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Review Article

The Role of Glicodelin in the Diagnosis and Prognosis of Outcomes of Early Fetal Dimese

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Abstract

This study was aimed at developing proposals and recommendations for optimizing the diagnostic process and predicting the outcomes of non-developing pregnancy. The developed algorithm allows using the safest and most informative methods to reliably determine the functional state of the uterine endometrium and the mechanisms of implantation disorders in patients with missed miscarriage.

Keywords: Glicodelin; Fetal dimese; Non-developing pregnancy; Endometrium; Implantation.

Introduction

The prevalence of spontaneous interruption of gestation is a fourth of all recorded pregnancies, while the share of non-developing pregnancy (NB) accounts for 45 to 88.6%. The most relevant period for the study of NB is the first trimester of pregnancy, since most of the cases of NB (up to 80%) occur precisely in it. Reliable statistics on population prevalence and assignment of NB in early pregnancy are difficult to assess. Loss can occur before a woman knows of the pregnancy and whether a woman can seek medical care will depend on the availability of medical care, the severity of symptoms, and the women's circumstances. Issued estimates range from 5% to 52% of pregnancies, with the weight of estimates ranging from 13% to 30% [1-5].

It is known that full-fledged implantation is of fundamental importance for the normal development of pregnancy, which is possible only in the presence of an endometrium sensitive to it, an embryo that has reached the blastocyst stage, and local immunosuppression [6,7]. In women with

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early miscarriage, the content of glycodelin in the periovulatory period is reduced.

Summarizing the knowledge accumulated to date about glycodelin, it can be stated that this glycoprotein plays a significant role in the functioning of the reproductive system of both women and men [8]. This protein regulates the processes of reproduction of offspring at the stages of gamete migration through the genital tract and activation of the acrosomal reaction, participates in the course of a normal pregnancy, in the development of its complications and perinatal pathology. This knowledge has already made it possible to use glycodelin as an indicator of the functional state of the reproductive system and a diagnostic marker of pregnancy complications [4,8].

Given the large volume of clinical studies conducted with the proven diagnostic value of determining glycodelin in various biological media, the technical simplicity and availability of analyzes (including cost), it is believed that in the future it is possible to include these tests in the protocols and clinical recommendations of obstetrics and gynecology and services, in the first place associated with preconception preparation. Promising is the development of express methods for determining the level of glycodelin in semen and menstrual blood in the form of test strips. The development of preparations based on glycodelin to restore human fertility and maintain pregnancy may become important for practice.

This study was aimed at developing proposals and recommendations for improving the diagnostic process of the functional state of the endometrium by determining the concentration of glycodelin in the blood. Based in the effects of a survey of 120 women with a history of non-pregnancy, an algorithm for preconception preparation was developed. The developed algorithm allows a non-invasive and most informative method to reliably determine the functional state of the endometrium of the uterus and the mechanism of implantation disorders in women with non-developing pregnancy.

A prospective, controlled clinical study was conducted at the Department of OBGYN No. 3 of The Samarkand State Medical University in the Maternity Complex No. 1 in Samarkand, The Republic of Uzbekistan.

General characteristics of glycodelin as a marker of the functional conditional of the endometrium

The character of glycodelin in the body

It is known that full-fledged implantation is of fundamental importance for the normal development of pregnancy, which is possible only in the presence of an endometrium sensitive to it, an embryo that has reached the blastocyst stage, and local immunosuppression [5,9,10].

A possible mechanism that allows the embryo to penetrate the epithelial barrier before it implants deep into the stroma is the induction of apoptosis in the endometrium by the implanting blastocyst. The readiness of the endometrium for implantation is maximum only during the existence of the so called "conception window", the presence of which is ensured by the complex interaction

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of hormones, receptors, immunocompetent cells, and proteins associated with pregnancy.

One such protein is a2-fertility microglobulin (AMGF), or glycodelin, which is a dimeric glycoprotein produced by secretory endometrial glands. The synthesis of glycodelin in the endometrium begins in the periovulatory period, sharply increases in the peri-implantation period, and remains at a high level in the event of pregnancy. The data of many authors suggest that implantation and/or placentation disorders leading to early pregnancy loss are associated with a deficiency in glycodelin production in the endometrium. In domestic and foreign literature, there are conflicting data on the information content of indicators of serum and tissue levels of glycodelin for predicting reproductive disorders [11]. However, at present, insufficient data have been accumulated on the relationship between serum and tissue protein levels, and the significance of the level of glycodelin production in the first trimester of pregnancy has not been sufficiently studied [2,12]. Also, no data was found on the dependence of the level of glycodelin in pregnant women on age.

