INTRODUCTION
The successful onset of pregnancy and its development requires simultaneous favorable combination of three factors: genetically good embryo, the state of immunologically tolerant acceptance by the body of a pregnant woman and sufficient implantation potential of the endometrium [1]. It is the last component of this triad that can often be the cause of reproductive losses and unfavorable pregnancy outcomes [2]. Carrying of a pregnancy and occurrence of such pathology as placental insufficiency, intrauterine growth retardation and preeclampsia is associated with the disorders of the processes of gestational rearrangement of the uterine spiral arteries and formation of the trophoblast [3]. Therefore, implantation capabilities of the endometrium are crucial for the successful onset and progress of pregnancy [2].

Consequently, detection and successful treatment of chronic endometritis (CE) at the stage of pregravid preparation is of particular importance [2], especially for the patients with reproductive losses in the past history [4, 5]. Apparently, termination of pregnancy, especially missed abortion, is accompanied by the formation of CE in the endometrium with high concentration of pro-inflammatory cytokines, and occurrence of the succeeding pregnancy along with such endometrial changes is doomed to repeated termination [4, 6].

Since the clinical picture of CE is oligosymptomatic, thorough analysis of the anamnestic data, namely, recurrent pregnancy loss, experienced intrauterine interventions (hysterosalpinography; curettage, made with therapeutic or diagnostic purposes; intrauterine contraception; in vitro fertilisation, etc.) is of critical importance to reveal the risk factors for this pathology. The onset of CE is also possible in high level of contamination of the lower and upper genital tracts with pathogen bacteria even in women without invasive intrauterine interventions in the past history [7]. Although the frequency of detection of infection in the lower genital tract is significantly higher the frequency of intrauterine infection, the spectrum of microorganisms in the cervical canal and vagina generally coincides with the similar one in the uterus [7].

The accurate CE diagnosis requires endometrial biopsy (pipelle biopsy or target biopsy during hysteroscopy) for histological confirmation of the diagnosis, associated with the intrauterine intervention [8]. Diagnostic curettage is an old-fashioned, though still used method of obtaining the material, which is the most traumatic and problematic among other invasive diagnostic methods. It is the fact that...
of intrauterine intervention that is problematic in the perception of this group of diagnostic activities for both a physician and a patient.

Practically, the gap between a high significance of CE in the concept of the development of the reproductive losses and low level of its diagnosis (and, consequently, treatment) could be reduced by the presence of non-invasive diagnostic marker. Substances that are synthesized by the endometrium itself and easily identified in the biological materials, available for sampling, can play the role of the marker.

Such marker is the fertility α2-microglobulin (FAMG, glycodelin), i.e., a dimeric glycoprotein, which is synthesized by the endometrial glands [9,10]. The methods of immunodiffusion and immunohistochemical analysis show that the FAMG is presented in the epithelium of the fallopian tubes and decidua. The protein was not expressed in the normal tissues of the vagina, ovaries, myometrium, mammary glands, as well as in any tissues, which are not related to the reproductive system [11].

FAMG is synthesized and secreted by glandular epithelium only, but not endometrial stromal cells [10]. It appears in the endometrial tissue within a few days before a possible implantation, its amount increases during the “implantation window” and preserves in high amount to the onset of menstruation and during the first days of the next cycle, after which the production of protein in the endometrium temporarily ceases [10,12]. Once the pregnancy occurred, the synthesis of FAMG continues and in the first gestation trimester its amount in the decidual tissue constantly grows [9,13].

FAMG is crucial in the embryo implantation (as a local immunosuppressor), protecting it from the maternal immune response [13]. FAMG also plays one of the leading roles in the processes of trophoblast invasion, since it is involved in the cascade activation of the cell adhesion molecules [9,13]. Moreover, the transport of hydrophobic molecules from the tissue environment that are essential for fetal development can be the important function of FAMG in early pregnancy at the stage of the placenta formation and no placental circulation exists [13].

The efficacy of the FAMG synthesis is dependent from the functional state of endometrial glands and the level of progesterone [12]. It enables to use FAMG as a specific protein, decreasing production of which is accompanied by the damage to the mucous membrane of the uterus and may serve as a non-invasive marker for CE detection.

