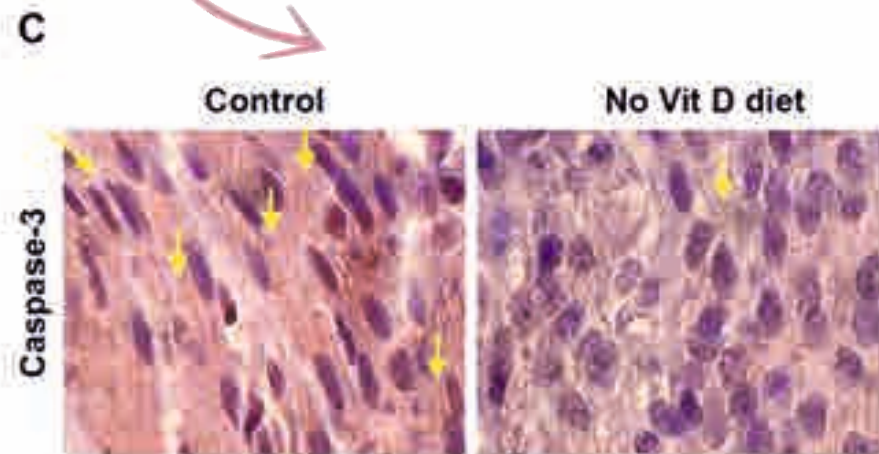


INCREASED MYOMETRIAL PROLIFERATION

Vitamin D & cell cycle



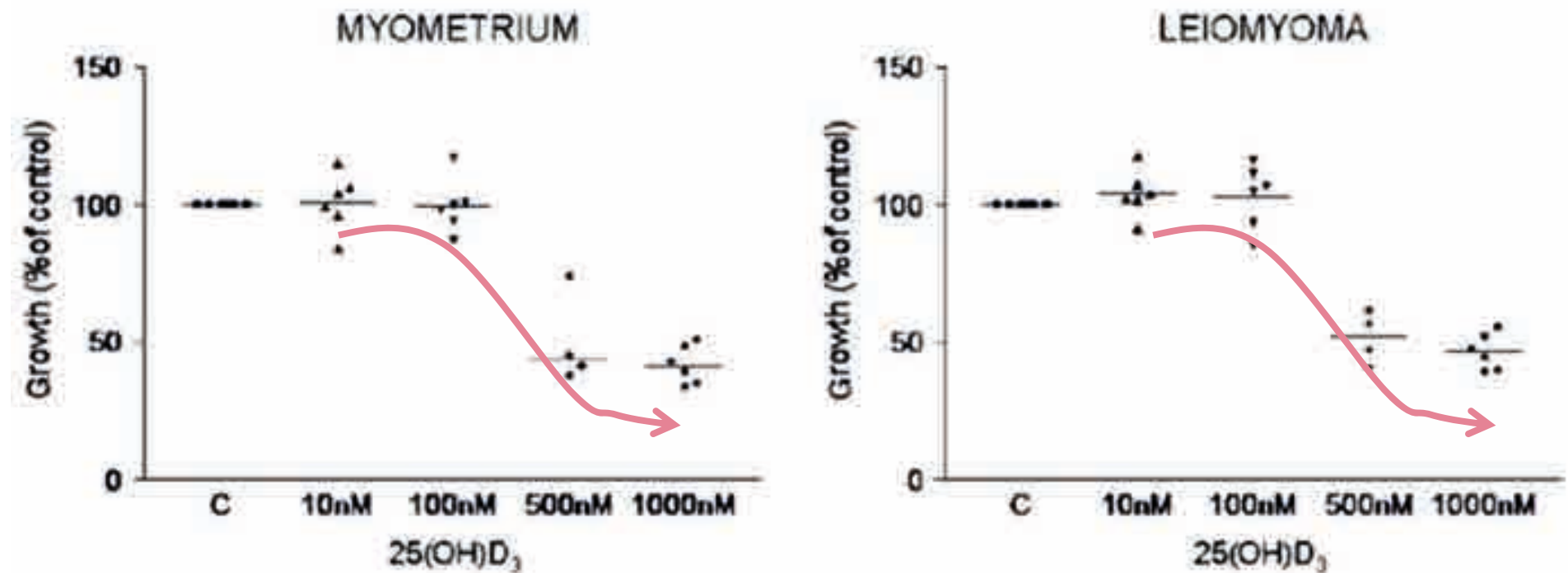
PARP: Poly (ADP-ribose) polymerase



DECREASED MYOMETRIAL APOPTOSIS



Vitamin D as growth inhibitor

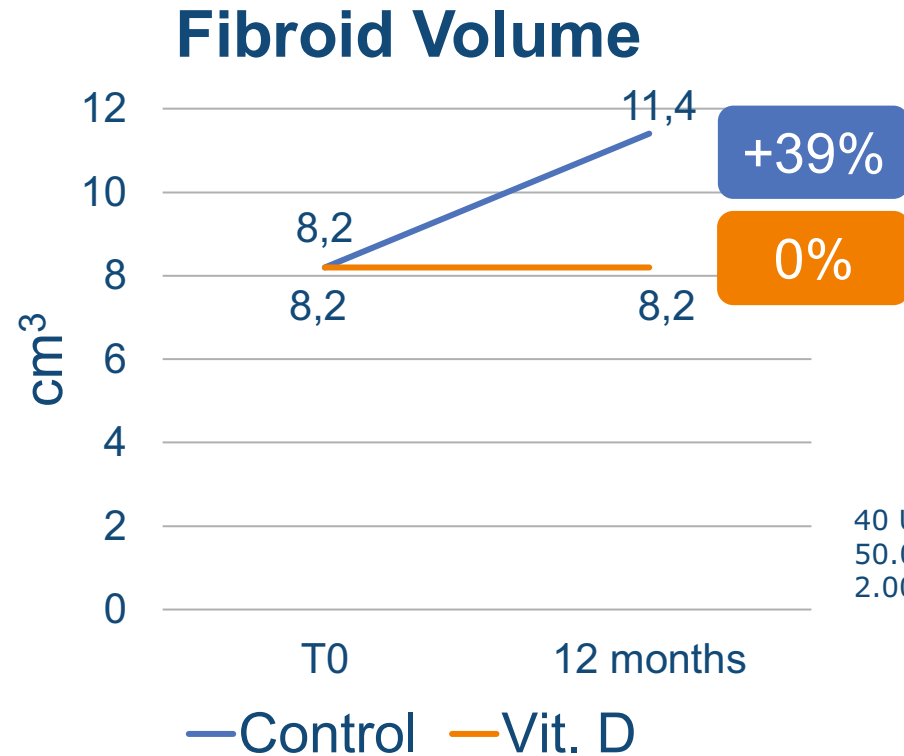
