

## Relationship between endometriosis and vitamin D status – a review

M. Paliga<sup>1</sup>, S. Horák<sup>2</sup>

<sup>1</sup>Medical Center Angelius, Katowice; <sup>2</sup>Chair and Clinical Department of Gynecology,  
Obstetrics and Oncological Gynecology in Bytom, Bytom (Poland)

### Summary

The impact of vitamin D on multiple biological processes is nowadays widely accepted. Vitamin D deficiency has been linked with many diseases, including cardiovascular and neurological diseases, as well as with immune system function and its role during infections. An influence of vitamin D on the reproductive functions of women and men has been also reported. Endometriosis is one of the conditions responsible for infertility in women, and the contribution of vitamin D on the development of the disease has been investigated. Yet, a direct link between predisposition to endometriosis or severity of the disease and vitamin D status has not been defined. Some studies report no changes in vitamin D levels in endometriosis patients, compared to healthy controls, while others show a significant increase or decrease in vitamin D concentration in women suffering from endometriosis. Therefore, further studies are needed to establish the relationship between endometriosis and vitamin D status, which may be useful in designing vitamin D supplementation schedules for endometriosis patients, or in monitoring women at risk of developing the disease.

*Key words:* Endometriosis; Vitamin D; Fertility; Reproductive functions.

### Introduction

Epidemiological studies reveal that over one billion people suffer from vitamin D deficiency (VDD) worldwide [1]. The major causes of insufficient vitamin D concentration are a limited exposure to sunlight and problems with the absorption of the vitamin [2]. Vitamin D is a steroid hormone with pleiotropic effects. It plays a role in calcium-phosphorus homeostasis, which is responsible for the correct mineralisation of bone tissue. In consequence, VDD leads to development of rickets and osteomalacia, and it is believed to contribute to osteoporosis and increased susceptibility to bone fractures [3]. Besides its skeleton-related function, vitamin D influences a wide spectrum of processes, including the correct function of the cardiovascular, respiratory, neural and muscular systems, and regulation of the immune response [1, 4, 5]. Nowadays, the association of vitamin D status with the regulation of reproductive functions attracts much attention. Studies suggest that an adequate vitamin D level facilitates procreation, improves the well-being of the pregnant woman and the fetus, and positively influences the health of the new-born baby [6]. On the contrary, VDD may contribute to the development and severity of pathologies of the reproductive system, including endometriosis [7, 8].

In this review, the authors summarise the current state of knowledge of the impact of vitamin D on the function of the female genital tract, with special focus on the incidence and development of endometriosis. They describe the role of vitamin D and the consequences of its deficiency on human

health, and they specifically address the impact of vitamin D on fertility.

### Vitamin D and its functions

Vitamin D is produced mainly in the skin exposed to UVB light, and only a little fraction is obtained through food. Vitamin D<sub>3</sub> is naturally produced in animals and is derived from 7-dehydrocholesterol, while vitamin D<sub>2</sub> derives from the plant sterol ergosterol [4]. Throughout this article the term vitamin D refers to both types, unless otherwise stated. After UVB-induced conversion, enzymatic processing is necessary to generate the biologically active form of vitamin D. First, 25-hydroxyvitamin D (25(OH)D) is produced in the liver, and it is subsequently converted to 1,25-dihydroxycholecalciferol in the kidneys (1,25(OH)<sub>2</sub>D) [4]. As recommended by the Endocrine Society, circulating serum 25(OH)D level should be measured to assess vitamin D status. VDD is defined as a 25(OH)D serum level below 50 nmol/l (20 ng/ml) [2].

The action of 1,25(OH)<sub>2</sub>D is mediated via binding to the vitamin D receptor (VDR), which is a transcription factor with thousands of binding sites spread throughout the genome [4]. Since VDR is present in most tissues and cells in the body, vitamin D impacts the expression of multiple genes and controls many biological processes [2]. Additionally, vitamin D acts directly by inducing calcium translocation across intestinal membranes and by triggering signaling cascades originating at vitamin D-binding membrane receptors, such as membrane-associated rapid response steroid binding protein (MARRS) [4, 5].