THE AIM
The paper was aimed at evaluation of the possibility to use FAMG as a marker of the high risk for CE, differentiation of CE with luteal phase deficiency (LPD), as well as identification of effective treatment of CE during pregravid preparation.

MATERIALS AND METHODS
We examined 120 women of reproductive age who were planning pregnancy in the offices of family planning in Poltava during the period from 2010 to 2017. In addition to general clinical examination, pippile biopsy of the endometrium was made on the 18th -25th day of the cycle with subsequent histological study of the biopsy material. Menstrual blood was collected in all women to determine the level of FAMG by the enzyme-linked immunosorbent assay (ELISA) using the “FAMG – Fertitest-M” test system. The ultrasound structure of the endometrium was also studied. Special attention was given to the CE signs: discrepancy between the thickness of endometrium and the day of menstrual cycle, uneven thickening of the functional and basal layers of the endometrium, occurrence of fibrosis, sclerosis, calcifications, deformation of the linear structure or polyposis, thinning of the transitional zone of endometrium before menstruation (< 5 mm).

Histological study of pippile biopsy collected from 70 women confirmed the events of CE (the main group). 40 women out of 70 (subgroup A) received the appropriate treatment, which included antibiotic therapy, anti-inflammatory, antiviral and metabolic drugs, as well as hormone therapy for 3 months with the use of progesterone (in hypertrophic forms of CE) or 2/10 femoston (in case of atrophic form of CE). After the treatment, the repeated control of FAMG was made. The other 30 women in this group (subgroup B) refused from the proposed treatment for various reasons and that was documented by the relevant statements. The control group involved 30 women without CE and LPD.

Patients with absolute hypoprogesteronemia and luteal phase deficiency (LPD) have not been assigned to the main group of examined women, since the occurrence of this pathology itself has a regulating effect on the synthesis of endometrial proteins, including FAMG. However, considering that FAMG may be reduced both in CE and LPD, it was appropriate to investigate, which differential values of FAMG are specific for women with CE and LPD. Therefore, we have examined an additional group of individuals (20 women) with LPD but without signs of CE.

In order to confirm or exclude the LPD, folliculometry was made to all women with subsequent determination of the duration of the luteal phase of the cycle from the moment of ovulation to the onset of menstrual bloody discharge. The increase in progesterone in the luteal phase was also determined by calculating the ratio between the level of the hormone at the beginning of menstrual cycle (MC) (3-5 day from the beginning of menstruation) and in its second phase (6-8 day after ovulation). The discrepancy between the ultrasound structure of the endometrium and a day of menstrual cycle was also considered.

RESULTS
We have found that among 70 women with histologically confirmed CE, ultrasound signs, which can indicate the presence of this pathology, were detected in 52 women (74.3%). The ultrasound examination of other 18 women (25.7%) showed no signs that indicated the change in the structure of endometrium.
Discrepancy between the endometrium and the phase of menstrual cycle occurred the most often among the ultrasound signs of CE: the endometrium was too thin for the corresponding day of the menstrual cycle (20 women; 28.57% of the total number of women of the main group). In the main group other signs of CE were also found: thickening of the functional and basal layers of the endometrium (16 women; 22.86%), polyposis (12 women; 17.14%), presence of hypoechoic inclusions in the endometrium (4 women; 5.71%).

In the additional group (women with LPD) the findings of the ultrasound examination revealed discrepancy between the endometrium and the phase of menstrual cycle only. This feature occurred in 80% of women (16 patients).

The comparison of the increase in progesterone in the luteal phase (on the 6-8 day after ovulation, confirmed by folliculometry) relative to its original level, defined at the beginning of the menstrual cycle (3-5 day from the beginning of mensturation) has found that this index was 16.6 ± 2.8 in women of the control group. In women with LPD the index of the increase in progesterone was on the average of 6.5 ± 2.1 that is 2.5 times lower than in the control group. In women with CE the increase in the level of progesterone in the second phase of the cycle was almost similar to the one in the control group (16.3 ± 2.1).

The duration of the luteal phase was also almost similar to the one in the control and main groups (13.2 ± 0.8 days and 13.6 ± 1.2 days, respectively). In women of additional group (LPD) the second phase of the cycle was shortened to 7.6 ± 0.7 days that reliably differed from the reference values (p<0.05).

