

# Pelvic Pain is Correlated with Vitamin D Serum Levels in Ovarian Endometriosis

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## Abstract

**Objective:** To determine whether Vitamin D serum levels are correlated with pelvic pain in patients with ovarian endometriomas.

**Design:** Prospective study.

**Setting:** Tertiary-care university hospital.

**Patient(s):** vitamin D serum levels were prospectively analyzed in 43 patients (group A, asymptomatic patients or patients with mild dysmenorrhea; group B, moderate dysmenorrhea and group C, severe dysmenorrhea and/or chronic pelvic pain and/or dyspareunia) who were diagnosed for cystic ovarian endometriosis to assess whether a correlation exists between Vitamin D serum levels and pelvic pain.

**Intervention(s):** Vitamin D serum levels determination.

**Main outcome measure(s):** Vitamin D serum levels and pelvic pain.

**Result(s):** From 43 patients, five cases were ultimately excluded because patients didn't continuous). The mean ( $\pm$  SD) vitamin D serum levels in group A were  $26,9 \pm 04.17$  pg/mL in group B were  $16,2 \pm 1,4$  pg/mL. and group C  $10,4$  pg/ml  $\pm 2,4$  pg/ml

**Conclusion(s):** Pain symptoms in ovarian endometriosis is correlated with vitamin –D serum levels.

**Keywords:** Vitamin D • Ovarian endometriosis • Pain

## Introduction

Endometriosis is a common disorder, affecting women of reproductive age that causes pelvic pain and contributes to infertility in approximately 15% of infertile women. The main sites of the disease are the pelvic peritoneum, ovaries, and rectovaginal septum. Extra genital disease is also frequent. When endometriosis implant foci become walled off by adhesions or are embedded inside the tissue, endometrioma results. However, it is not precisely known why ovarian endometriomas develop only in some patients.

The precise mechanism of pelvic pain associated with endometriosis is not completely understood; probably multiple factors are involved. Although it still remains unclear, it is thought that fresh peritoneal implants may cause functional pain such as dysmenorrhea, whereas deep-infiltrating endometriosis and ovarian endometriomas are responsible for organic-type pain such as dyspareunia and chronic pelvic pain [1,2].

Angiogenesis seems to be one of the processes involved in the pathogenesis of endometriosis [3], and was specifically associated with disease activity [4] and pain [5].

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Ultrasonography is commonly used as a diagnostic imaging tool in women with suspected endometriosis. Its efficiency was demonstrated in the diagnosis of ovarian endometrioma [6]. Transvaginal color and power-Doppler allows for the assessment of ovarian endometrioma vascularity [6,7].

We speculated that ovarian endometriomas in patients who present with pelvic pain would be more vascularized than those in asymptomatic women. The results of our previous study supported this hypothesis [8-14].

Endometriosis is gynecological benign disease with an occasional malignant behavior. The prevalence of the endometriosis is unknown although literature estimated in 5%-10% of women in reproductive age.

Since 2008 our group has been investigated with the ovarian endometriosis and the correlation with angiogenesis. One of our report showed that pelvic pain is associated with the level of angiogenesis in ovarian endometrioma. Women with severe pelvic pain showed more angiogenesis in ultrasound doppler and in micro vessel density.w

Other reports have analyzed a multiple different angiogenesis biomarker like VEGF, IL-8, Thrombospondin Only VEGF is correlationate with angiogenesis process and pelvic pain. Our group studied IL8 and thrombospondin 1 as biomarker of pelvic pain. Our results showed that both of them nor correlated with pelvic pain [15,16]

Since few years ago we follow up all patients with endometriosis and determinate vitamin D serum levels. Our results show a low levels of vitamin d serum levels in women with ovarian endometriosis and severe pelvic pain, we believe that vitamin D play an importante role in the angiogenesis of ovarian

endomterioma.

Vitamin D is a name for a group of steroid compounds, soluble in fats, which exert powerful effects on the human body, and whose receptors are found in various organs [17], vitamin D takes part in cell cycle regulation and cell differentiation, and it also has anti-angiogenic activities. Many tissue and cells express a vitamin D receptor. VDR Vitamin D play an important role in female reproduction: VDR is expressed in ovarian tissue, endometrium and vitamin D levels are correlated with several gynecological disease like endometriosis and uterine fibroids [18].

