THE ROLE OF VITAMIN D DEFICIENCY IN THE DEVELOPMENT OF LUTEAL PHASE DEFICIENCY

O.V. BULAVENKO
MD, Professor, Obstetrics and Gynecology Department № 2 of the Vinnytsya National Memorial Medical University named after M.I. Pirogov

N.P. DZIS
Obstetrics and Gynecology Department № 2 of the Vinnytsya National Memorial Medical University named after M.I. Pirogov

O.V. FURMAN
Obstetrics and Gynecology Department № 2 of the Vinnytsya National Memorial Medical University named after M.I. Pirogov

INTRODUCTION

There is renewed interest in vitamin D (VD) synthesis, metabolism, and its function. The two principal driving forces for increased interest can be traced to:

1) the deteriorating, worldwide trend to nutritional vitamin D deficiency [1, 2];

2) new knowledge regarding the non-hormonal, intracrine, and paracrine actions of 1-hydroxylated vitamin D metabolites [3].

The major endogenous synthetic source of vitamin D for humans is the epidermis. Vitamin D3 is produced in the skin by a UVB-mediated, photolytic, non-enzymatic reaction that converts 7-dehydrocholesterol to pre-vitamin D3 [3]. Pre-vitamin D3 undergoes a subsequent non-enzymatic, thermal isomerization conversion to vitamin D3 as well as on the surface of the skin. Vitamin D3 finds its way from the skin into the general circulation. In the hepatic parenchyma vitamin D3 is converted by one of several, high-capacity cytochrome P450s to 25-hydroxyvitamin D3 (25OHD); the microsomal CYP2R1 appears to have the highest affinity for substrate vitamin D [4]. 25OHD is the richest and stable metabolite of vitamin D in human serum, its qualities are determined by the increased affinity where 25OHD is bound by the serum of vitamin D binding protein and other members of the albumin super family of proteins found in the blood. So the 25OHD level in the serum is the best indicator of vitamin D entering the host, either by cutaneous synthesis or by ingestion in the diet. In cross-sectional studies, especially those performed in populations living at relatively elevated latitudes in North America, Europe, and Asia, serum levels of the 25OHD metabolite are maximal, some 30-60 d after peak sunlight exposure in the summer months. 25OHD is a prohormone or immediate precursor metabolite to the active form of vitamin D – 1,25-dihydroxyvitamin D (1,25(OH)2D). 1,25(OH)2D is the product of a single enzyme mitochondrial CYP27B1-hydroxylase, and it serves as a high-affinity ligand for the vitamin D receptor (VDR) in target tissues where it modulate expression of vitamin D-directed genes. 1,25(OH)2D circulates in the serum at concentrations that are roughly 0,1% that of the prohormone 25OHD.

A defines the evolutionarily distinct, but preserved functions as vitamin D. The more evolutionarily advanced function of vitamin D is that of a hormone. This function is reserved for species bearing an endoskeleton where the 1,25(OH)2D hormone serves as a circulating regulator of both mineral and skeletal homeostasis. The only recognized source of the hormone in humans is the CYP27B1-hydroxylase; this enzyme is confined principally but not entirely to the proximal tubular epithelial cells of the kidney. 1,25(OH)2D synthesis in the kidney is regulated by other hormones. It is stimulated primarily by PTH and inhibited by circulating fibroblast growth factor 23 (FGF23) made by osteocytes.

The more evolutionarily primitive function of vitamin D is a cytokine generated to protect the inside environment of the host (single cell organisms to man) from microbial invaders in the external environment [6]. The 1,25(OH)2D cytokine is synthesized primarily by monocyte-macrophages and acts in an intracrine mode via interaction with the VDR to modulate the innate immune response to invading microbial agents. When produced in sufficient quantities, 1,25(OH)2D can escape the confines of the monocyte-macrophage to interact with and control the cytokine profiles of activated, VDR-expressing T- and B-lymphocytes in the local inflammatory microenvironment. A key distinction between the 1,25(OH)2D hormone and cytokine systems is an inadequate supply of substrate 25OHD will stimulate the renal CYP27B1-hydroxylase to maintain or increase production of the active, 1,25(OH)2D metabolite via secondary hyperparathyroidism, whereas a deficiency of sub-strate for the extrarenal CYP27B1-hydroxylase leads to a

decrease in production of 1,25(OH)2D and a reduction of the efficiency of intestinal calcium absorption.