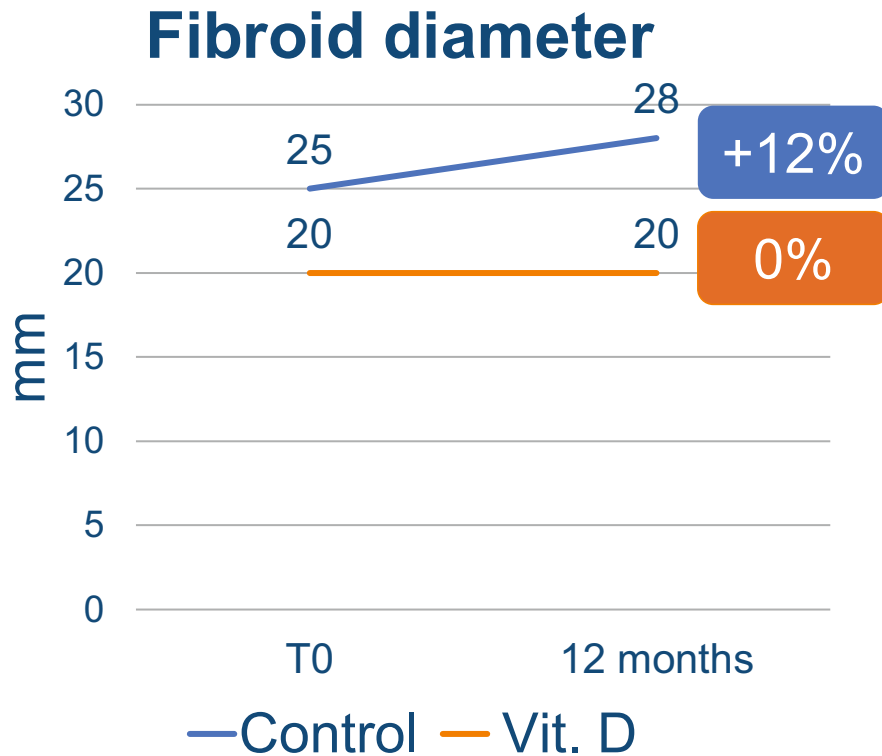


Dose-dependent inhibiting effect



Vitamin D vs. Fibroids (trial)

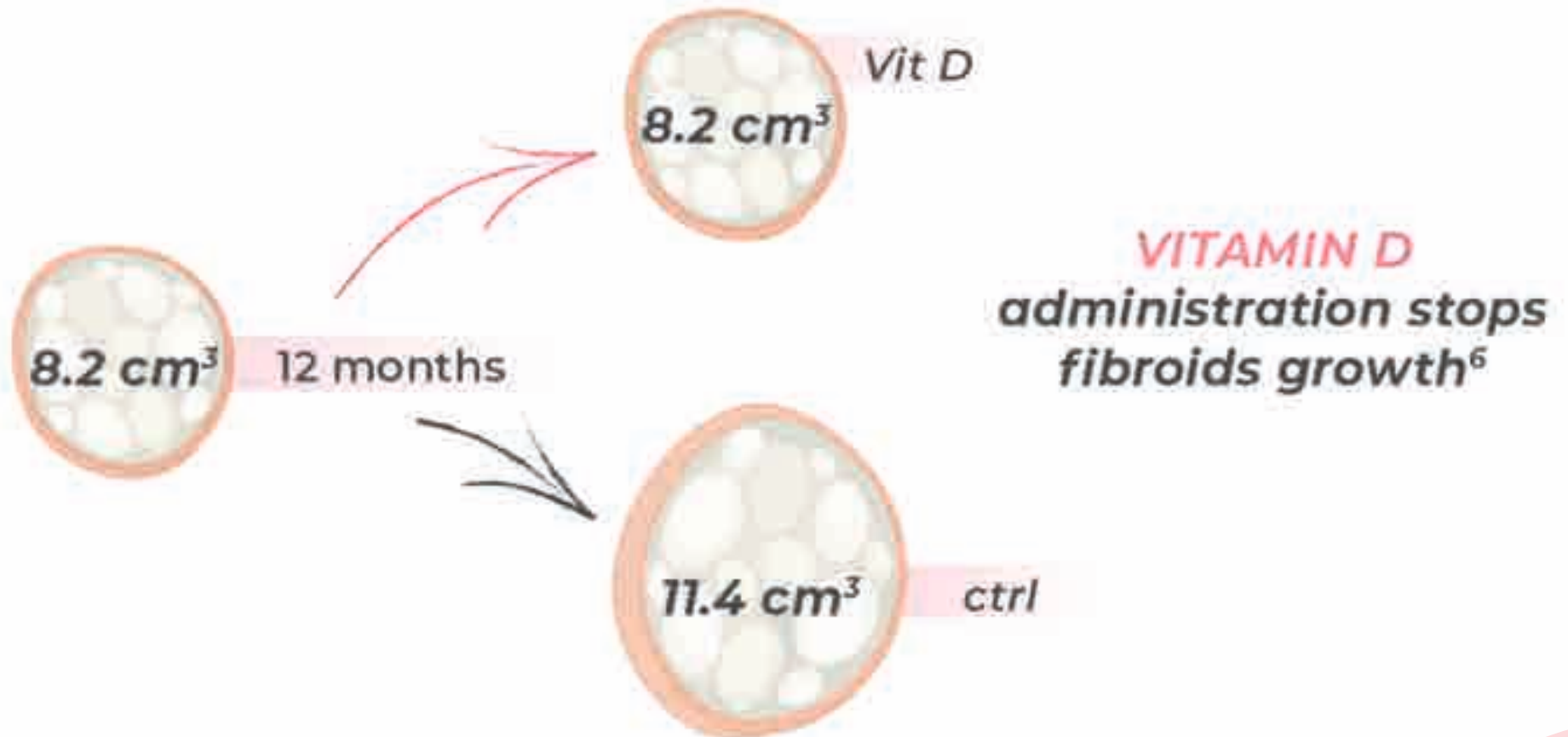
208 women; oral Vit D: 50.000 IU/week for 8 weeks, followed by 2.000 IU/day for 1 year



40 UI = 0,1 mcg
50.000 UI = 1,25 g
2.000 UI = 50 mcg

STOP!

