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OVULYASIYAYA UĞRAMAMIŞ FOLLİKULUN LUTEİNLƏŞMƏ SİNDROMUNUN SONOQRAFİK XÜSUSİYYƏTLƏRİ

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Menstruasiya siklinin (MS) 12 və 22-ci günlərində dominant follikulun (DF) ovulyasiyaya uğramadan follikulun luteinləşməsi (OUFL) olan 53 qadında və müqayisə qrupunda (28 qadın) ultrasəs monitorinqinin retrospektiv təhlili aparılmışdır. Hər iki qrupdakı qadınların yaşı 19-36 arasında olub. MQ-da ovulyasiya baş verib və sarı cisim (SC) yaranıb, OUFL sindromu olan qadınlarda isə ovulyasiya ümumiyyətlə baş verməyib. OUFL sindromunda dominant follikulun diametri $23,4 \pm 1,1$ mm, MQ-da isə $21,7 \pm 0,8$ mm ($p < 0,05$) olmuşdur. MS-in 22-ci günündə OUFL sindromunda DF-nin diametri $27,9 \pm 1,8$ mm-ə qədər artmışdır ($p < 0,05$), MQ-da isə SC-in diametri $16,8 \pm 0,9$ mm olub, siklin 12-ci gününə ($20,3 \pm 0,7$ mm) nisbətən əhəmiyyətli ($p < 0,05$) dərəcədə az olub. Dominant follikulun divarındakı yumurta daşıyan qabarığın MQ-da vizuallaşdırılması $89,3 \pm 5,8\%$, OUFL sindromunda – $32,1 \pm 6,4\%$ ($P < 0,001$), diametri isə müvafiq surətdə $4,5 \pm 0,8$ mm və $2,1 \pm 0,7$ mm ($P < 0,05$) təşkil etmişdir. OUFL sindromunda DF divarının vaskulyarizasiyası müqayisə qrupundakına nisbətən əhəmiyyətli dərəcədə ($p < 0,001$; $p < 0,05$) daha az qeydə alınıb.

Beləliklə, müəlliflərin fikrincə, dominant follikulun diametrinin böyük olması, yumurta daşıyan qabarığın olmaması, follikul divarının aşağı sürətli vaskulyarizasiyası OUFL sindromunun mövcudluğunu proqnozlaşdırmağa imkan verir.

Açar sözlər: hormonal sonsuzluq, ultrasonografiya, ovulyasiyaya uğramamış follikulun luteinləşmə sindromu

Ключевые слова: гормональное бесплодие, ультразвукография, синдром лютеинизации неовулировавшего фолликула

Key words: hormonal infertility, ultrasonography, luteinized unruptured follicles syndrome

SONOGRAPHIC FEATURES OF LUTEINIZED UNRUPTURED FOLLICLES (LUF) SYNDROME

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A retrospective analysis of ultrasound monitoring of the dominant follicle (DF) on days 12 and 22 of the menstrual cycle (MC) was performed in 53 women with luteinization of the unruptured follicle (LUF) and 28 women in the comparison group (CG). The ages of women in both groups ranged from 19 to 36 years. In the CG, ovulation occurred and the corpus luteum (CL) was formed, whereas in the LUF syndrome, ovulation did not occur at all. The DF diameter in the LUF syndrome was 23.4 ± 1.1 mm, and in the CG – 21.7 ± 0.8 mm ($p < 0.05$). On the 22nd day of the cycle, the diameter of the DF in LUF syndrome increased to 27.9 ± 1.8 mm ($p < 0.05$), while in the CG the diameter of the CL was 16.8 ± 0.9 mm, which was significantly

($p < 0.05$) less than on the 12th day of the cycle (20.3 ± 0.7 mm). Visualization of the ovarian fossa in the DF wall in the CG was $89.3 \pm 5.8\%$, with LUF syndrome – $32.1 \pm 6.4\%$ ($p < 0.001$), and the diameter was 4.5 ± 0.8 mm and 2.1 ± 0.7 mm ($P < 0.05$). In LUF syndrome – vascularization of the DF wall and systolic velocity were significantly ($p < 0.001$; $p < 0.05$) lower than in the CG.