The role of vitamin D is widely acknowledged in multi-

Revised manuscript accepted for publication October 9, 2018

ple medical areas. Vitamin D was first associated with bone health and calcium and phosphorus homeostasis [4], but more functions of vitamin D have since been discovered. VDD is associated with the development of cardiovascular diseases and accompanying arterial stiffness [9]. It has also been suggested that vitamin D status may be reflected by the parameters describing muscle strength [10]. Interestingly, vitamin D is also regarded as a neurosteroid involved in the proper function and development of the brain [5]. Neurons and glial cells express VDR, and dysregulated vitamin D homeostasis has been implicated in the pathologies of neurocognitive, neurodegenerative, and neurological diseases, as well as in neuropsychological disorders [5]. It has also been suggested that VDD impacts reproductive functions, influences fertility and the outcome of in vitro fertilisation, and is involved in hyperandrogenisms, polycystic ovary syndrome, and endometriosis [7]. Furthermore, vitamin D plays an important role in controlling the immune response, impacting immune cell generation and differentiation, and modulating cytokine production [11]. VDD has been associated with impaired control of multiple infectious diseases, including tuberculosis, HIV, and fungal infections [11].

Epidemiological data demonstrate that as much as 85% of the Polish population has VDD after the winter season [12]. An adequate vitamin D status was recorded in only 2.5% of study participants, and those were people taking vitamin D supplements who declared regular physical activity and more UVB exposure [12]. Surprisingly, VDD was also detected in almost half of the study participants during the summer months, suggesting an insufficient exposure to sunlight [13]. Therefore, exposure to UVB and vitamin D supplementation are highly recommended to maintain an adequate vitamin D level. Some types of food, such as milk, soy milk, mushrooms, and fish, especially salmon, mackerel, tuna, and sardines constitute a limited additional source of vitamin D. Food fortification is also common, and milk, orange juice, and yogurts enriched with vitamin D are available on the market [3]. Recommendations for vitamin D supplementation differ depending on the population of origin, age, and health of an individual. The typical daily supplementation dose of vitamin D<sub>3</sub> is 800-2,000 IU for adults [3].

Some health conditions, such as obesity, liver, and kidney diseases, which lead to decreased 25(OH)D synthesis and increased 25(OH)D loss through urine, may contribute to VDD [14]. However, overdosing vitamin D may also have deleterious effects related to hypercalcemia, including gastrointestinal disorders, kidney stones, bone, muscle and joint pains, and irregular heartbeat [14].

### **Endometriosis, a common problem in women of reproductive age**

Endometriosis is a chronic and often painful disease,

characterised by the presence of estrogen-dependent lesions outside the uterus [15]. It is estimated that as much as 10% of all women of reproductive age may be affected by the disease [15]. Endometriosis is classified into three main types: superficial (peritoneal), ovarian (endometrioma), and deep endometriosis with severe lesions exceeding 5 mm in depth [16]. Endometriosis is primarily located on the pelvic peritoneum, on the ovaries, or on the rectovaginal septum, but in some cases endometrium-like tissue is found on the diaphragm or in the pleura [17]. Endometriosis is often related to infertility. Approximately 35-50% of women attending fertility clinics are diagnosed with endometriosis [17]. The most common manifestations of endometriosis are related with pain and include chronic pelvic pain, dysmenorrhoea, dyspareunia, dysuria, and dyschezia.