S



VITAMIN D

01

Deficit is associated to **increased proliferation** of uterine fibroids

02

Uterine fibroid cells are **vitamin D deficient**

03

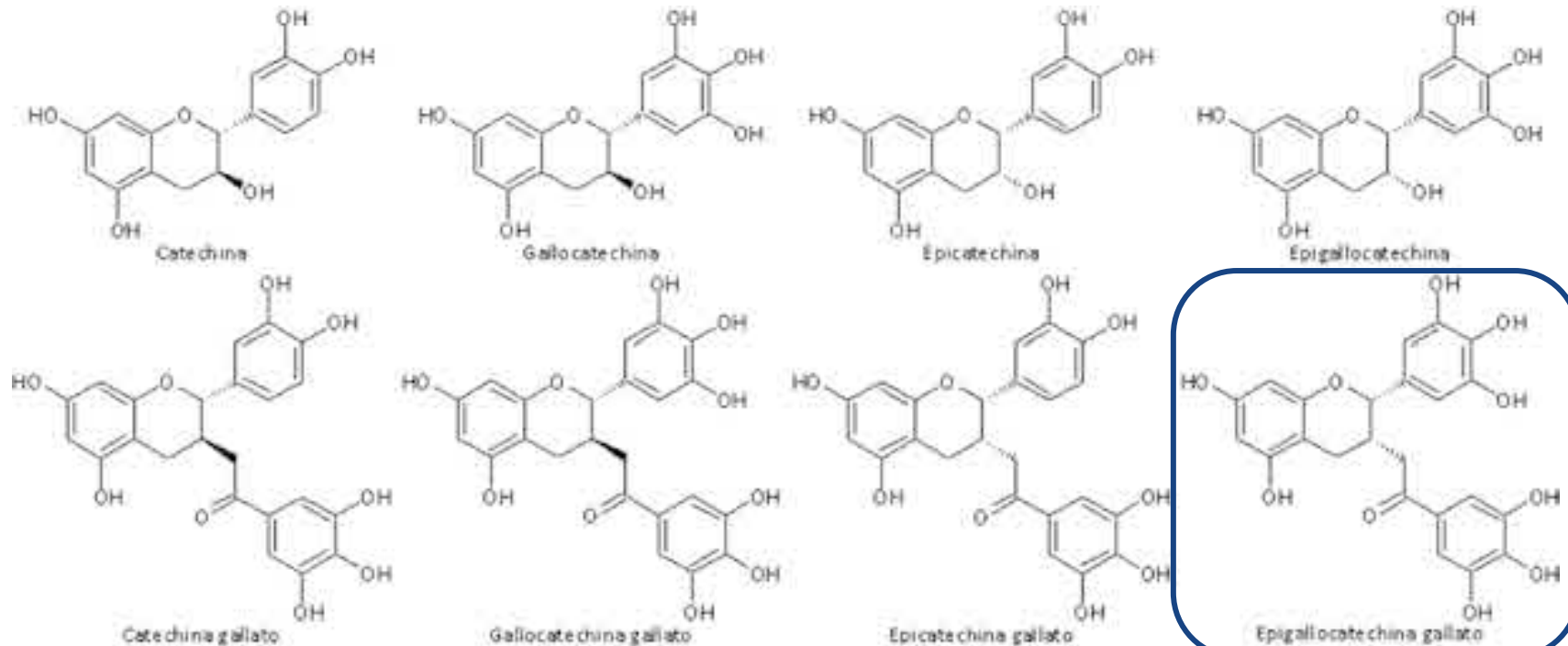
Vitamin D is able to **STOP** fibroids growth

Epigallocatechin Gallate (EGCG)