In women, glycodelin is synthesized in the ovaries (follicles, corpus luteum), fallopian tubes, secretory endometrium, maternal part of the placenta, and in men, in the seminal vesicles [6]. Glycodelin was found in the ciliated and secretory epithelium of the mucous membrane of all sections of the fallopian tubes by the immunoperoxidase method. Its content in the fimbrial region is higher in the secretory phase of the cycle [8,9]. Glycodelin was found in preovulatory and atretic ovarian follicles of fertile women, primordial ovarian follicles of the fetus [1]. Glycodelin is found in menstrual blood and endometrial tissue extracts. In the endometrium of the proliferative stage, glycodelin, according to the method of immunodiffusion analysis, is absent [10]. In men, glycodelin was found in sperm plasma, seminal vesicle tissue (epithelium) and was not found in testicular, epididymal, and prostate extracts [10,2].

Meanwhile, the detection of mRNA encoding glycodelin in the epithelial cells of the epididymis, prostate gland, ampullar part of the vas deferens, as well as in spermatogonia and spermatocytes of the convoluted tubules of the rat testes indicates that all glandular formations of the male genital tract are able to participate in the synthesis in that or another degree in the secretion of this glycoprotein [7]. Glycodelin is found in endometriosis foci, extracts of malignant and benign tumors of the ovaries and uterus [8,12]. Apparently, it is impossible to recognize glycodelin as a strictly specific protein of the human reproductive system. Already at the very beginning of the study of this problem, there were reports of finding glycodelin in isolated cases in the bone marrow, mammary gland, breast cancer, pancreatic cystadenoma, hydradenoma, and parabronchial excretory glands [6,11].

Glycodelin has 3 main isoforms that are found in various tissues and environments of the reproductive system, depending on the place of their production: amniotic fluid (glycodelin A), endometrium (glycodelin A), seminal plasma (glycodelin S) and follicular fluid (glycodelin S). Depending on the place of lineage, the same protein skeleton is

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glycosylated otherwise, giving glycodelins with else biological effects. Glycodelin A, derived from human endometrium, is composed of unique lacdiNAc oligosaccharide sequences and inhibits the binding of sperm to the egg, thereby exhibiting contraceptive properties. In addition, this isoform of glycodelin modulates the endocrine function and differentiation of trophoblast cells [13]. In contrast, glycodelin S from seminal vesicles does not have such oligosaccharide sequences and does not have contraceptive activity [3]. Follicular fluid glycodelin is a differentially glycosylated isoform of glycodelin, which, like glycodelin A, effectively inhibits the interaction between human spermatozoa and oocytes [4]. In the female genital tract, spermatozoa are exposed to glycodelins A and F, which inhibit the binding of spermatozoa and the zona pellucida.

Glycodelin-a marker of the functional state of the endometrium

The study of the effect of glycodelin on the immunoregulatory cells of pregnant women in experiments in vitro showed that the development of the threat of abortion in the early and late periods is accompanied by a decrease in the ConA-induced activity of lymphocytes. After incubation of immunocompetent cells with glycodelin, an increase in their activity was noted [6].

In experiments in vitro, glycodelin is able to reduce the functional activity of peritoneal macrophages. One of the main functions of glycodelin S is the regulation of the process of capacitation of spermatozoa. Seminal plasma glycodelin S maintains spermatozoa in a non-capacitated state, being a factor blocking capacitation during their passage through the cervical mucus [13]. Glycodelin C realizes its effects by controlling the state of aggregation of spermatozoa membranes, suppressing the release of cholesterol from them [9]. The weakening of glycodelin supervision in the chain "albumin-cholesterol-membrane viscosity-capacitation" is one of the signs of overripe or "old" spermatozoa. Insufficiency of glycodelin in sperm means not only pseudocapacitation, but also the difficulty of penetration of spermatozoa into the egg, and if it occurs against this background, in most cases there are numerous complications of pregnancy [1,8].

An increase in the amount of antisperm antibodies in the blood serum of women with a decrease in the level of glycodelin in the spermatozoa of their spouses has been proven. It is possible that sperm glycodelin functions as an immunosuppressive protein in the formation of antisperm immunity in women [10]. There is also an opinion that glycodelin deficiency, which develops with infertility of unknown origin, indicates a malfunction in the "friend or foe" system, as a result of which the spermatozoon can be perceived by the egg as a foreign cell [2]. There is evidence of the regulatory effect of glycodelin on the mobility of male gametes. In ejaculates with oligozoospermia, the addition of glycodelin enhances gamete motility [7].