An understanding of the above-stated physiology led Chapuy et al. to define endocrine vitamin D (25OHD) insufficiency/deficiency in terms of a significant increase in serum immunoreactive PTH (iPTH) levels. It is generally agreed that the serum PTH will start to rise significantly once the serum 25OHD drops to less than 20 ng/ml considered to represent vitamin D insufficiency, whereas those less than 10 ng/ml or 50 nmol/liter fall into the frankly vitamin D-deficient.

VDR and VD metabolizing enzymes have been detected in female reproductive tissues, such as ovary, uterus and placenta. The presence of VD metabolites was demonstrated in follicular fluid (FF). The recent studies show that VD regulates the expression of a large number of genes in reproductive tissues implicating a role for VD in female reproduction and pregnancy outcomes. There is an increasing human data suggesting that VD status may be associated with impaired fertility, endometriosis, polycystic ovary syndrome, and ovarian cancer. The presence of VDR in human ovarian tissue has raised the question of a possible direct role for 1-α,25-dihydroxyvitamin D (1-α,25(OH)2D3) in the regulation of steroid hormone synthesis and secretion. Our recent data have demonstrated that 1-α,25(OH)2D3 may affect in vitro insulin- and follicle-stimulating hormone (FSH)-induced progesterone secretion by porcine ovarian granulosa cells. The molecular mechanisms of this action should be further investigated.

VDR was detected in the main important reproductive organs such as hypothalamus, pituitary gland, ovaries, fallopian tubes and the uterine endometrial cells as well as in the immune cells residing within the uterine endometrium [5].

Luteal phase deficiencies (LPD) of the menstrual cycle are the violations that are caused by hypofunction of the corpus luteum resulting in insufficient synthesis of the major hormones of the endocrine organs – progesterone and estradiol.

Alterations in life style (exercise, diet, and stress) and abnormal endocrine dynamics are known to cause an ovulation; however, their role in milder menstrual cycle phenotypes such as LPD is less known.

Clinically, LPD may be associated with:

- abnormal luteal phase progesterone and estradiol production;
- shortening of the menstrual cycle (by shortening of the luteal phase);
- premenstrual spotting or bleeding;
- pregnancy-related disorders such as infertility (via impairment of endometrial development) and early pregnancy loss.

While LPD is thought to occur in 3-20% of women who are infertile and in 25-60% of women with recurrent spontaneous abortion, data also suggest that 6-10% of women with normal fertility demonstrate an inadequate luteal phase.

STUDY METHODS

The study involved 97 women of reproductive age (29,89 ± 4,16). Women had LPD and polycystic ovary syndrome with ovulatory phenotype that were diagnosed with infertility. Surveys were conducted at the Department of Obstetrics and Gynaecology № 2 of Vinnytsya National Memorial Medical University named after M.I. Pirogov, specialized Clinic «Motherhood and Life» (Lublin, Poland), Reproductive Health Clinic «Remedy» in Vinnitsa. Patients were divided into 3 groups according to the level of reduction of vitamin D. The first group consisted of patients with levels < 10 ng/ml (deficiency), the second group – 10–20 ng/ml (insufiency), a third group – 20–40 ng/ml (suboptimal). The examination included the clinical symptoms of LPD – duration of luteal phase, levels of luteal progesterone and estradiol and thickness of endometrium. Menstrual cycle monitoring performed by Creighton Model Fertility Care System with detecting of premenstrual spotting duration and post peak phase.

STUDY RESULTS

During the analysis of post peak phases significant difference between longest of luteal and level of vitamin D was not found: in group C – 8,562 ± 0,866 ($p > 0,005$), D1 – 8,118 ± 1,269 ($p > 0,05$), D2 – 8,689 ± 0,633 ($p > 0,05$), D3 – 8,727 ± 0,786 ($p > 0,05$) (Fig. 1).

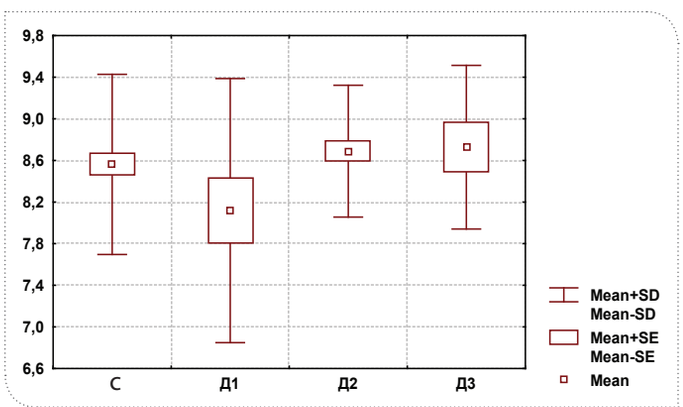

FIGURE 1.
DURATION OF POST PEAK PHASE (DAYS)*
*Here and in the future:
C – total group of women;
D1 – levels of vitamin D3 < 10 ng/ml;
D2 – level of vitamin D3 – 10 to 20 ng/ml;
D3 – the level of vitamin D3 – 20 to 40 ng/ml;
Mean – the average of the sample;
Mean +SE – error of the mean;
Mean +SD – standard deviation.