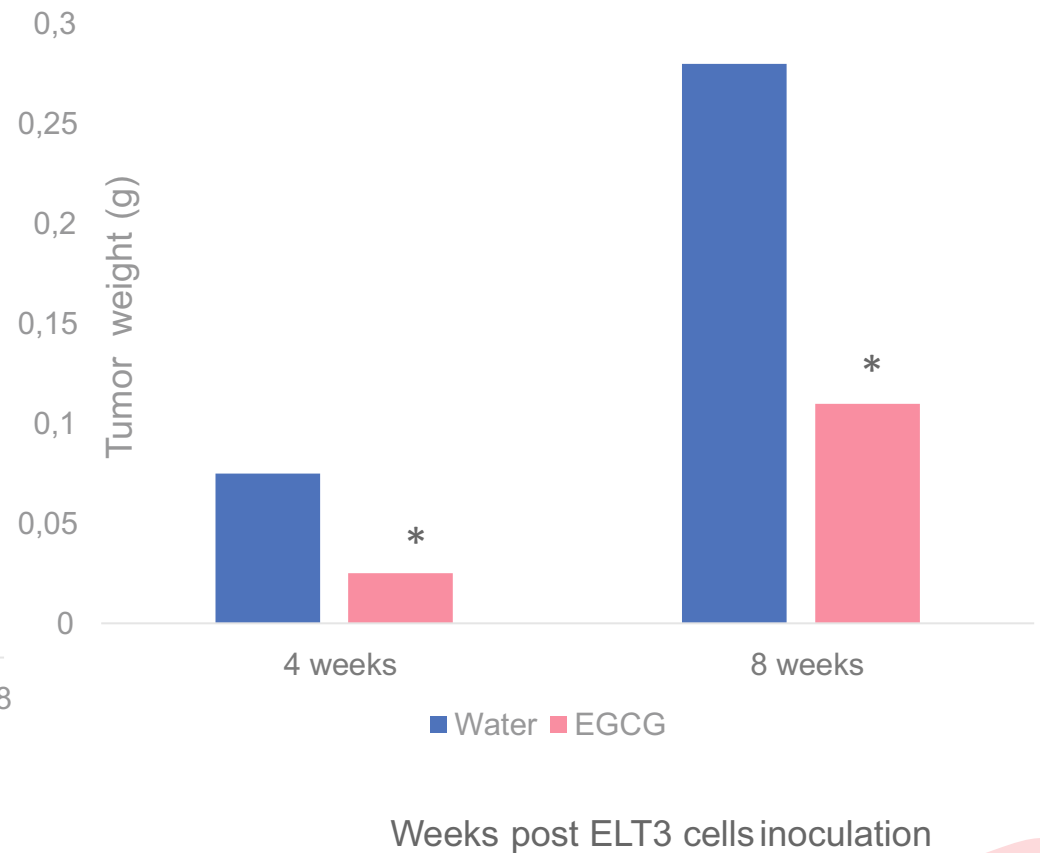
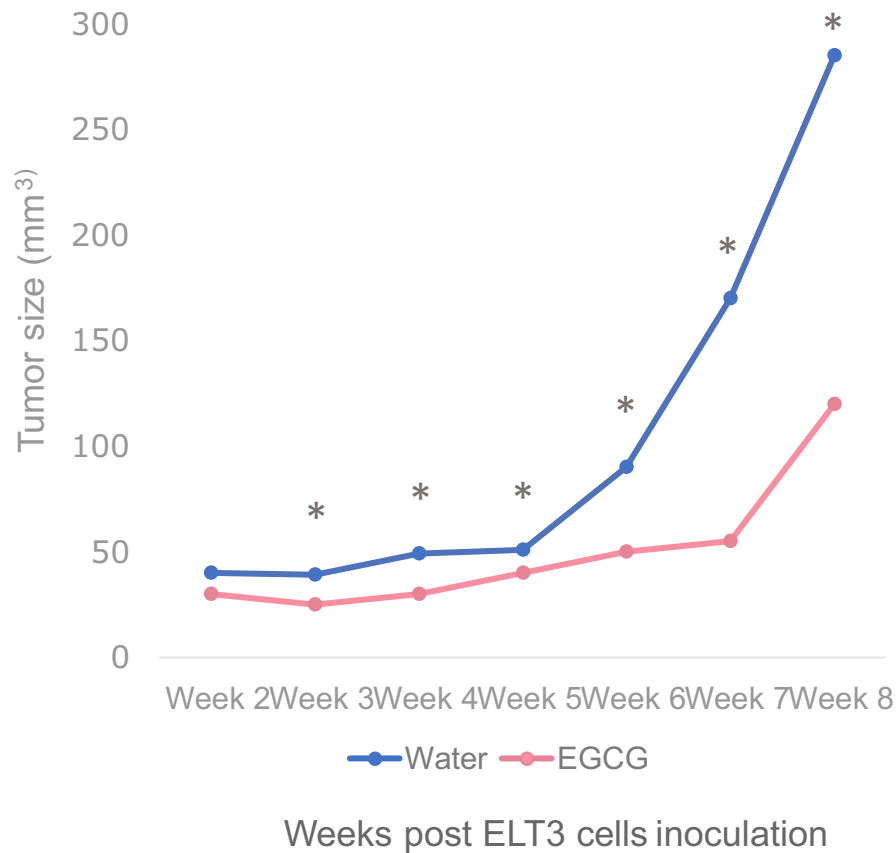