## Physiology of vitamin D

The active metabolite of vitamin D, 1,25(OH)<sub>2</sub>D<sub>3</sub>, is a lipophilic steroid hormone. Cholecalciferol (vitamin D<sub>3</sub>) can be obtained from food, but the major source of vitamin D<sub>3</sub> is the skin, where the precursor 7-dehydrocholesterol is converted to vitamin D<sub>3</sub> upon exposure to ultraviolet radiation in sunlight. In the liver, the enzyme 25-hydroxylase converts vitamin D<sub>3</sub> to 25-hydroxyvitamin D<sub>3</sub> (25D), the major circulating form of vitamin D<sub>3</sub>; 25D is further hydroxylated in the kidney by the enzyme 1 $\alpha$ -hydroxylase to form the biologically active form of vitamin D, 1,25-dihydroxyvitamin D<sub>3</sub> (1,25D). While the kidney is the primary site of 1,25D production, 1 $\alpha$ -hydroxylase is also expressed in extrarenal sites, allowing for local synthesis of 1,25D<sub>5</sub>, [13].

It has been found that vitamin D has a role in normal cellular growth regulation [17]. Vitamin D has immune regulatory effects in chronic inflammatory responses. Vitamin D increases anti-inflammatory cytokines production and decreases pro-inflammatory cytokines. Vitamin D induces apoptosis and suppression of angiogenesis in vitro and in vivo [18]

## Materials and Methods

In this observational study, 43 premenopausal women (mean  $\pm$  SD) age, 34.38  $\pm$  7.07 years) were enrolled. Patients were divided in three groups according to clinical complaints. Group A included asymptomatic patients or patients presenting mild dysmenorrhea (n=17); group B moderate dysmenorrhea, but without dyspareunia or chronic pelvic pain (n=11). Group C included patients presenting severe dysmenorrhea (with no response to conventional analgesic, treatment such as antiprostaglandins, and requiring bed rest) and/or dyspareunia and/or chronic pelvic pain (N=10). The degree of pain was established using a visual analogue scale. 5 patients no continuous by own decision.

All patients provided informed consent after the nature of the study was fully explained, and institutional review board approval was obtained before starting the study.

All patients underwent a transvaginal ultrasound examination, performed by the same senior gynecologists' (MGM), with a 3,5-5,5 MHz probe and a Voluson S 8 (GE healthcare, Milwaukee, MI). A "typical" Ovarian endometriosis was diagnosed when a unilocular cyst with ultrasound features or regular wall. Ground glass echogenicity of the cyst content, and capsular vascularization. Volumes of ovarian endometrioma were calculated using the formula for prolate ellipsoid  $\rightarrow$  [12].

All patients included did not intake oral contraceptive or progestin intrauterine device users. In addition women intake vitamin D supplements.

On the day of initial diagnosis of endometriosis, Blood samples were collected from all patients by venipuncture into 10-cc sterile tubes and were kept at room temperature until centrifugation at

400  $\times$  g for 10 minutes. There were <2 hours allowed between blood collection and processing. Serum aliquots were then frozen at  $-80^{\circ}\text{C}$  until measurement of vitamin D serum levels. The hypovitaminosis D condition was defined as a 25 OH D<sub>3</sub> serum level <30 ng/ml [14].

Statistical software SPSS 20 (SPSS Inc., Chicago, IL) was used for data analysis. All continuous variables were tested for normality with the D'Agostino-Pearson test. Normally distributed variables were expressed as mean  $\pm$  SD, while skewed variables were reported as median and interquartile range (IQR). The Mann-Whitney test or the t-test was used for comparison as appropriate. Qualitative variables were expressed as proportions and were compared with the Chi-square test or the Fisher's exact test as appropriate. A Pearson coefficient was determined to evaluate the correlation between 25-OH-D<sub>3</sub> level and pelvic pain. A  $p < 0.05$  was considered statistically significant.