Endometriosis has a complex etiology, and its development is dependent on numerous factors, which can be hormonal, genetic, immunologic, and environmental [7]. The most widely accepted theory suggests a retrograde menstruation flow as the source of sloughed endometrial cells that reach the pelvic cavity and lead to endometriotic lesion implementation [18]. However, not all women that experience retrograde menstruation develop endometriosis, which suggests that the process is more complex and multifactorial [18]. Defects in immune-mediated recognition and elimination of endometrial fragments in the peritoneal cavity are thought to be crucial [19]. Moreover, endometriosis is an estrogen-dependent disease, and its development and severity have been associated with dysregulated estrogen homeostasis. It has been demonstrated that ectopic endometrial cells express surface receptors for estrogen, progesterone, and androgen. In addition, such cells produce an enzyme that is able to convert androgens into estrogens and is not a feature of a healthy endometrium [20]. Prostaglandin, the strongest activator of the enzyme, is generated through the action of cyclooxygenase-2 action, which is triggered by estrogens. In this way, a positive feedback loop is created, leading to high estrogen concentrations and enabling the implementation and non-natural proliferation of endometrial cells [20].

Laparoscopy is the gold standard in the diagnosis of endometriosis. Aside from its diagnostic use, this medical procedure also allows for the surgical removal of diseased areas, which contributes to decreasing endometriosis-associated pain [17]. It is recommended, however, that every laparoscopy be preceded by a thorough medical history preparation accompanied by non-invasive diagnostic methods such as ultrasound and magnetic resonance imaging [16].

### **Association between vitamin D status and the development of endometriosis**

Although some associations between vitamin D status and the incidence and severity of endometriosis have been

found, an analysis of the available literature reveals conflicting observations.

The case control study by Buggio *et al.* demonstrated no difference in vitamin D status between endometriosis patients and healthy controls, as well as between women with ovarian endometrioma and those suffering from deep endometriosis [21]. Similarly, in another study, no differences in 25(OH)D concentration were recorded between endometriosis patients and healthy controls [22]. Yet, the same study demonstrated that VDR expression in the endometriotic cyst from the ovary was elevated compared to the expression in normal ovarian cells, which may implicate vitamin D in endometriosis development [22]. Hartwell *et al.* also reported no differences in 25(OH)D levels between endometriosis patients and healthy controls. However, endometriosis patients had elevated levels of 1,25(OH)<sub>2</sub>D, which suggests that these patients may have a different vitamin D metabolism compared to healthy women [23]. Additionally, a potential role of VDR polymorphism on the prevalence of endometriosis-related infertility and idiopathic infertility has been studied. No statistically significant differences were found either between infertile and fertile women or between infertile women with and without endometriosis [24]. Binding of 1,25(OH)<sub>2</sub>D to VDR induces transcription of the *HOXA10* gene [25]. *HOXA10* is a transcription factor engaged in the embryogenesis of the uterine epithelium, stroma, and muscle. Its expression is cyclically induced in the adult endometrium by estrogen and progesterone [25].

Upregulation of *HOXA10* in the endometrium occurs during a nidation window. Taylor *et al.* observed that such an upregulation is significantly lower in eutopic endometrium of endometriosis patients than in the control group, which may, at least in part, contribute to infertility associated with endometriosis [26].

Differences in vitamin D status between endometriosis patients and the control groups have also been reported. Pagliardini *et al.* demonstrated that infertile patients with endometriosis had higher levels of 25(OH)D compared to women with other infertility-causing disorders [8]. Somigliana *et al.* reported higher 25(OH)D levels in endometriosis patients compared to controls, and a positive gradient of the disease severity was noted [19]. A large prospective study from the USA comprised over 70 thousand women for whom predicted plasma vitamin D concentrations were calculated based on the age, season of blood draw, ethnicity, geographical region, dietary vitamin D intake, BMI, alcohol intake, and physical activity. According to the authors, predicting the vitamin D level allowed them to correlate vitamin D status with endometriosis prevalence. In contrast, measuring vitamin D level at the time of endometriosis diagnosis was not useful to distinguish whether potential changes in vitamin D status were the cause or result of endometriosis. Nevertheless, the results obtained in this study suggested that higher

predicted plasma 25(OH)D levels were associated with decreased risk of endometriosis [27].

