PROGESTERONE INSUFFICIENCY AS A PREDICTOR OF FUTURE REPRODUCTIVE LOSSES

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Abstract: The article presents new data on the significance of vitamin D deficiency in the formation of endometrial structure disorders in women with luteal phase defect and unrupted follicle syndrome. Disorders of the menstrual cycle caused by a progesterone deficiency from the position of influence on the onset and progression of pregnancy are considered. Fertility of women, especially with endocrine imbalances, deserves special attention, since the frequency of early pregnancy loss in them is about 67 %.

Aim: study of the effects of vitamin D deficiency and progesterone deficiency in the luteinized unruptured follicle syndrome (Geis-Genes) and the luteal phase defect on the reproductive potential of women.

Materials and methods: a hormonal study, determination of vitamin D levels, a sonographic study conducted on days 5–7 and 21–24 of the menstrual cycle in the periconceptional supplementation program of 45 women with luteal phase deficiency (LPD) and luteinized unruptured follicle syndrome (LUF).

Results: The relationship between the content of vitamin D and the hormonal levels of the reproductive system of women with LPD and LUF is traced. The role of reducing vitamin D levels in the formation of hormonal imbalances in women of reproductive age has been established.

Conclusions:

– progesterone deficiency entails changes in various regulatory substances of the reproductive system, and therefore the periconceptional supplementation must be individual.

– the introduction of the definition of vitamin D in the periconceptional supplementation plan and its correction are justified and necessary to improve the structure of the endometrium and its secretory transformation in women with progesterone imbalance.

Keywords: reproductive function of women, hormonal imbalance, vitamin D.

1. Introduction

Menstrual disruptions (MD) are one of the most misunderstood problems in modern gynecology. Over the past decade, there has been an increase in the frequency of MDs in women of reproductive age almost 11 times in the world. In the structure of gynecological morbidity, according to most authors [1, 2], menstrual disorders account for about 60 % of all dishormonal disorders, and the frequency of early pregnancy loss in progesterone deficiency ranges from 67 % to 80 % [3]. According to data [4], LPD is registered in 46.6 % of women with infertility with a regular menstrual cycle and in 85 % with habitual miscarriage [4]. The term "luteal phase deficiency" is introduced to describe conditions in which the level of endogenous progesterone does not provide the functional secretory activity of the endometrium, which leads to disruption of the processes of implantation and development of the embryo. Reproductive health disorders of a woman can occur with any kind of hormonal imbalance: insufficiency or excess of estrogens, insufficiency or excess of androgens, violation of physiological boundaries for the tropic hormones of the hypothalamus, hormones synthesized in the pancreas or the small intestine. Uniting for these conditions is absolute or relative deficiency of progesterone and the resulting violations of the structural-receptive potential of the endometrium and mucous membranes of the genital tract of women. The etiopathogenesis of LUF syndromes as well as LPD has not been fully studied. Today, the role of vitamin D deficiency in the formation of various endocrine imbalances and infertility is widely debated [5].

Aim of the research: study of the effect of vitamin D deficiency and progesterone deficiency in the luteinized unruptured follicle syndrome (Geis-Genes) and the luteal phase deficiency on the reproductive potential of women.

2. Methods

Hormonal studies were carried out in the biochemical laboratory of the Ukrainian scientific and practical center for endocrine surgery, transplantation of endocrine organs and tissues of the Ministry of Health of Ukraine.

The study design included 45 women with progesterone deficiency (main group):

1) 32 of them are with LPD and 13 are LUF. LPD markers were: dysfunction of the corpus luteum: the endometrium was 2 or more days behind in its development;

2) short luteal phase: less than 8 days from the peak of luteinizing hormone (LH), associated with low levels of follicle-stimulating hormone (FSH), impaired release of FSH and LH or FSH/LH ratio;

3) inadequate luteal phase with progesterone secretion less than normal. The markers of LUF syndrome – follicle persistence – are established in the process of folliculometry as a progressive growth in the first phase of the antral follicle cycle to the size of a periovulatory and gradual reverse development during the second phase to the initial value. In this case, LUF syndrome is manifested by a thickening and an increase in the echogenicity of the wall of the follicle against the background of cyclic changes in the thickness and echogenicity of the endometrium, characteristic of a two-phase cycle [8]. Ultrasound examination was performed on an Aloka Hitachi device (Japan) with a sensor frequency of 7 MHz. A hormonal study was conducted in the 1st phase of the menstrual cycle (5–7 days) and on 21–24 days of the menstrual cycle. Chemiluminescent immunoassay was performed to determine FSH, LH, prolactin, progesterone, estradiol. The study of 25-hydroxyvitamin D (nmol/l) was done with solid-phase enzyme-linked immunosorbent assay with Sunrise Tecan device (conducted in the DILA laboratory). Reference standards – according to laboratory data. Correction of vitamin D was carried out according to the recommendations of the Endocrinological community [6].