Conducted more than 40 years of clinical studies by domestic and foreign authors clearly demonstrate the relationship between the level of glycodelin in biological fluids and reproductive health, human reproductive

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function, and methods for diagnosing and predicting reproductive dysfunction, developed using glycodelin, have found their application in obstetric and gynecological practice.

Determination of glycodelin in peripheral blood

The secretion of glycodelin into the circumferential blood in men and non-pregnant women is carried out in small amounts and is bound with their years. In women of childbearing age, there is a rather noticeable variation in the layer of glycodelin (from 14 to 113ng/ml). In menopausal women and in men older than 60 years, the level of glycodelin in the blood is sharply reduced [12]. The content of glycodelin in the blood serum of healthy young non-pregnant women depends on the phase of the menstrual cycle: it increases in the secretory phase and 5 days before menstruation exceeds the protein level in the proliferative phase by 1.5–2 times [5,11]. During anovulation, the secretion of glycodelin is monotonous, its content in the peripheral blood of women does not change throughout the entire menstrual cycle [4,13].

In the peripheral blood, glycodelin is released from the endometrium in small amounts, determining the increase in the main protein level in the 2nd phase of the menstrual cycle. Since an increase in the content of glycodelin in the venous blood serum in the 2nd phase is due to the intake of protein not only from the endometrium, but also from the fimbrial part of the fallopian tubes, measuring the level of glycodelin in the peripheral and menstrual blood makes it possible to indirectly assess the secretory activity of the fallopian tubes. With a normal level of glycodelin in the menstrual blood, but reduced in the peripheral blood, one can probably judge the reduced secretory activity of the fimbrial tubules. With secondary infertility, there is no rise in the level of glycodelin in the 2nd phase of the cycle, which is probably associated with a decrease in the production of this protein in the fallopian tubes (fimbrial region) and endometrium, both due to their organic pathology and impaired hormonal activity of the gonads [6].

In women with early miscarriage, the content of glycodelin in the periovulatory period is reduced. With stillbirth and the birth of children with gross congenital malformations in history, the level of glycodelin is reduced both in the 1st phase of the cycle and in the periovulatory period, which may reflect dysfunction of the granulosa tissue and negatively affect the development of the follicle, delay ovulation and thereby lead to " aging" of the egg. In women with recurrent miscarriage and infertility of unknown origin, there is a decrease in the content of glycodelin in the peripheral blood during the "implantation window" [6,8].

Glycodelin was determined in the blood serum of women included in the study by enzyme immunoassay (ELISA). In the analysis, test kits from Ray Biotech, USA with PP14 96 components were used. The method for the determination of glycodelin was based on the principle of an enzymatically enhanced three-stage analysis of the "sandwich" type.

In women with aggravated reproductive function, primarily with early miscarriage,

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low levels of glycodelin in the endometrium is a considerable pathogenetic factor in spontaneous abortion. A low level of glycodelin in the menstrual blood reflects its lessened secretion in the endometrium and is determined in most women with repeated spontaneous pathological abortions in early pregnancy and in cases of birth of children with severe perinatal pathology [11].

It is hypothesized that elevated levels of glycodelin A in the endometrium may be a predictor of implantation success. This suggestion is supported by the thing that the contraceptive effect of emergency contraception with levonorgestrel (LNG) is determined in part by altered glycodelin production.

Characteristics of the functional state of the endometrium according to ultrasound data in patients with non-developing pregnancy

The role of US in assessing the condition of the endometrium

The actual problem of objective diagnosis of the receptive function of the endometrium today remains the question of the exclusive definition of the functional state of the endometrium. Diagnostic markers of the functional state and receptivity of the endometrium are not stratified in terms of information content, do not have a sufficient evidence base in terms of effective results, which are difficult to reproduce in clinical practice, and many of them are still used only in scientific studies [6,9]. According to a number of observations [3-5,11,13], there is a correlation between the thickness of the endometrium in the period of the "implantation hole" according to the results of ultrasound diagnostics and the frequency of pregnancy in spontaneous cycles and in the program of assisted reproductive technologies (ART), as well as in relation to pregnancy outcomes. Morphological and marker indicators of non-receptive endometrium are not important. This definition of the presence of unified approaches to the formation of evaluation and evaluation of the effectiveness of therapy.

It is also recommended that the amount of biological material for diagnostic procedures for endometrial hypoplasia is very small, which dictates particular relevance in the choice of accurate diagnostic methods for the treatment of non-receptive endometrium, which determine the medical tactics of the doctor.