It has been also speculated that the influence of vitamin D on the development of endometriosis may be dependent on the vitamin D-binding protein (VDBP). Indeed, as demonstrated by Borkowski *et al.*, endometriosis patients tended to have higher serum VDBP levels compared to the controls. Also, a subtle, yet not statistically significant, rise in VDBP concentration has been noted with increased severity of endometriosis [28]. The polymorphisms in VDBP have been identified as a genetic risk factor contributing to endometriosis, and a higher prevalence of the GC\*2 allele was found in endometriosis patients compared to the controls. This suggests that some women may be predisposed to the development of endometriosis [29].

Endometriosis develops spontaneously only in primates, which significantly limits the experimental work due to the ethical and financial issues associated with the use of these animal models. However, rats and mice may be implanted with human endometriotic tissue, either by injection of endometriotic cells or by intraperitoneal transplantation of endometrial tissue, and serve as a model to investigate the development of the disease [30]. Studies on rodents demonstrated that different modes of supplementation with vitamin D prevented implantation of endometriotic cells and improved regression of endometriotic lesions [30, 31].

Encouraging effects of vitamin D in vitro treatment of stromal cells obtained from endometriosis patients have been reported. Vitamin D-exposed cells increased cell adhesion, decreased invasion and proliferation capabilities and decreased expression of apoptotic markers, suggesting an improvement of endometriosis-related features of the stromal cells [32]. While a high, single dose of vitamin D has proven to reduce the pain in primary dysmenorrhea [33], clinical studies do not support positive effects of vitamin D supplementation on the severity of pain experienced by women after ablative surgery for endometriosis [34]. Moreover, a growing body of evidence points to the fact that the hypervitaminosis D may cause undesirable effects. Increased vitamin D levels in follicular fluid contributed to decreased in vitro fertilization rate. Also, excessively high, and low, vitamin D levels negatively influenced spermatozoa count, their morphology, and motility [35].

## Conclusions

Endometriosis is a disease which is associated with impaired immune control. Therefore, the contribution of vitamin D, a well-known immunomodulator, to the development and severity of endometriosis has been widely studied. However, the available data have not unambiguously defined the correlation between the serum level of vitamin D and the predisposition to endometriosis development. Many studies report no significant differences between en-

ometriosis patients and control groups, while others have found a relationship between prevalence of endometriosis and vitamin D status. Interestingly, some researchers have reported increased vitamin D levels in endometriosis patients, while others have noted diminished vitamin D levels in women suffering from the disease. Yet, the impact of vitamin D on endometriotic cells has been demonstrated in vitro. This suggests that 25(OH)D serum levels may not reflect the action of vitamin D at the cellular level, as differences in VDR expression have been noted between endometriotic cells and their healthy counterparts. Clearly, more research is needed to establish the connection between endometriosis and vitamin D status and to find a potential cause-effect relationship. A better understanding of the influence of vitamin D on the pathology of endometriosis could lead to setting up an optimal schedule of vitamin D supplementation for endometriosis patients and women at risk of developing the disease.

### Acknowledgments

The authors would like to thank Proper Medical Writing sp. z o.o., for the assistance in writing this manuscript.