Premenstrual bleedings were significantly longer with decreasing of vitamin D level. In group C – 2,456 ± 2,128 ($p > 0,05$), D1 – 2,824 ± 2,186 ($p > 0,05$), D2 – 2,711 ± 2,2,030 ($p < 0,05$), D3 – 0,818 ± 1,834 ($p < 0,05$) (Fig. 2).

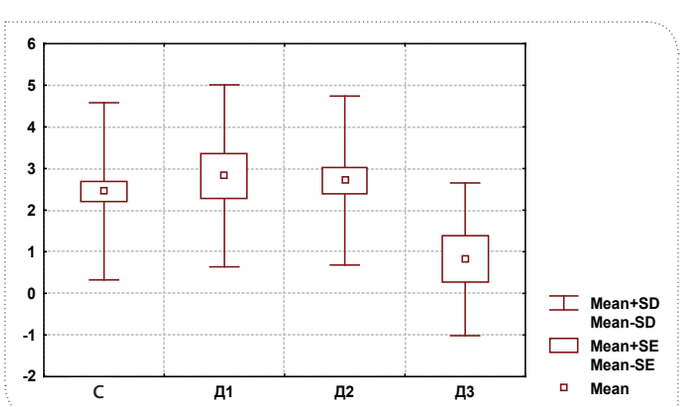

FIGURE 2.
PREMENSTRUAL BLEEDING (DAYES)

The level of luteal β-estradiol is significantly highest with increase of vitamin D level. Groups C – 97,66 ± 18,07(p < 0,01), D1 – 86,96 ± 12,50 (p < 0,05), D2 –98,90 ± 18,03 (p < 0,01), D3 – 109,1 ± 18,1 (p < 0,05) (Fig. 3).

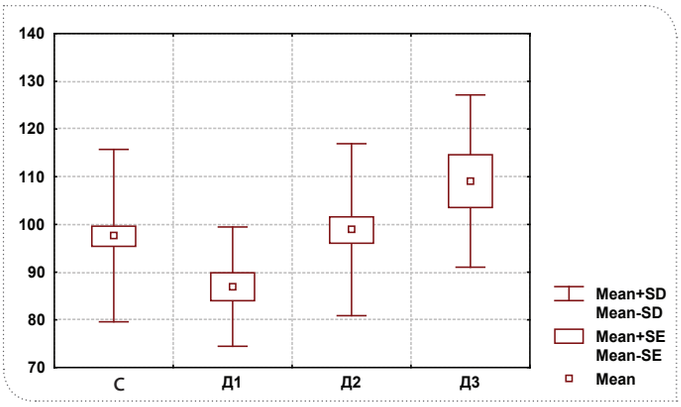

FIGURE 3.
LUTEAL B-ESTRADIOL LEVEL E (PG/ML)

The progesterone level is significantly decrease with increase of vitamin D. Group C – 13,53 ± 3,27 (p > 0,05), D1 – 12,81 ± 2,67 (p > 0,05), D2 – 13,50 ± 3,51 (p > 0,05), D3 – 14,74 ± 3,01 (p < 0,05) (Fig. 4).

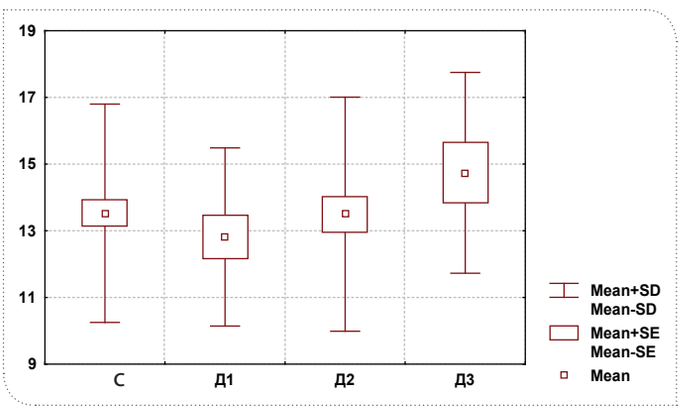

FIGURE 4.
LUTEAL PROGESTERONE LEVEL (NG/ML)

The thickness of endometrium is in direct correlation to the level of Vitamin D, the lower level of Vitamin D the thinner endometrium is observed. Group C – 8,852 ± 1,394 (p = 0,0572), D1 – 8,169 ± 1,174 (p > 0,05), D2 – 8,946 ± 1,473 (p < 0,05), D3 – 9,527 ± 0,946 (p < 0 < 01) (Fig. 5).