Successful implantation of an embryo can only be in a receptive uterus. In humans, the uterus becomes receptive in the middle of the secretory phase (days 19-23) of the menstrual cycle, the functional period commonly known as the implantation window (IW) 1-3. During this transient OI, the endometrium undergoes the release of molecular changes that promote the development of a blastocyst to contact the luminal epithelium invading the underlying stromal layer [10]. Importantly, the detection of a receptive phenotype in the luminal epithelium derived from the underlying stromal cells [2]. In essence, VOI is characterized by marked changes in this stromal compartment, which includes a set of specialized natural killer cells, vascular remodeling, and perhaps most strikingly, the transformation of stromal

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fibroblasts into specialized rounded decidual cells [7,10,12]. These observations are in place. Ultrasound findings are widely used to detect uterine features such as endometrial thickness, endometrial structure, and uterine blood flow that can predict pregnancy, especially when assisted reproductive technologies are identified. In addition, the development of three-dimensional (3D) ultrasound and 3D Doppler studies has significantly improved the study of uterine morphology, visualization of the prostate. Several studies have examined the endometrium. measurement using ultrasound in predicting the likelihood of pregnancy. The data was inconsistent. While the endometrium has been reported to be thicker in conception cycles than non-conception cycles, this has not been confirmed by another study. In vitro fertilization population (IVF), endometrial thickness per day after embryo transfer was reported to be higher in patients who subsequently became pregnant. The appearance of the endometrium by detection depending on the cycle. Consequently, endometrial morphology has been widely used to predict the likelihood of pregnancy.

The results were comparative endometrial measurements corresponding to the normal three-layered appearance of the endometrium (layered or presence of a median echo) has a low positive predictive value (PPV) for pregnancy (33.1%), while the absence of a multilayered pattern does not produce conception, but makes it unlikely (RR, 85.7%).

Figure 1: The state of the receptive endometrium in patient A, 28 years old, control group.

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Despite considerable interest in PZ for diagnosing adenomyosis, no studies have been conducted. to date, possible changes in PP or morphology associated with early implantation events have been reported in rare cases. Judging by the above observations, the health care that PZ is particularly sensitive in relation to pregnancy hormonal and fetal signals.

As stated above, 3D visualization appears to be more accurate than typical 2D visualization in characterizing changes in the PP. The increased resolution of the ultrasound also means that it has begun to visualize the likelihood of an implantation site. Early implantation sites are usually characterized by the presence of a hyperechoic ring around the concept, which improves the lumen of the endometrium Figure 1.

This ultrasound appearance is in good agreement with the emerging notion that the implanting embryo is rapidly and actively encapsulated by migrating decidual cells. It remains to be seen whether the absence of decidual protrusion or encapsulation found on ultrasound can serve as an indirect marker of inadequate decidualization, and thus predict subsequent pregnancy loss.

Ultrasound semiotics of the endometrium in patients with non-developing pregnancy

The methodological recommendation was developed on the basis of the results of examination and treatment of 120 patients with non-developing pregnancy. In ICD 10, a non-developing pregnancy or intrauterine death of the fetus (embryo) has the code O 02.1.

A prospective comparative controlled study was conducted, including 120 patients in two observation groups. Group 1 included 90 patients with endometrial hypoplasia, clinically manifested as miscarriage, including unsuccessful attempts at ART; The 2nd (control) group consisted of 30 conditionally healthy fertile patients without somatic and gynecological diseases, with a history of urgent delivery, ending in the birth of healthy children. The required sample size was calculated according to the M. Bland formula with a study power of 95% and a significance level of $p<0.05$, which allows us to consider the described sample size sufficient for this study.

Ultrasound of the pelvic organs with color Doppler mapping and Doppler of the pelvic vessels was performed using a Voluson 8 device using a multi-frequency abdominal sensor with a frequency of 3.5-5MHz and a transvaginal transvaginal convex sensor with a frequency of 6.5MHz with software for implementing the triplex scanning mode (greyscale B-mode combined with real-time color and pulsed Doppler).

When conducting ultrasound of the pelvic organs on the 5-11th and 20-22nd days of the menstrual cycle, the position of the uterus in the pelvic cavity was assessed; its shape, the structure of the myometrium, ascertained the presence of myomatous nodes and adenomyosis, noted the presence of dilated veins of the small pelvis, excluded the pathology of the cervix, fallopian tubes. In addition, the state of the ovarian follicular

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apparatus was assessed, the ovarian-uterine index was calculated (to exclude polycystic ovary syndrome), and the presence of ovarian masses was excluded. Particular attention was paid to the study of the median uterine M-echo. Its thickness, structure, symmetry, contours, presence of inclusions were determined, and the state of the uterine cavity was also assessed (presence of liquid and echogenic contents, foreign bodies).