Straight from green tea



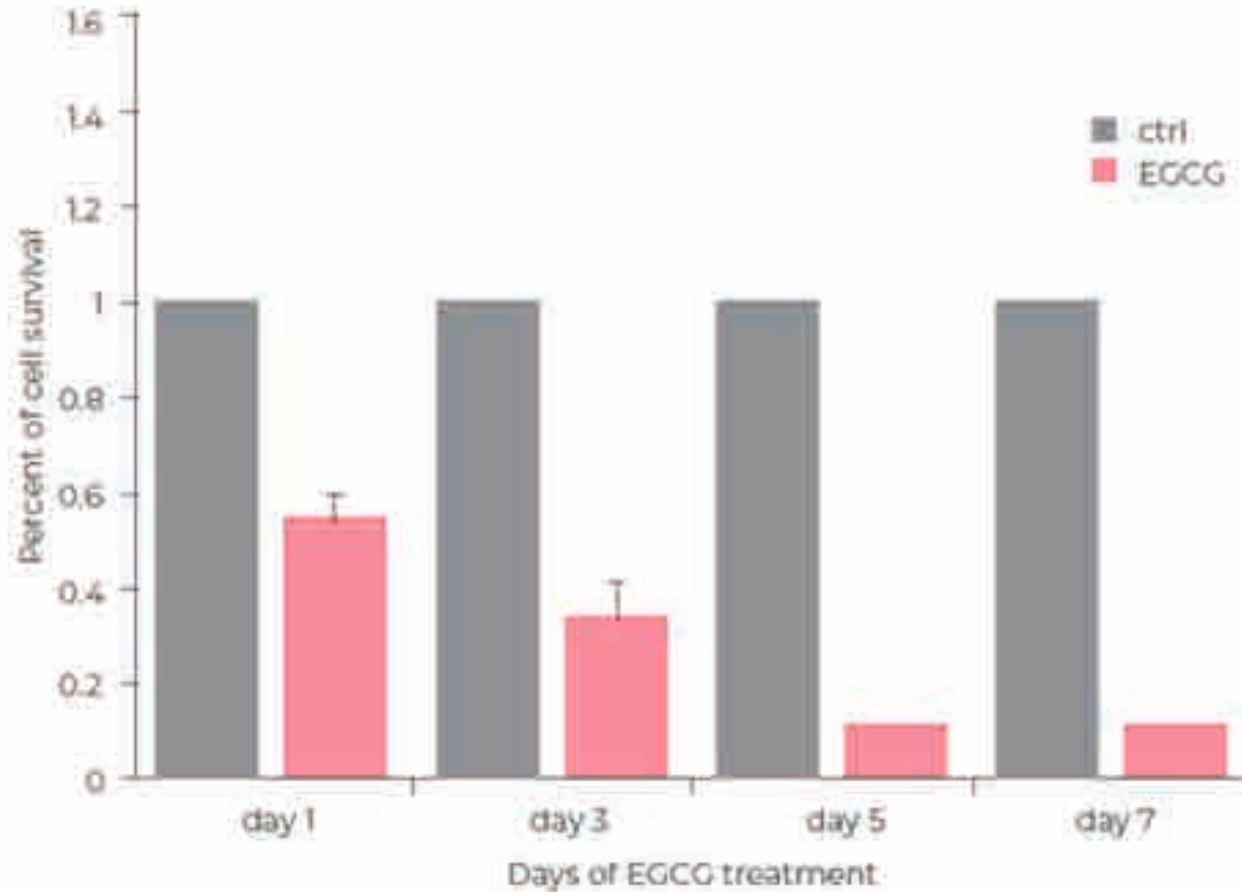


Fibroid reduction with EGCG (oral)



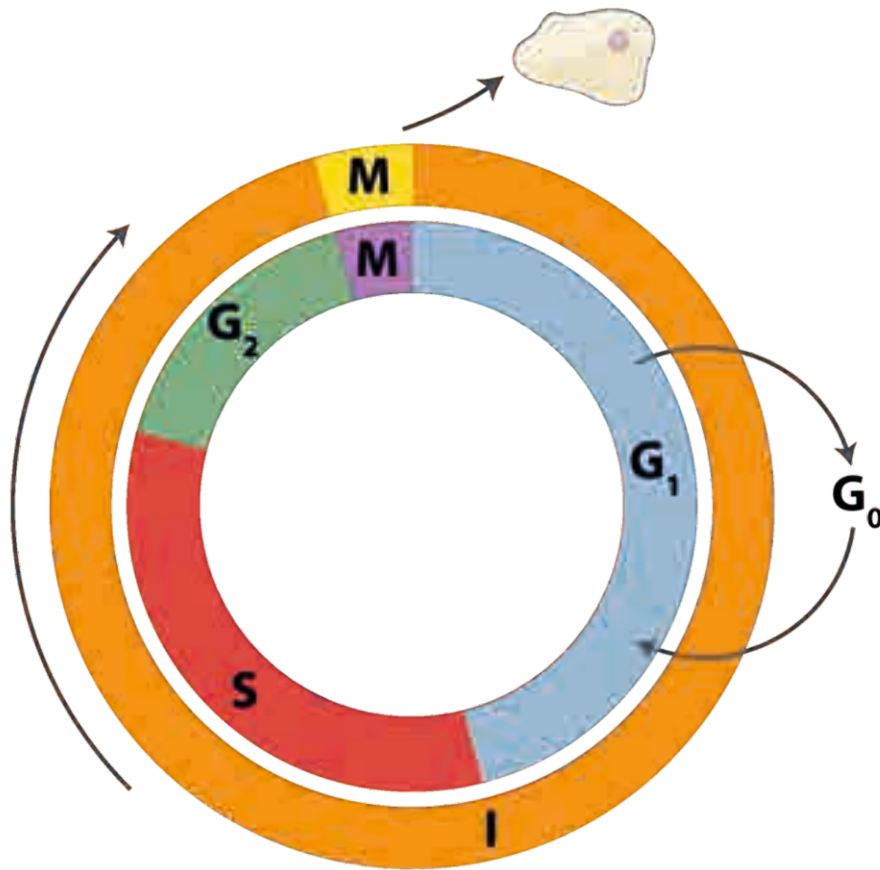


Uterine fibroid & EGCG



**EGCG inhibites and
REVERSES human
fibroids growth³**

EGCG as pro-apoptotic

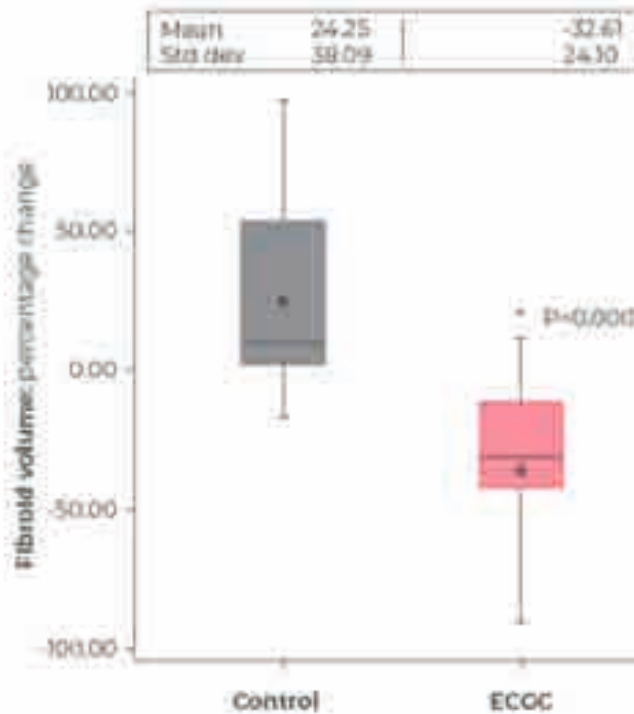


- Checkpoints: “genome guardians” check for mistakes
- **Mistakes → apoptosis**
- Cells with altered proliferation avoid these checkpoints
- **EGCG reduces Cycline-dependent proteins that block apoptosis**