The authors believe that a large diameter of the dominant follicle, the absence of the oviparous tubercle, and low vascularization of the follicle wall predict the presence of LUF syndrome.

As is known, infertility is defined as the inability to become pregnant after one year of unprotected intercourse in women under 40 years of age. Ovulatory cycle disorders account for 21% of infertility causes. About 15.5% of women suffer from infertility. Infertility testing includes an assessment of ovarian reserve, the condition of the endometrium and fallopian tubes, thyroid function, prolactin levels in the blood, and confirmation of polycystic ovary syndrome [1-3].

Successful ovulation is essential for natural conception and fertility. Defects in the ovulatory process are associated with various infertility or subfertility conditions in women. However, understanding of the intraovarian biochemical mechanisms underlying this process in women lags behind animal models. In recent years, steady progress has been made in improving the knowledge of the ovulatory process in women by: collecting granulosa cells during the IVF interval, establishing a new approach to collecting follicular cells and tissues during the periovulatory period in normally cycling women, and developing unique in vitro models to study the luteinizing hormone (LH) surge or ovulatory changes in gene expression induced by human chorionic hormone (hCG) administration, the regulatory mechanisms underlying ovulatory changes, and the specific functions of ovulatory factors [4, 5].

Assisted reproductive technologies have been rapidly developing in recent years [6]. In vitro ovulation usually uses a hormone replacement therapy cycle or a physiological ovulation cycle for endometrial preparation [7]. Some researchers believe that frozen embryo transfer significantly improves clinical outcomes [8]. The difference between hormone replacement therapy cycle (HRT) and natural ovulation cycle (NC) is the absence of a corpus luteum, which produces crucial hormones for implantation, placentation, and pregnancy maintenance [9]. A number of authors note that the absence of the corpus luteum has a negative

impact on vascular health, leading to insufficient adaptation of the cardiovascular system in early pregnancy and increasing the risk of preeclampsia [10].

It is known that the normal menstrual cycle consists of the follicular and luteal phases. By the end of the follicular phase, estradiol is produced by the granulosa cell of the dominant follicle, which in turn stimulates the release of luteinizing hormone, which is produced in the anterior pituitary gland. After ovulation, the follicle turns into the corpus luteum, which produces progesterone from granulosa lutein. In the luteal phase, an increase in progesterone levels stimulates the endometrium, thereby preparing it for blastocyst implantation [11].

According to some authors, luteinization of an unovulated follicle (LUF) is characterized by the presence of regular menstrual bleeding against the background of cyclic changes in hormone levels similar to changes in a normal ovulatory cycle, but without ovulation of the follicle. If the dominant follicle has reached preovulatory dimensions, but ovulation has not occurred, then in the second phase of the menstrual cycle it undergoes luteinization due to hypertrophy of granulosa and theca cells located along the outer surface of the basement membrane [12]. Luteinised unruptured follicle syndrome (LUFS) is a cause of infertility consisting in the unruptured of the dominant follicle after the luteinised hormone (LH)-surge [13].

Diagnosis of female infertility includes: determination of the levels of the relevant hormones of the ovaries, pituitary gland, thyroid gland with an assessment of the ovarian reserve; the hysterosalpingography; dynamic ultrasound visualization of the endometrium and ovaries in the follicular and luteal phases of the menstrual cycle [14-16].

Previous studies have shown changes in the Doppler spectrum of blood flow in the uterine and ovarian arteries with hormonal imbalance [17, 18]. It is of interest to study changes in the

endometrium and ovaries in different phases of the menstrual cycle in women with impaired luteinization of the preovulatory follicle using ultrasonography.

The purpose of the study is to study the features of structural and functional changes in the ovaries in luteinization syndrome of anovulatory follicle using duplex scanning.