The control group – 31 healthy women of reproductive age at the stage of preparation for pregnancy.

Statistical data processing was carried out on a personal computer using a standard software package of applied statistical analysis (Statistica for Windows v.6). using both parametric criteria (Student's t-test) and non-parametric (Mann-Whitney χ^2), Pearson correlation criteria, and regression analysis.

3. Results

The average age of the examined main group was 20.3±±1.7 years, in the control group – 20.9±1.6 years. The average age of menarche for women in both groups was 13–14 years old

(13.3±0.34 in the main group and 13.0±0.23 in the control group (p>0.05)). Women of both groups were preparing for gestational debut. An analysis of the menstrual function of women in the main group in 15 (33.3 %) revealed the presence of menopausal and painful menstruation, in 21 (46.7 %) a spotting in the perimenstrual period. The main indicator of the echographic structure of the corpus luteum of the ovaries and endometrium in women with LPD was an increase in the echogenicity of the M-echo in the peripheral regions with a hypoechoic zone in the center (noted in 29 (90.6 %). No secretory changes in the endometrium (21–24 days of the cycle) was characterized by the presence of its three-layer structure, typical for the pre-ovulatory period, with hypogenic functional layers (96.8 %). In 26 (81.25 %) patients a decrease in <0.22 of the volume of the yellow body to the volume of the ovary was noted, in 6 (18.75 %) the yellow body was represented by the cystus cavity of a homogeneous internal structure with a high conductivity and a completely heterogeneous structure with small echoic inclusions. The wall thickness of the corpus luteum was 1.2±0.5 mm. For all women with LUF, a sonographic study showed a thickening and increase in the echogenicity of the wall of the follicle against the background of cyclic changes endometrial thickness and echogenicity characteristic of a two-phase cycle.

The study of hormonal background showed low levels of follicle-stimulating hormone (FSH) in the first phase of the menstrual cycle at 3.45±1.23 U/l, which was significantly different from the control group 6.12±1.23 U/l, and 5.22±1.64 U/l at LUF (p<0.05). The ratio of FSH/LH in women with LPD was 0.83±0.13, with LUF 1.26±0.24, in the control group – 1.51±0.32. The level of prolactin also significantly exceeded these indicators in women of the control group, while it did not differ among women with LPD and LUF (with NLF: 15.25±1.73 ng/ml, with LUF: 14.15± ±1.56 ng/ml control indicator 7.23±1.45 ng/ml). The analysis of the estradiol index at the beginning of the cycle was also different for LPD and LUF: 56.83±3.23 pg/ml for LPD; 79.27±12.21 pg/ml and 89.27±12.21 pg/ml in the control group. Analysis of progesterone in women with LUF in the 1st phase of the menstrual cycle did not differ from the control group, at the same time with LPD – was reduced: 0.83±2.43 ng/ml with LPD, against 1.2± ±0.92 ng/ml at LUF, and 1.1±0.12 ng/ml in the control group. In the second phase: with LPD 17.6±2.23 ng/ml, with LUF: 14.15±1.56 ng/ml, and 23.12±11.23 ng/ml in the control group.

The level of prolactin in women of the main group was increased in comparison with the control group 15.25±1.73 ng/ml against 10.23±1.45 ng/ml.

During the periconceptional supplementation, the patients were divided into groups: I-a: 15 patients with LPD and 13 with LUF (33 women), in addition to the generally accepted progesterone in the 2nd phase of the menstrual cycle, received vitamin D3 – in an individually selected dose – 3 months. I-b: 17 patients with LPD received traditional progesterone therapy (didrogesterone 10 mg×2 times a day).

At the end of the 3-month therapy, an ultrasound, hormonal study and the determination of the level of vitamin D were performed.