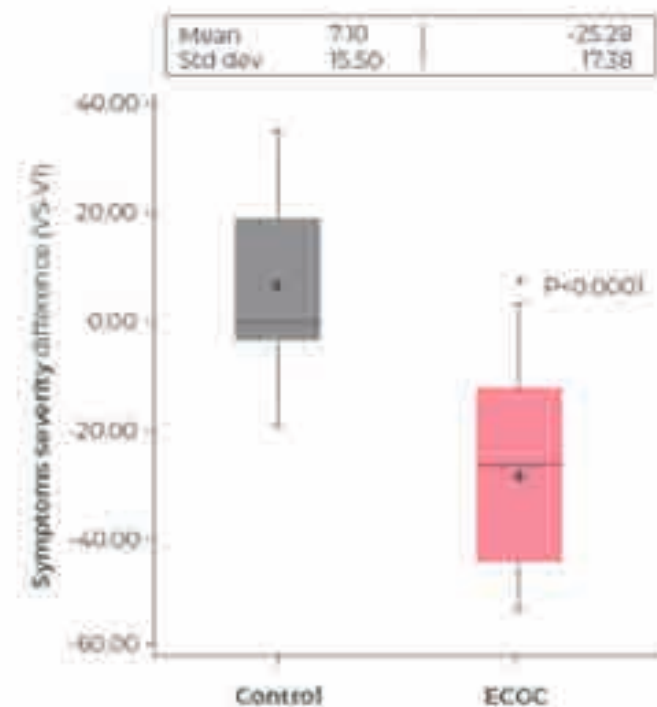


EGCG vs. Uterine Fibroids (trial)

360 mg/day of EGCG for 4 months in 22 women with uterine fibroids (>2 cm³)



**32.6% fibroid volume
REDUCTION⁴**



**32.4% symptoms
IMPROVEMENT⁴**

EGCG

01

EGCG are specific catechins from green tea, exerting **anti-proliferative effects**

02

In vitro data on animals and on humans plus clinical data

03

EGCG are able to REVERT fibroids growth

Vitamin B6



BALANCE!

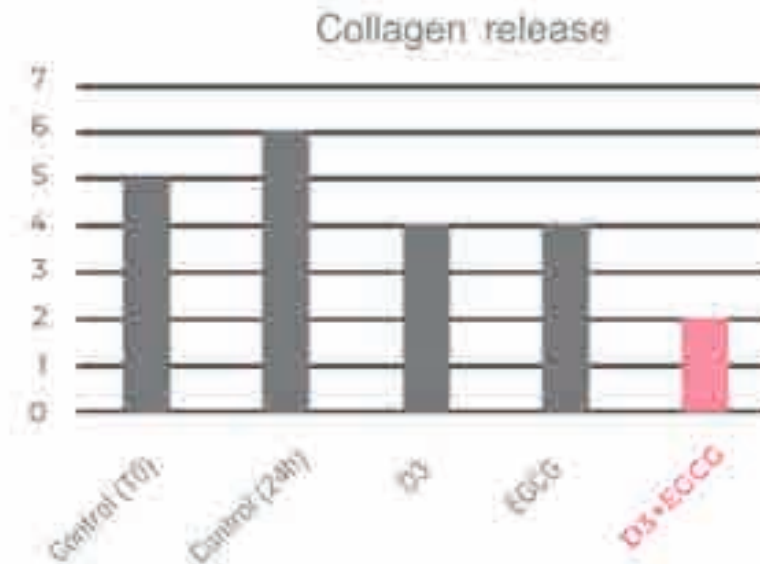
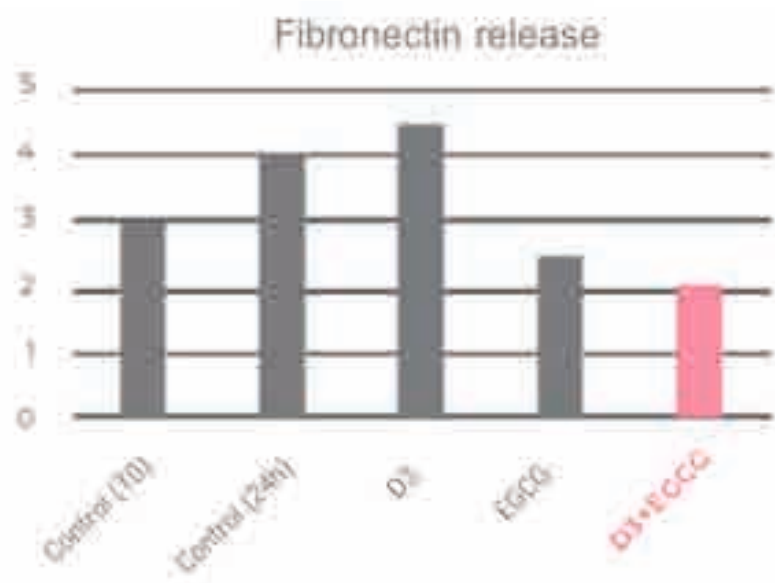
- EFSA claim
- **Extremely useful: hormonal balance is linked to receptors hyper-expression**

Combination



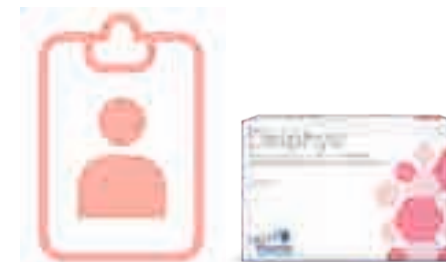
EGCG + Vit. D

In vitro study: Fibroblasts treated with EGCG (0,03 mg/ml) and/or vitamin D3 (0,005µg/ml) for 24 hours



Synthesis of
main
components of
UFIs inhibited

Delphys[®] Clinical Trial



European Review for Medical and Pharmacological Sciences

2020; 24: 3344-3351

Vitamin D plus epigallocatechin gallate: a novel promising approach for uterine myomas

G. PORCARO¹, A. SANTAMARIA², D. GIORDANO², P. ANGELOZZI¹

- 15 patients / group
- 4 months of treatment
- 2 tablets per day

Table 1. Clinical characteristics of patients by group at baseline.