The significant decrease in the level of FAMG in relation to the indices in the control group was revealed in all 70 women with histologically confirmed events of CE. In this way, in the healthy women of control group this index was 39.8 ± 8.3 μg/ml. In women with CE the level of FAMG was 16.3 ± 3.9 μg/ml (p < 0.05), that was 59% lower than the reference values.

In women of additional group the recorded level of FAMG was reduced to 7.0 ± 2.2 μg/ml. It is reliably lower than the reference values (by 75.9%; p < 0.01) and indices in women with CE (by 42.9%; p < 0.05). In the case of anovulatory cycles (they were detected in 6 women of additional group) the level of FAMG was so low, that could not be identified within the sensitivity of the method.

**DISCUSSION**

The resulting data revealed insufficient diagnostic value of histological approach in diagnosis of CE, showing that in women with histologically confirmed CE the ultrasound signs of this pathology were found only in 74.3% of women, whilst no ultrasound signs of pathological state of the endometrium were found in the every fourth woman. Determination of the FAMG level in the menstrual blood of a woman is more informative method, since reduction of this index in women with CE was recorded in all 100% of examined women.

Ultrasoundography has shown that discrepancy between the thickness of endometrium and the day of menstrual cycle (28.57%) was detected more often than other ultrasound signs in women with CE. Noteworthy, histological study of endometrial biopsy showed that such discrepancy was recorded in 100% of examined women. It can be explained by the fact that ultrasound examination reveals the thickness of the endometrium only, not considering the fact that the glands of the endometrium with normal thickness have insufficient secretory transformation that can be assessed histologically.

Apparently, the discrepancy between the endometrium and one or another phase of menstrual cycle, detected by ultrasoundography or confirmed histologically, is the specific feature for both women with CE and patients with LPD. However, in CE (the main group) it is due to the altered structure of the cells of glands and stroma, whereas in CE (additional group) it is the consequence of a limited influence of low concentration of progesterone on the endometrium, synthesized insufficiently by the yellow body of the ovary. It is evidenced by the folliculometry, showing the shortened luteal phase of the cycle (7.6 ± 0.7 days) and low increase in progesterone in the second phase of menstrual cycle (6.5 ± 2.1) in women of additional group.

Reduced amount of FAMG in menstrual blood in the luteal phase of menstrual cycle was also recorded in women of additional group; however, it is more prominent than in women with CE. In this way, in CE and LPD the level of FAMG was 2.4 and 5.6 times, respectively, lower as compared with the reference values. We hypothesize that this fact can be explained by the ability of FAMG to be synthesized by the secretory transformed endometrium only that is confirmed by other authors [11,12]. The successful transformation of the endometrium in the second phase of menstrual cycle can be performed due to histologically normal structure of the endometrium in the first phase, well expressed and sensitive progesterone receptors [10] and sufficient level of progesterone. In CE the first factor is violated, limiting production of FAMG. In case of LPD both mechanisms are disturbed (primarily, progesterone effect on the structure of the endometrium decreases and secondly, its secretory transformation is disrupted), which causes even more marked suppression of synthesis of FAMG.

We also evaluated the changes in FAMG in women with CE after individualized comprehensive treatment with antibacterial, metabolic, anti-inflammatory drugs, antiviral drugs and hormonal therapy, provided to some of them. It has been found that after treatment the level of FAMG reached the control values that are specific for healthy women. We hypothesize that it is associated with the elimination of the causative agent, enhancement of the trophism and receptivity of the endometrium under the effect of treatment, which led to the activation of the synthesis of FAMG by the endometrial glands.

**CONCLUSIONS**

Determination of FAMG in menstrual blood of women in the late second phase of the cycle is a simple and informative
method of estimation of the functional state of the uterine glandular epithelium. Its application under the conditions of the exclusion of absolute hypoprogesteronemia and LPD can be very useful both for non-invasive diagnosis of CE and subsequent assessment of treatment of this pathology.

REFERENCES

1. Kovaleva YV. The application of low-frequency ultrasound for the comprehensive treatment and rehabilitation of the patients presenting with chronic endometritis. Vopr Kurortol Fizioter Lech Fiz Kult. 2017;94(3):32-38


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