## Results

Number of patient's recruitment was 43. Five patients were excluded. The mean ( $\pm$  SD) vitamin D serum levels in group A were 26,9  $\pm$  04.17 pg/mL in group B were 16,2  $\pm$  1,4 pg./mL. and group C 10,4 pg/ml  $\pm$  2,4 pg/ml. To verify whether this observation could have been biased by the lack of control for several possible confounders, the mean vitamin d serum levels were adjusted with respect to gravidity, length of menses, infertility, and body mass index in a univariate general linear model [8]. Using this model, no significant difference was observed in mean vitamin D levels among three groups.

## Discussion

Endometriosis is considered a multifactorial disease. Multiple theories have been proposed to explain the origin of enigmatic disease like genetic, hormonal immunological and inflammatory theories [11]. Recent theories have investigated the potential correlation between vitamin D and endometriosis. Ciavattini [10]. suggested the potential role of vitamin D in the regulation of the immunological function and assessed that vitamin D might influence the development and progression of endometriosis through its role in the reduction of proinflammatory process.

Pain is defined as unpleasant sensory and emotional experience associated with actual or potential tissue damage. Our study is limited to ovarian endometriosis in which one nerves fibers have shown more density in the lining ovarian endometriosis than the normal ovarian tissue. Our previous report show that pelvic pain was correlate with angiogenesis level and these theory it is supported by the new neuroangiogenesis theory.

Neuroangiogenesis and angiogenesis are essential for the development of endometriosis [9]. Anti-angiogenic compounds may inhibit early-stage or post-surgical endometriotic lesions. Numerous drugs have been shown to exert anti-angiogenic effects. Anti-angiogenic substances include growth factor inhibitors, endogenous angiogenesis inhibitors, COX-2 inhibitors, phytochemical compounds, immunomodulatory, dopamine agonists, peroxisome proliferator-activated receptor agonists, progestins, GnRH agonists, and angiogenesis inhibitors [11]. Vitamin D is a prohormone with multiple actions mediate by tissue receptor. VDR. An important mechanism of actions is inhibit neovascularization and subsequently regresses endometriotic implant and reduce pelvic pain [18].

In this preliminary investigation our results show that all

patients with ovarian endometriomas have vitamin D low levels under the 30 normally level. So more, this report show that pain is directly correlated with the vitamin level and patient with severe pain presented a lower vitamin D level than mild or asymptomatic patients,

A multiple studies report the important role of Vitamin d in gynecological disease like POCs, uterine fibroids and endometriosis. A recent report postulated vitamin d as a new treatment of endometriosis by decreased prostaglandin levels. However, another studies reported that vitamin D not improve pelvic pain endometriosis [17].

Our results show a high incidence of hypovitaminosis D in endometriosis women and correlate the vitamin serum levels with the intensity of pelvic pain. According with previous report we believe that vitamin levels is a possible modifiable risk factor for endometriosis and pain symptoms. It's necessary a multiple randomized study to determine vitamin d supplementation but it possible that the diet gives an important contribution to improve vitamin d serum level. Our group investigated if patients with uterine fibroids and ovarian endometriosis can improve hypovitaminosis D through seven eggs/week intake – Hayes et al asses that weekly consumption of 7 vitamin D-enhanced eggs has an important impact in vitamin d status in adults. Advantages of food intake it's impossible vitamin D toxicity levels like supplements vitamin d bail. ENMIOVO –D study will show if a vitamin D enhanced eggs intake improve vitamin D serum levels and reduce ovarian endometrioma and uterine fibroids [13].

On the other hand, Almassinokiani et al assess that vitamin D was not effective in the treatment of endometriosis related pain. Our study shows the relationship between endometriosis angiogenesis and pelvic pain and we believe that a normal vitamin D level its necessary to improve the pelvic pain by angiogenesis via and it's can be associated to another pathogenesis via treatment. Endometriosis pelvic pain has a multifactorial pathogenesis therefore; treatment will be multiple to find synergic respond.

## Statement of authorship:

All the authors contributed intellectually in the work, meet the conditions of authorship and approved the final version of it.

Patricia Díaz Ortega: conception and design of the study, acquisition of data, drafting the article or revising it critically for important intellectual content.

Manuel García Manero: conception and design of the study, analysis and interpretation of data, final approval of the version to be submitted Juan Luis Alcazar: analysis and interpretation of data, final approval of the version to be submitted.

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