Material and methods. A retrospective analysis of the results of transvaginal ultrasonography of the uterus and ovaries of 53 women aged 21-37 years, who had a dominant follicle, but did not ovulate during dynamic observation, was performed. The level of follicle-stimulating and luteinizing hormones (FSH and LH), the LH/FSH index, estradiol (E) and 17-OH-progesterone were determined in all women.

The comparative group (CG) consisted of 28 fertile women with a regular menstrual cycle, registration of the fact of ovulation with the formation of the corpus luteum. In order to determine the day of ovulation, ultrasound monitoring of the development of the dominant follicle (DF) from days 11 to 15 of the cycle was carried out in the study groups. The diameter of the DF, the presence of the oviparous tubercle in its wall, systolic velocity (Vs), resistance index (RI) and pulsatility index (PI) of blood flow in the DF wall were determined.

Duplex scanning was carried out using a Philips HD-11 ultrasound machine with a transvaginal

sensor in a frequency mode of 4-9 MHz. Statistical analysis was carried out using the nonparametric Mann-Whitney method. If the p value <0.05, the difference between the compared groups was considered statistically significant.

Results and discussion. As shown in Table 1, the level of follicle-stimulating and luteinizing hormones (FSH and LH), estradiol (E), progesterone (P) in all phases of the menstrual cycle varies over a wide range, which significantly complicates their interpretation [13].

We studied the frequency of ovulatory days among women in the comparative group using transvaginal ultrasound monitoring from the 10th to the 15th day of the menstrual cycle (Table 2). On the 11th day of the menstrual cycle, ovulation occurred in 1 ($6.1 \pm 3.4\%$) women, on the 12th day – in 4 ($14.3 \pm 6.6\%$), on the 13th day – in 13 ($46.4 \pm 9.3\%$), on the 14th day of the cycle – in 9 ($32.1 \pm 8.8\%$) and on the 15th day – in 1 ($6.1 \pm 3.4\%$) women, respectively. It is evident that in fertile women, ovulation occurred significantly more often on day 13 of the cycle than on days 11th ($p < 0.001$), 12th ($p < 0.01$), 14th ($p < 0.05$), and 15th ($p < 0.001$). On day 14 of the menstrual cycle, ovulation occurred statistically significantly more often than on days 11th and 15th ($p < 0.01$).

Table 1. Hormones reference range in women of reproductive age

Hormons	Menstrual cycle phase and hormones reference range		
Estradiol	Follicular phase	Midcycle peak	Luteal phase
Luteinizing hormone	20-350 pg/mL	150-750 pg/mL	30-450 pg/mL
Folliculstimulating hormone	1.4 to 9.9 mIU/ml	6.2 to 17.2 mIU/mL	-
Progesterone	0.1 to 0.7 ng/mL	-	2 to 25 ng/mL

Table 2. Ovulatory days in fertile women (comparative group)

Days of the menstrual cycle				
11	12	13	14	15
1	2	3	4	5
1 ($3.6 \pm 3.5\%$)	4 ($14.3 \pm 6.6\%$)	13 ($46.4 \pm 9.4\%$) P 3-4 < 0,05 P 3-2 < 0,01 P 3-1 < 0,001 P 3-5 < 0,001	9 ($32.1 \pm 8.8\%$) P 4-1 < 0,01 P 3-5 < 0,01	1 ($3.6 \pm 3.5\%$)

Table 3. Dynamics of USG parameters of the dominant follicle in women with luteinized unruptured follicle (LUF) syndrome and the comparative group (CG)