### References

- [1] Holick M.F.: "The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention". *Rev. Endocr. Metab. Disord.*, 2017, 18, 153.
- [2] Holick M.F., Binkley N.C., Bischoff-Ferrari H.A., Gordon C.M., Hanley D.A., Heaney R.P. *et al.*: "Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline". *J. Clin. Endocrinol. Metab.*, 2011, 96, 1911.
- [3] Hossein-nezhad A., Holick M.F.: "Vitamin D for health: a global perspective". *Mayo. Clin. Proc.*, 2013, 88, 720.
- [4] Bikle D.D.: "Vitamin D metabolism, mechanism of action, and clinical applications." *Chem. Biol.*, 2014, 21, 319.
- [5] Di Somma C., Scarano E., Barrea L., Zhukouskaya V.V., Savastano S., Mele C., *et al.*: "Vitamin D and Neurological Diseases: An Endocrine View". *Int. J. Mol. Sci.*, 2017, 18, pii: E2482.
- [6] Heyden E.L., Wimalawansa S.J.: "Vitamin D: Effects on human reproduction, pregnancy, and fetal well-being". *J. Steroid. Biochem. Mol. Biol.*, 2018, 180, 41.
- [7] Shahrokhi S.Z., Ghaffari F., Kazerouni F.: "Role of vitamin D in female reproduction". *Clin. Chim. Acta.*, 2016, 455, 33.
- [8] Pagliardini L., Vigano' P., Molgora M., Persico P., Salonia A., Vailati S.H., *et al.*: "High Prevalence of Vitamin D Deficiency in Infertile Women Referring for Assisted Reproduction". *Nutrients*, 2015, 7, 9972.
- [9] Burt M.G., Mangelsdorf B.L., Stranks S.N., Mangoni A.A.: "Relationship between Vitamin D Status and Autonomic Nervous System Activity". *Nutrients*, 2016, 8, 565.
- [10] Kara M., Ekiz T., Kara Ö., Tiftik T., Malas F.Ü., Özbudak Demir S., Özgirgin N.: "Does vitamin D affect muscle strength and architecture? An isokinetic and ultrasonographic study." *Asia Pac. J. Clin. Nutr.*, 2017, 26, 85.
- [11] Gois P.H., Ferreira D., Olenski S., Seguro A.C.: "Vitamin D and Infectious Diseases: Simple Bystander or Contributing Factor?" *Nutrients*, 2017, 9, 651.
- [12] Kmiec P., Żmijewski M., Waszak P., Sworczak K., Lizakowska-Kmiec M.: "Vitamin D deficiency during winter months among an adult, predominantly urban, population in Northern Poland". *Endokrynol. Pol.*, 2014, 65, 105.
- [13] Kmiec P., Żmijewski M., Lizakowska-Kmiec M., Sworczak K.: "Widespread vitamin D deficiency among adults from northern Poland (54 degrees N) after months of low and high natural UVB radiation". *Endokrynol. Pol.*, 2016, 66, 30.
- [14] Alshahrani F., Aljohani N.: "Vitamin D: deficiency, sufficiency and toxicity". *Nutrients*, 2013, 5, 3605.
- [15] Rogers P.A., D'Hooghe T.M., Fazleabas A., Giudice L.C., Montgomery G.W., Petraglia F., Taylor R.N.: "Defining future directions for endometriosis research: workshop report from the 2011 World Congress of Endometriosis In Montpellier, France". *Reprod. Sci.*, 2013, 20, 483.
- [16] Kho R.M., Andres M.P., Borrelli G.M., Neto J.S., Zanluchi A., Abrão M.S.: "Surgical treatment of different types of endometriosis: Comparison of major society guidelines and preferred clinical algorithms". *Best. Pract. Res. Clin. Obstet. Gynaecol.*, 2018, 51, 102.
- [17] Giudice L.C.: "Clinical practice. Endometriosis." *N. Engl. J. Med.*, 2010, 362, 2389.
- [18] Sourial S., Tempest N., Hapangama D.K.: "Theories on the pathogenesis of endometriosis". *Int. J. Reprod. Med.*, 2014, 2014, 179515.
- [19] Somigliana E., Panina-Bordignon P., Murone S., Di Lucia P., Vercellini P., Vigano P.: "Vitamin D reserve is higher in women with endometriosis". *Hum. Reprod.*, 2007, 22, 2273.