	Treated T ₀ Mean ± SEM	Control T ₀ Mean ± SEM	p-value
Age	37.27 ± 1.15	37.67 ± 1.71	0.8475
Height	165.73 ± 1.78	167.73 ± 1.09	0.3469
Weight	62.13 ± 2.21	64.00 ± 1.64	0.5023
BMI (kg/m ²)	22.67 ± 0.64	22.72 ± 0.49	0.9542
N° myomas	23	21	
Mean n° myomas	1.53 ± 0.19	1.40 ± 0.19	0.6256
Volume myomas cm ³	10.84 ± 1.16	10.17 ± 1.43	0.7188
SS	22.67 ± 1.76	27.13 ± 2.04	0.1086
QoL	91.60 ± 5.55	84.93 ± 6.13	0.4270

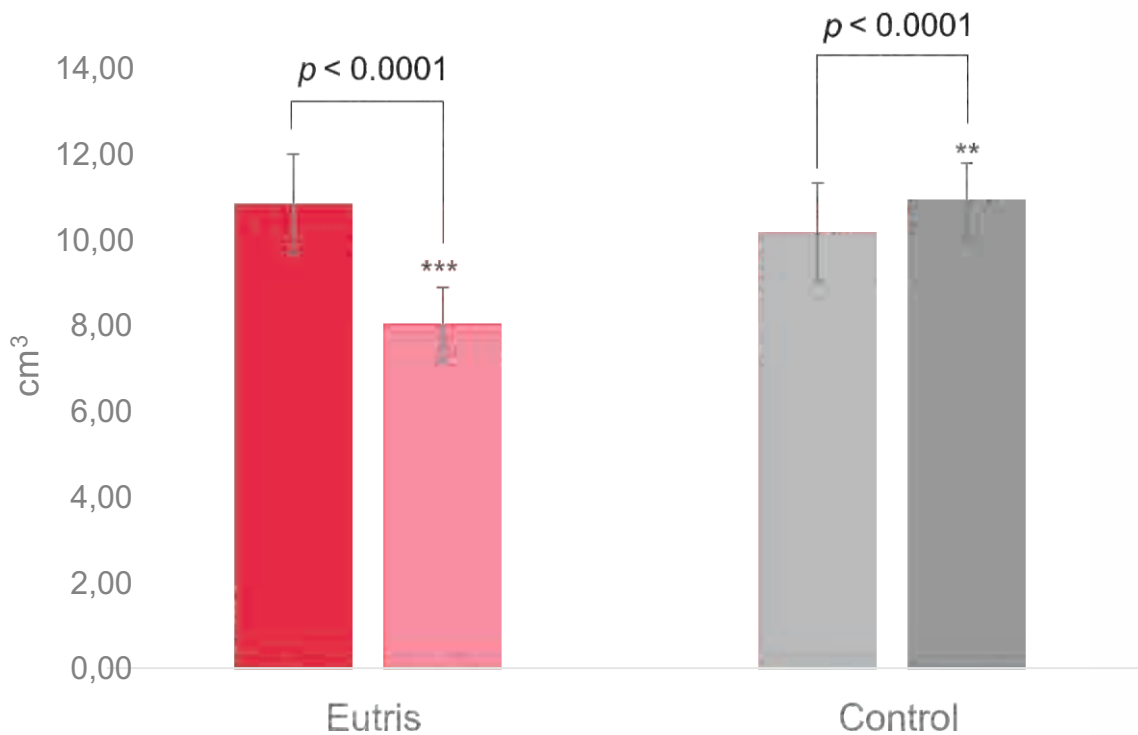
RESULTS:




Outcome VOLUME CHANGE

-37%

+6,9%



MYOMA VOLUME REDUCTION

 AVOID SURGERY

RESULTS:



Outcome: Bleeding

Incidence of number, type of myomas and correlated symptoms at visit 1 and visit 2

	Delphys T0 n° patients (%)	Delphys T1 n° patients (%)	Control T1 n° patients (%)	Control T1 n° patients (%)
Intramural myomas	7 (43.5%)	7 (43.5%)	9 (47.4%)	9 (47.4%)
Subserosal myomas	2 (12.5%)	2 (12.5%)	2 (10.4%)	2 (10.4%)
Submucosal myomas	7 (43.5%)	7 (43.5%)	8 (42.1%)	8 (42.1%)
Normal bleeding	3 (20 %)	5 (33.3 %)	3 (20 %)	3 (20 %)
Heavy bleeding	8 (53.3 %)	0 (0 %)	6 (40 %)	6 (40 %)
Medium Bleeding	4 (26.7 %)	10 (66.7 %)	6 (40 %)	6 (40 %)
Fatigue	10 (66.7 %)	3 (20 %)	8 (53.3 %)	8 (53.3 %)
Pelvic pain	8 (53.3 %)	1 (6.7 %)	8 (53.3 %)	8 (53.3 %)

**MENSTRUAL BLEEDING
REGULARIZATION**



FATIGUE REDUCTION



IMPROVEMENT OF QoL

Vitamin D plus epigallocatechin gallate: a novel promising approach for uterine myomas

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²Department of Obstetrics and Gynecology, University of Messina, Messina, Italy

Abstract. – OBJECTIVE: Uterine myomas are the most common benign tumors in females. Most myomas are asymptomatic and require no intervention or further investigations; however, almost a third of women with myomas will require a therapy. Treatment options include pharmacological approaches or surgery, and depend on symptomatology, size, number and desire for future pregnancy. Minimally invasive procedures or alternative medical treatments for handling myomas are preferred, when possible, to the radical abdominal surgery. Vitamin D and epigallocatechin gallate (EGCG) recently proved effective in the management of these benign tumors. Our aim was to verify the effect of combined oral vitamin D and EGCG supplementation in symptomatic women with myomas.

PATIENTS AND METHODS: Symptomatic women with myomas were enrolled in this pilot study and divided in two groups: one group treated daily with two tablets of 25 µg vitamin D + 150 mg EGCG + 5 mg vitamin B6, for 4 months; the other group received no treatment (control), for the same period. Volume, number of myomas as well as severity of symptoms (SS) and quality of life (QoL) were analyzed.

RESULTS: The total myoma volume significantly decreased by 34.7% in the treated group, whereas it increased by 6.9% in the control group. An improvement in the QoL of women treated with vitamin D, EGCG and vitamin B6 was reported along with a reduction of the SS.

CONCLUSIONS: The combined supplementation of vitamin D and EGCG seems to be an optimal approach for the management of myomas and correlated symptoms. For the first time, we showed the cooperative effectiveness as a promising and novel treatment for myomas.