USG parameters of the dominant follicle (DF)	Patient groups and menstrual cycle days			
	12		22	
	LUF (n=53)	CG (n=28)	LUF (n=53)	CG (n=28)
Diameter of the DF, or corpus luteum, mm	23,4±1,1 P<0,05	21,7±0,8	27,9±1,8 P* $<0,05$	-
Visualization frequency of the corpus luteum, %	-	4 (14,3±6,6%)	-	27 (96,4±3,5%) P<0,001
Diameter of the corpus luteum, mm	-	20,3±1,2	-	16,8±0,9 P* $<0,05$
Visualization frequency of the oviparous tubercle, %	17 (32,1±6,4)	25 (89,3±5,8) P<0,001	-	-
Diameter of the oviparous tubercle, mm	2,1±0,7	4,5±0,8 P<0,05	-	-
Mild vascularization of the DF wall, %	8 (15,1±4,9)	13 (46,4±9,4) P<0,01	7 (13,2±4,6)	16 (57,1±9,4)
Moderate vascularization of the DF wall, or corpus luteum, %	3 (5,7±3,2)	15 (53,6±9,4) P<0,001	-	12 (42,9±9,4)
Vs on the DF wall, cm/s	18,2±3,4	32,5±3,9 P<0,01	15,9±3,2	29,7±4,1 P<0,01
RI on the DF wall	0,51±0,03	0,42±0,03 P<0,05	0,57±0,03	0,46±0,03 P<0,05

Note: P – the difference between LUF and CG; P* – the difference between 12-th and 22-th days inside of LUF and CG groups.

To determine the characteristics of menstrual cyclic transformations in the dominant follicle, we compared the ultrasound parameters of fertile women (CG) and women with luteinized unruptured follicles (LUF) on the 12th day of the cycle - before the most probable ovulatory days (13th and 14th days of the cycle) and in the middle of the secretory phase on the 22nd day of the cycle. We determined the size of the dominant follicle, the frequency of visualization and the size of the corpus luteum, the frequency of visualization and the size of the oviparous tubercle, the intensity of vascularization of the dominant follicle, the maximum systolic velocity (Vs) and the index of peripheral resistance (RI) of blood flow on the follicle wall (Table 3).

As can be seen from the table, the diameter of the dominant follicle on the 12th day of the menstrual cycle among patients with LUF averaged 23.4±1.1 mm, while in the comparative group it was 21.7±0.8 mm

(P<0.05). On the 22nd day of the cycle, the diameter of the persistent follicle increased to 27.9±1.8 mm (P* <0.05).

Since ovulation did not occur in the group of patients with LUF, the corpus luteum was also absent. On the 12th day of the cycle, corpus luteum was recorded in 4 cases (14.3±6.6%), and on the 22nd day of the cycle – in 27 cases (96.4±3.5%) (P<0.001). The average diameter of the corpus luteum on the 12th day of the cycle was 20.3±1.2 mm, and on the 22nd day it decreased to 16.8±0.9 mm (P* <0.05), respectively.

On the 12th day of the cycle, the oviparous tubercle on the wall of the dominant follicle in the SG was recorded in 25 (89.3±5.8%) cases, and among patients with LUF – in 17 (32.1±6.4%) cases (P<0.001). The average diameter of the oviparous tubercle in the SG was 4.5±0.8 mm, and in patients with LUF – 2.1±0.7 mm (P<0.05), respectively (Fig. 1).