- [20] Bednarowska-Flisiak A.: "Endometriosis – new trends in pathogenesis therapy". *Post. Nauk. Med.*, 2008, 8, 258.
- [21] Buggio L., Somigliana E., Pizzi M.N., Drudi D., Roncella E., Vercellini P.: "25-Hydroxyvitamin D Serum Levels and Endometriosis: Results of a Case-Control Study." *Reprod. Sci.*, 2018, 1, 1933719118766259.
- [22] Agic A., Xu H., Altgassen C., Noack F., Wolfler M.M., Diedrich K., *et al.*: "Relative expression of 1,25-dihydroxyvitamin D3 receptor, vitamin D 1 alpha-hydroxylase, vitamin D 24-hydroxylase, and vitamin D 25-hydroxylase in endometriosis and gynecologic cancers". *Reprod. Sci.*, 2007, 14, 486.
- [23] Hartwell D., Rodbro P., Jensen S.B., Thomsen K., Christiansen C.: "Vitamin D metabolites—relation to age, menopause and endometriosis". *Scand. J. Clin. Lab. Invest.*, 1990, 50, 115.
- [24] Vilarino F.L., Bianco B., Lerner T.G., Teles J.S., Mafra F.A., Christofolini D.M., Barbosa CP.: "Analysis of vitamin D receptor gene polymorphisms in women with and without endometriosis". *Hum. Immunol.*, 2011, 72, 359.
- [25] Sayegh L., Fuleihan Gel H., Nassar A.H.: "Vitamin D in endometriosis: a causative or confounding factor?" *Metabolism*, 2014, 63, 32.
- [26] Taylor H.S., Bagot C., Kardana A., Olive D., Arici A.: "HOX gene expression is altered in the endometrium of women with endometriosis". *Hum. Reprod.*, 1999, 14, 1328.
- [27] Harris H.R., Chavarro J.E., Malspeis S., Willett W.C., Missmer S.A.: "Dairy-food, calcium, magnesium, and vitamin D intake and endometriosis: a prospective cohort study". *Am. J. Epidemiol.*, 2013, 177, 420.
- [28] Borkowski J., Gmyrek G.B., Madej J.P., Nowacki W., Goluda M., Gabryś M., *et al.*: "Serum and peritoneal evaluation of vitamin D-binding protein in women with endometriosis". *Postepy. Hig. Med. Dosw.*, 2008, 62, 103.
- [29] Faserl K., Golderer G., Kremser L., Lindner H., Sarg B., Wildt L., Seeber B.: "Polymorphism in vitamin D-binding protein as a genetic risk factor in the pathogenesis of endometriosis". *J. Clin. Endocrinol. Metab.*, 2011, 96, E233.
- [30] Muscogiuri G., Altieri B., de Angelis C., Palomba S., Pivonello R., Colao A., Orio F.: "Shedding new light on female fertility: The role of vitamin D". *Rev. Endocr. Metab. Disord.*, 2017, 18, 273.
- [31] Abbas M.A., Taha M.O., Disi A.M., Shomaf M.: "Regression of endometrial implants treated with vitamin D3 in a rat model of endometriosis". *Eur. J. Pharmacol.*, 2013, 715, 72.
- [32] Delbandi A.A., Mahmoudi M., Shervin A., Zarnani A.H.: "1,25-Dihydroxy Vitamin D3 Modulates Endometriosis-Related Features of Human Endometriotic Stromal Cells." *Am. J. Reprod. Immunol.*, 2016, 75, 461.

- [33] Lasco A., Catalano A., Benvenga S.: “Improvement of primary dysmenorrhea caused by a single oral dose of vitamin D: results of a randomized, double-blind, placebo-controlled study”. *Arch. Intern. Med.*, 2012, 172, 366.
- [34] Almassinokiani F, Khodaverdi S, Solaymani-Dodaran M, Akbari P., Pazouki A.: “Effects of Vitamin D on Endometriosis-Related Pain: A Double-Blind Clinical Trial”. *Med. Sci. Monit.*, 2016, 22, 4960.
- [35] Laganà A.S., Vitale S.G., Ban Frangež H., Vrtačnik-Bokal E., D’Anna R.: “Vitamin D in human reproduction: the more, the better? An evidence-based critical appraisal”. *Eur. Rev. Med. Pharmacol. Sci.*, 2017, 21, 4243.

Corresponding Author:  
M. PALIGA, M.D.  
Medical Center Angelus  
Katowice (Poland)  
e-mail: m.paliga@angelius.org