Key Words:

Uterine myoma, Uterine fibroids, Leiomyoma, Vitamin D, Epigallocatechin gallate, EGCG.

Introduction

Uterine myomas, also named uterine leiomyomas or uterine fibroids, are monoclonal tumors

of the smooth muscle cells of the myometrium. They are the most common benign uterine neoplasm and are classified by their size, shape and location in the uterine cavity¹. Myomas consist of accumulation of collagen, fibronectin and/or proteoglycan that may form in or on the uterus. They develop in women of childbearing age, mainly between 35 and 50 years. The worldwide incidence of myomas ranges between 5.4% to 77%, as it may vary in different ethnic groups. Indeed, African American women have 3-4 times higher risk of developing myomas, compared to Caucasian^{2,3}. Recent molecular studies suggest that there may be different phenotypes of myoma disease⁴.

The exact cause of myomas is still unknown, but their development and growth seem to be under the influence of steroid hormones. Estrogens and progesterone, through their nuclear receptors, are the main factors initiating uterine muscle differentiation and abnormal growth, leading to myoma pathogenesis^{5,6}.

The development of myomas varies greatly in relation to age, heredity, obesity, hormonal and environmental factors. Additional environmental factors, such as diet (particularly vitamin D deficiency) and toxins, are the subjects of ongoing investigations. Myomas often develop asymptotically; however, they may be associated with an increased risk of menorrhagia, dysmenorrhea, chronic pelvic pain, compression of the surrounding organs, painful sexual intercourse, infertility, recurrent abortion, preterm delivery and anemia^{1,7,8}.

Transvaginal ultrasound is the gold standard method for diagnosis⁹. In a small portion of women, regression of untreated myomas may be observed during the premenopausal period or during pregnancy or postpartum involution. In menopause, when the hormone levels decrease, the risk for new myomas decreases as well.

Normally, the size of preexisting formations may reduce. Most myomas are asymptomatic and require no intervention or further investigations (“watching and waiting”); however, almost a third of women with myomas require treatment due to symptoms. Indeed, they are generally severe and affect women’s quality of life (QoL). Treatment options for myomas depend on symptoms, size, number and desire for future pregnancy. Surgery, such as myomectomy, hysterectomy, myolysis, uterine artery embolization (UAE) and magnetic resonance imaging-guided focused ultrasound surgery (MRgFUS), is generally adopted for large myoma. According to the American Journal of Obstetrics and Gynecology, more than 400,000 hysterectomies were performed in the United States in 2015. Hysterectomy may cause short term and long term sequelae, and in a minor portion of operated women even death (between 0.4-1.1 per 1000 surgeries)¹⁰. The conservative management mainly consists of medical treatment such as selective progesterone receptor modulators (sPRMs), gonadotropin-releasing hormone agonist (GnRHa), hormones such as estroprogestins or progestogens, non-steroidal anti-inflammatory drugs (NSAIDs), and tranexamic acid. This interventional therapy is preferred with mild symptomatology, and it is commonly used for reducing pain and blood loss during menstruation. In particular, ulipristal acetate (UPA), a sPRM, is effective in controlling the bleeding and reducing the number of surgical procedures^{11,12}. However, concerns about the adverse estrogenic activity and liver toxicity were raised¹³⁻¹⁶. Recently, the role of two natural molecules, vitamin D and epigallocatechin gallate (EGCG), in managing myomas has been investigated. Hypovitaminosis D is associated with a higher prevalence of myomas, and correlated with their severity¹⁷. Administration of vitamin D in insufficient women (serum level <30 ng/mL) proved to restore the normal vitamin D status and to reduce the mild symptoms of myomas¹⁸. Likewise, the daily administration of EGCG for 4 months reduced the myoma size in premenopausal women¹⁹. Therefore, there is considerable interest in further investigating the role and the possible synergistic effect of vitamin D and EGCG in the treatment of myomas. This study aims to investigate the effects of a combined oral supplementation of vitamin D and EGCG in women presenting with symptomatic myomas.

Patients and Methods

This was a pilot study involving women with myomas, referring to our Outpatient Unit between March and October 2019. All women enrolled gave their oral informed consent after the explanation of the study purpose. This study was conducted following the Ethical Principles of the Helsinki Declaration and the national laws. Subjects were included in the study if they were: 18 years of age or older, in premenopausal stage, with at least one myoma ≥ 2 cm³ (intramural, subserosal and/or submucosal) detected by vaginal and abdominal ultrasound, with moderately severe myoma-related symptoms, and do not require treatment other than regular observation. The exclusion criteria of the study were: pregnant women or intended to become pregnant during the following four months, currently breastfeeding, with severe anemia or medical morbidity, eligible to surgery, elevated liver enzymes, treatment (within the past 3 months) of hormones (estrogen, progestin, oral contraceptives), corticosteroids, food supplements having possible hormonal effects, use of sPRMs or GnRH analogues within the past 6 months. In this pilot study we enrolled 30 women with myomas. Patients were divided in two groups: one group (15 patients) treated by oral route with 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 (15 patients) received no treatment (control), for 4 months. The primary outcome was the change of myoma volume analyzed by transvaginal ultrasonography (TVU), and/or transabdominal ultrasonography. The secondary outcomes were the variation of the number of myomas, distress by bleeding during the menstrual period, pressure feeling in the pelvic area, sense of fatigue, QoL and the severity of symptoms (SS). The subjective experience of bleeding was indicated as heavy, medium and normal, through a self-administered bleeding assessment. The SS and QoL were evaluated with a questionnaire consisting of 37 questions in the LiKert format, divided in 2 parts. The first part is composed of 8 questions evaluating the SS, with points (1 to 5) assigned to each answer option. This domain allows raw total scores from 8 to 40 with an increase in the score proportional to the SS. The second part evaluated the QoL, divided in six areas (concern, daily activities, changes in mood and energy, self-control, self-consciousness and sexual function). This domain consists



1 or 2 tablets each day

- ✓ **FIBROIDS GROWTH CONTROL**
- ✓ **SYMPTOMS REDUCTION**
- ✓ **FAVORS HORMONAL BALANCE**
- ✓ **NO SIDE EFFECTS**
- ✓ **BETTER QoL**