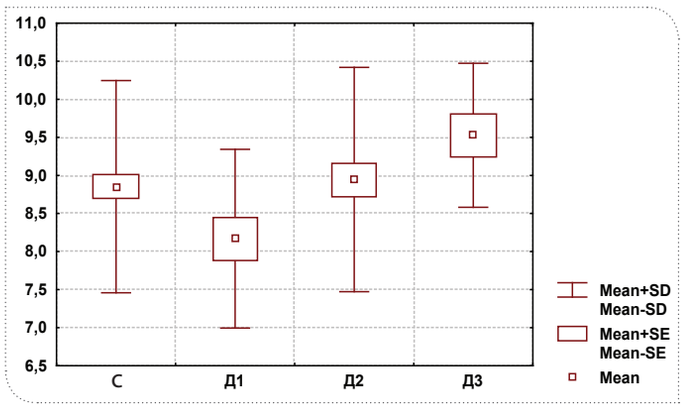

FIGURE 5.
THICKNESS OF ENDOMETRIUM IN LUTEAL PHASE (MM)

CONCLUSIONS

The role of Vitamin D deficiency has been confirmed in pathogenesis and in the development of deficiency of luteal phase. Vitamin D affects the development and functions of corpus luteum. The role between the main clinical signs of luteal phase deficiency (premenstrual bleeding, estrogen, and progesteron levels) and the thickness of endometrium has been confirmed. The correlation of the duration of the post-peak phase has not been found.

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N.P. Dzis, Obstetrics and Gynecology Department № 2 of the Vinnytsya National Memorial Medical University named after M.I. Pirogov

O.V. Furman, Obstetrics and Gynecology Department № 2 of the Vinnytsya National Memorial Medical University named after M.I. Pirogov

Vitamin D (VD) deficiency connecting with insufficient production in the skin and limited alimentation delivery, disrupts the function of all system of the body and increases the risk of women health. VD receptor and VD metabolizing enzymes have been detected in female reproductive tissues, such as ovary, uterus and placenta. There is an increasing human data suggesting that VD status may be associated with impaired fertility, endometriosis, polycystic ovary syndrome, and ovarian cancer. We studied the role of Vitamin D deficiency andpathogenesis role in the development of deficiency of Luteal Phase.Was detected the positive correlations with premenstrual bleeding, luteal progesterone and estradiol levels and no connecting with post peak duration.

Key words: vitamin D, luteal phase deficiency, premenstrual bleeding, progesterone, estradiol, endometrium, post peak phase.

РОЛЬ ДЕФІЦИТУ ВІТАМІНУ D У РОЗВИТКУ НЕДОСТАТНОСТІ ЛЮТЕЇНОВОЇ ФАЗИ

О.В. Булавенко, д. мед. н., професор кафедри акушерства та гінекології № 2 Вінницького національного медичного університету ім. М.І. Пирогова

Н.П. Дзись, кафедра акушерства та гінекології № 2 Вінницького національного медичного університету ім. М.І. Пирогова

О.В. Фурман, кафедра акушерства та гінекології № 2 Вінницького національного медичного університету ім. М.І. Пирогова

Дефіцит вітаміну D пов'язаний із проблемами процесів синтезу у шкірі та обмеженням постачання продуктами харчування. Це призводить до розладів у органах та системах організму людини та зокрема – репродуктивній. Рецептори до вітаміну D та метаболізуючі ферменти були виявлені в тканинах жіночої репродуктивної системи, таких як яєчники, матка та плацента. Багато досліджень свідчать про зв'язок зниженого рівня вітаміну D із порушенням фертильності (ендометріоз, синдром полікістозних яєчників, рак яєчників тощо). Ми вивчали роль дефіциту вітаміну D у патогенезі дефіциту лютеїнової фази. Були визначені позитивні кореляції із кровомазаням перед місячними, рівнями прогестерону і естрадіолу у лютеїнову фазу менструального циклу, та не було виявлено зв'язку із тривалістю післяпікової фази.

Ключові слова: вітамін D, недостатність лютеїнової фази, прогестерон, естрадіол, післяпікова фаза, передменструальні кровомазання.