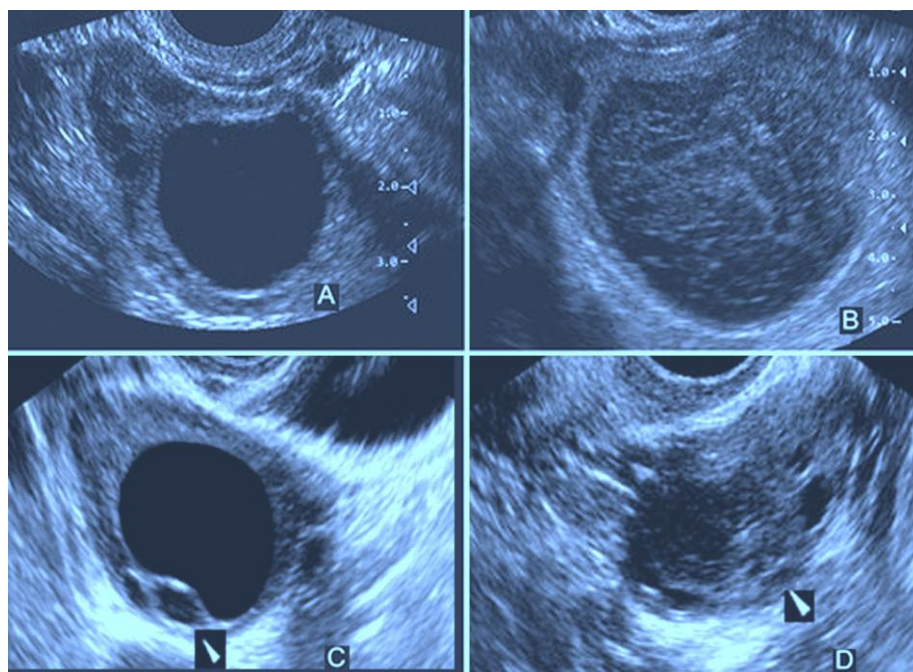


Fig. 1. A – day 12 of the menstrual cycle, anechoic preovulatory follicle without an oviparous tubercle in a woman with luteinized unruptured follicle (LUF). B – the same follicle on day 22 of the cycle. The sizes are increased, the structure is heterogeneous, the walls are thickened. C – anechoic preovulatory follicle with a oviparous tubercle (arrow) in a woman of the comparison group (CG). D – day 22 of the cycle, the corpus luteum is formed (arrow).

Mild vascularization of the dominant follicle wall on the 12th day of the cycle in the LNF group of patients was recorded in 8 cases ($15.1 \pm 4.9\%$), in the SG patients – in 13 cases ($46.4 \pm 9.4\%$) ($P < 0.01$). On the 22nd day of the cycle, weak vascularization of the dominant follicle wall was recorded in 7 cases ($13.2 \pm 4.6\%$) in the LNF group of patients, in 16 cases ($57.1 \pm 9.4\%$) in the SG patients

($P < 0.01$). Moderate vascularization of the dominant follicle wall on the 12th day of the cycle was recorded in 3 cases ($5.7 \pm 3.2\%$) in the LNF group of patients, in 15 cases ($53.6 \pm 9.4\%$) in the SG patients ($P < 0.001$). On the 22nd day of the cycle, moderate vascularization was observed only on the wall of the corpus luteum in the group of patients with SG – in 12 ($42.9 \pm 9.4\%$) cases (Fig. 2).

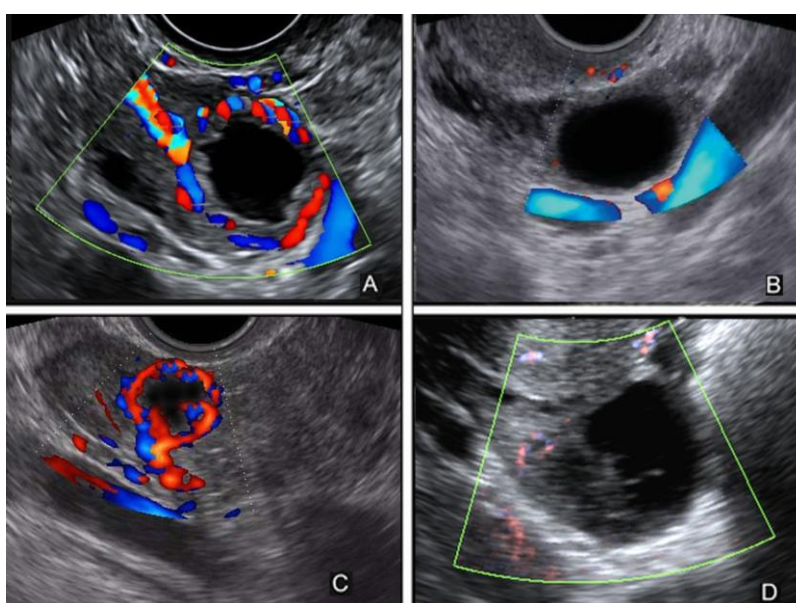


Fig. 2. Day 12 of the menstrual cycle. A - increased blood flow along the periphery of the preovulatory follicle in a woman of CG. B - Mild blood flow along the periphery of the preovulatory follicle in a woman with LUF. Day 22 of the cycle. C - Increased blood flow along the periphery of the corpus luteum in a woman of CG. D - Mild blood flow along the periphery of the enlarged persistent follicle in a woman with LUF.