The results of treatment are presented in **Table 1**.

Table 1

The results of the examination at the end of treatment

Indicator	Group I-a		Group I-b		Control group
	5 day of the menstrual cycle before treatment	5 day of the menstrual cycle after treatment	5 day of the menstrual cycle before treatment	5 day of the menstrual cycle after treatment	5 day of the menstrual cycle
FSH/LH	1.03±0.18	1.49±0.26	0.83 ±0.13	1.21±0.12	1.51±0.32
Prolactin ng/ml	15.25±1.73	10.47±1.34*	13.25±1.16	12.67±0.98	10.23±1.45
Vit D nmol/l	18.23±1.73	45.34±1.35*	17.43±1.18	47.21±1.76*	53.25±2.43
Ovarian structure	Follicles with a diameter of 6–9 mm with increased echogenicity of the wall of the follicle	Follicles with a diameter of 5–9 mm	Follicles with a diameter of 6–9 mm with an increase in the echogenicity of the wall of the follicle	Follicles with a diameter of 6–9 mm	Follicles with a diameter of 4–8 mm
Endometrial structure	Proliferative The thickness of the «M» echo 3.4±1.17 mm with an increase in the echogenicity of the wall of the follicle	Proliferative The thickness of the «M» echo 3.21±1.11 mm	Proliferative The thickness of the «M» echo 3.4±1.32 mm with an increase in the echogenicity of the wall of the follicle	Proliferative The thickness of the «M» echo 4.12±1.17 mm	Proliferative The thickness of the «M» echo 4.4±1.11 mm
	21 day of the menstrual cycle before treatment	21 day of the menstrual cycle after treatment	21 day of the menstrual cycle before treatment	21 day of the menstrual cycle. after treatment	21 day of the menstrual cycle
Progesterone ng/ml	15.412±1.51*	22.6±2.56	17.6±2.23	18.12±12.23	23.12±11.23
Ovarian structure	<0.22 decrease in the ratio of the volume of the corpus luteum to the volume of the ovary	the ratio of the volume of the yellow body to the volume of the ovary >0.22	<0.22 decrease in the ratio of the volume of the corpus luteus to the volume of the ovary and the corpus luteum was represented by the cystic cavity of a homogeneous internal structure with high conductivity and a completely heterogeneous structure with small echogenic inclusions	the ratio of the volume of the yellow body to the volume of the ovary >0.22 in the main part of the surveyed	
Endometrial structure	increased echogenicity of M-echo in the peripheral regions with a hypoechoic zone in the center; with LUF, there are cyclic changes in the thickness and echogenicity of the endometrium	secretory transformation of the endometrium, lag of secretory transformation in 10 (79.8 %) patients	increased echogenicity of M-echo in the peripheral regions with a hypoechoic zone in the center;	lag of secretory transformation in 2 (11.8 %) patients	secretory transformation of the endometrium

*Note: * – p<0.05 – significantly in relation to the indicator of the control group*

4. Discussion

The inverse correlation dependence of the average force between the decrease in vitamin D level and the prolactin index (r=–0.28; p=0.03), the straight line between the vitamin D index and FSH (r=+0.31; p=0.01) was traced. In our opinion, these disorders in the follicular phase of the menstrual cycle lead to a decrease in the levels of estrogen and progesterone in the luteal phase.

An analysis of the ultrasound examination of patients with LUF after the end of the periconceptional supplementation demonstrated practically no difference in the structure of the ovaries with the control group, in 10 (79.8 %) the endometrium lagged behind its secretory transformation, this picture of the endometrium was probably caused not only by a decrease in progesterone secretion the corpus luteum of the ovaries, but also a disorder at the level of the endometrial receptor apparatus, which requires additional immunohistochemical studies of the endometrium in this cohort of patients [7, 9].

Thus, progesterone deficiency entails changes in various regulatory substances of the reproductive system, and therefore the periconceptional supplementation must be individualized [10].

The introduction of the definition of vitamin D in the periconceptional screening plan and its correction are justified and necessary to improve the structure of the endometrium and its secretory transformation in women with progesterone imbalance. Similar conclusions came from other researchers [11].

Studying vitamin D receptor status in progesterone deficiency may be promising when developing a periconceptional screening algorithm for patients with LPD and LUF.

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