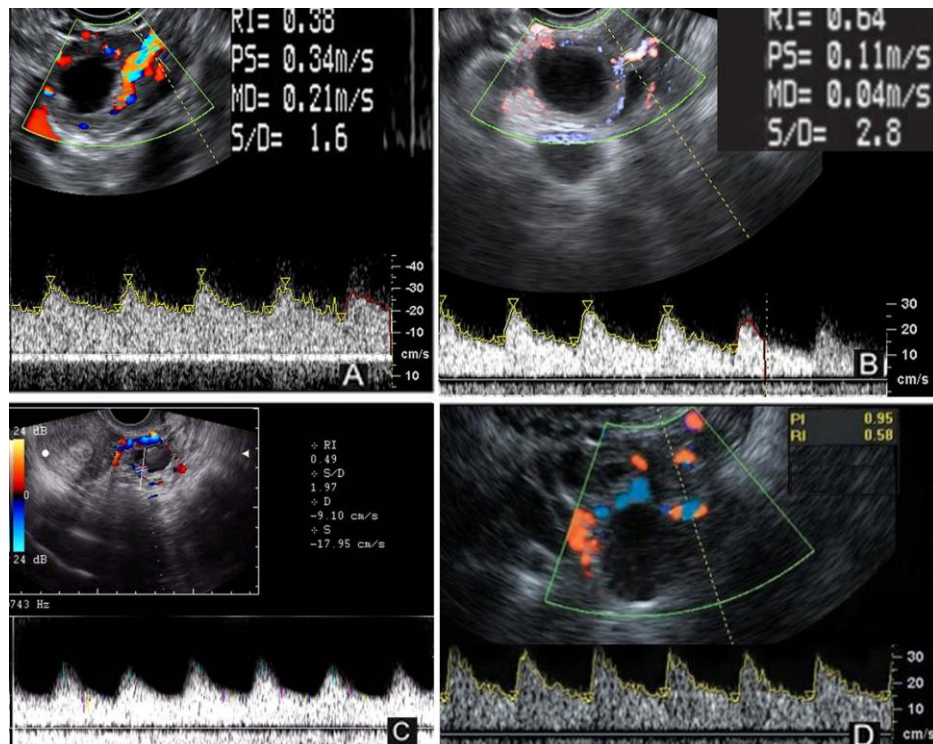


Fig. 3. Day 12 of the menstrual cycle. A - increased blood flow on the wall of the follicle in a woman with SG. Vs - 34 cm / s, RI - 0.38. B - weak blood flow on the wall of the persistent follicle in a woman with LUF. Day 22 of the menstrual cycle. C - persistent increased blood flow on the wall of the corpus luteum in a woman with SG. Vs - 17.95 cm / s, RI - 0.49. D - Mild blood flow with high peripheral resistance (RI - 0.58) along the periphery of the enlarged persistent follicle in a woman with LUF.

Systolic blood flow velocity on the wall of the dominant follicle on the 12th day of the cycle in the group of patients with LNF was 18.2 ± 3.4 cm/s, in the SG of patients – 32.5 ± 3.9 cm/s ($P < 0.05$), on the 22nd day of the cycle – 15.9 ± 3.2 cm/s, in the SG of patients on the wall of the corpus luteum – 29.7 ± 4.1 cm/s ($P < 0.05$), respectively. The resistance index (RI) of blood flow on the wall of the dominant follicle on the 12th day of the cycle in the group of patients with LNF was 0.51 ± 0.03 , in the SG patients – 0.42 ± 0.03 ($P < 0.05$), on the 22nd day of the cycle – 0.57 ± 0.03 , on the wall of the corpus luteum in the SG patients – 0.46 ± 0.03 ($P < 0.05$), respectively (Fig. 3).

Discussion. The process of ovulation is the release of a mature oocyte from a dominant follicle. It is precisely regulated by various sex hormones and factors, including the release of luteinizing hormone [19]. Ovulation requires a normal LH surge released by the pituitary gland and a well-developed periovulatory follicle. Previous publications have shown that in the syndrome

of luteinization of the unovulated follicle, in most cases the level of luteinizing hormone is low [20]. Larger diameter of preovulatory follicle, higher growth rate are the main characteristics of luteinization of non-ovulating follicle. Lower systemic concentration of luteinizing follicle in early stages of follicle development is the key factor in luteinization syndrome of non-ovulating follicle [21].

In recent years, ultrasound examination has taken an important place in the study of women for hormonal infertility. The method allows monitoring the development of a maturing follicle, the ovulation process, and the preparation of the endometrium for implantation of a fertilized egg. The use of various Doppler modes allows obtaining information about the blood supply to the preovulatory follicle, quantitative parameters of blood flow - systolic velocity, peripheral resistance indices make it possible to predict ovulation, determine the duration of the corpus luteum [9, 14].

Unlike previous studies, we determined the

presence and size of the oviparous tubercle, quantitative parameters of blood flow on the follicle wall on the eve of the most probable day of ovulation as prognostic signs of luteinized unruptured follicles syndrome. We found that small sizes of the oviparous tubercle (about 2 mm), low systolic velocity and increased resistance index can predict the

impossibility of ovulation of the dominant follicle.

Conclusions: a large diameter of the dominant follicle, the absence of the oviparous tubercle, and low vascularization of the follicle wall predict the presence of LUF syndrome.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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СОНОГРАФИЧЕСКИЕ ОСОБЕННОСТИ СИНДРОМА ЛЮТЕИНИЗАЦИИ АНОВУЛЯТОРНОГО ФОЛЛИКУЛА

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Резюме. Проведен ретроспективный анализ ультразвукового мониторинга доминантного фолликула (ДФ) на 12-й и 22-й дни менструального цикла (МЦ) у 53 женщин с лютеинизацией неовулировавшего фолликула (ЛНФ) и 28 женщин группы сравнения (ГС). Возраст женщин в обеих группах составлял от 19 до 36 лет. В СГ происходила овуляция и образовалось желтое тело (ЖТ), тогда как при синдроме ЛНФ овуляция не происходила вообще. Диаметр ДФ при синдроме ЛНФ составил $23,4 \pm 1,1$ мм, а в СГ – $21,7 \pm 0,8$ мм ($p < 0,05$). На 22-й день цикла диаметр ДФ при синдроме ЛНФ увеличился до $27,9 \pm 1,8$ мм ($p < 0,05$), тогда как в СГ диаметр ЖТ составлял $16,8 \pm 0,9$ мм, что было достоверно ($p < 0,05$) меньше, чем на 12-й день цикла ($20,3 \pm 0,7$ мм). Визуализация яйценосного пузыря в стенке ДФ в СГ составила $89,3 \pm 5,8\%$, при синдроме ЛНФ – $32,1 \pm 6,4\%$ ($p < 0,001$), а диаметр составлял $4,5 \pm 0,8$ мм и $2,1 \pm 0,7$ мм ($P < 0,05$). При синдроме ЛНФ васкуляризация стенки ДФ и систолическая скорость были значительно ($p < 0,001$; $p < 0,05$) ниже, чем в СГ.

Таким образом, большой диаметр доминантного фолликула, отсутствие яйценосного бугорка, и низкая васкуляризация стенки фолликула позволяют прогнозировать наличие синдрома ЛНФ.

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