Endometrial peristalsis was assessed by ultrasonography with a transvaginal transducer with a frequency of 6.5 MHz in the sagittal projection of the whole uterus with a fixed position for 5 minutes with a video recording of the entire scan. At the same time, the presence of peristaltic waves of the endometrium was recorded, their orientation was differentiated-cervicofundal or fundocervical, indicated in the study protocol.

The assessment of the presence of subendometrial blood flow was performed using color Doppler mapping in pulsed, constant wave and energy modes with a transvaginal sensor at a pulse repetition rate of 0.9kHz.

Statistical processing of the research results was performed using the Microsoft Excel (2016), StatSoft Statistica 6.0 (StatSoft, USA), SPSS Statistics version 22.0 (IBM Microsoft, USA) application packages. The results were processed by the methods of variation statistics and presented as M ± m. The significance of differences in mean values and relative indicators was assessed using student's t-test. The level of statistical significance in the study was taken as $p<0.05$. Differences between nonparametric variables were assessed using Pearson's χ^2 test. The direction of the features was determined by the method of correlation analysis using the Spearman's rank correlation coefficient (r). The null hypothesis was rejected at $p<0.05$. To build a forecast model, the method of stepwise discriminant analysis was used.

Correlation of indicators of glycodenin concentration and usage of endometrial semiotics

With an eye to study the diagnostic significance of ultrasound in assessing the receptivity of the endometrium, a correlation analysis of the ultrasound characteristics of the endometrium and markers of its receptivity, in this case, the serum concentration of glycodelin, was performed. There were no significant correlations between the M-echo thickness and the serum concentration of glycodelin ($p=0.32$). Thus, the thickness of the M-echo cannot be considered a sufficient criterion for determining the state of endometrial receptivity. Reliable diagnostic value is the determination of the echostructure of the endometrium during the "implantation window". The presence of a three-layer echostructure of the endometrium positively correlated with normal values of glycodelin concentration ($r=0.33$; $p=0.000$), and, on the contrary, negatively correlated with a reduced concentration of glycodelin ($r=-0.17$; $p=0.025$). Thus, the three-layer echostructure of the endometrium may indicate the correct rhythm of maturation of the endometrial glands, structural rearrangements of the apical surface of the gland membranes and stromal transformation of the endometrium

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during the "implantation window", which, according to reliable scientific literature, affects the concentration of glycodelin in the blood serum and determines the receptivity of the endometrium.

In women with early miscarriage, the content of glycodelin in the periovulatory period is reduced. With stillbirth and birth of children with gross congenital malformations in history, the level of glycodelin is reduced both in the 1st phase of the cycle and in the periovulatory period, which may reflect dysfunction of the granulosa tissue and adversely affect the development of the follicle, delay ovulation and thereby lead to " aging" of the egg. In women with recurrent miscarriage and infertility of unknown origin, there is a decrease in the glycodelin content in the peripheral blood during the “implantation window” [6].

The low diagnostic ability of ultrasound in determining intrauterine blues dictates the need for hysteroscopy to verify the diagnosis if any intrauterine organic pathology is suspected.

Endometrial peristalsis has the greatest diagnostic value in interpreting the receptive properties of the endometrium according to ultrasound data.

The presence of endometrial peristalsis strongly positively correlated with the thickness of the M-echo (r=0.155; p=0.035), the structure and thickness of the transitional zone (Junctional Zone) (r=0.138; p=0.009), secretory transformation of the endometrial glands (r=0.718; p =0.000), asperity of the vascular component of the stroma (r=0.210; p=0.004) and ultrastructural characteristics of pinopodiums (r=0.360; p=0.000). Thereby, it is the presence of a correct peristaltic wave (from the internal os to the bottom of the uterus) during ultrasound that is an ultrasound criterion for receptive endometrium.

Type of violations	TV-US	Serum concentration of glycodelin (from 14 to 113ng/ml is normal)	US sensitivity, %	Sensitivity of indicators of glycodelin, %	Specificity of US %	Specificity of indicators of glycodelin %	X^2	p
Micropolyps of the endometrium	7 (7, 8%)	19, 4 ± 6, 2	50, 0	67, 8	95, 4	90, 4	4, 38	<0, 05
Intrauterine synechia	11 (12, 2%)	8, 4 ± 2, 1	37, 5	82, 2	83, 3	96, 6	23, 17	<0, 01
Signs of endometritis	37 (41, 1%)	13, 1 ± 3, 4	92, 5	98, 4	95, 45	99, 1	2, 498	<0, 05

Table 1: Comparative analysis of indicators of TV-ultrasound and serum concentration of glycodelin in the detection of intrauterine pathology.

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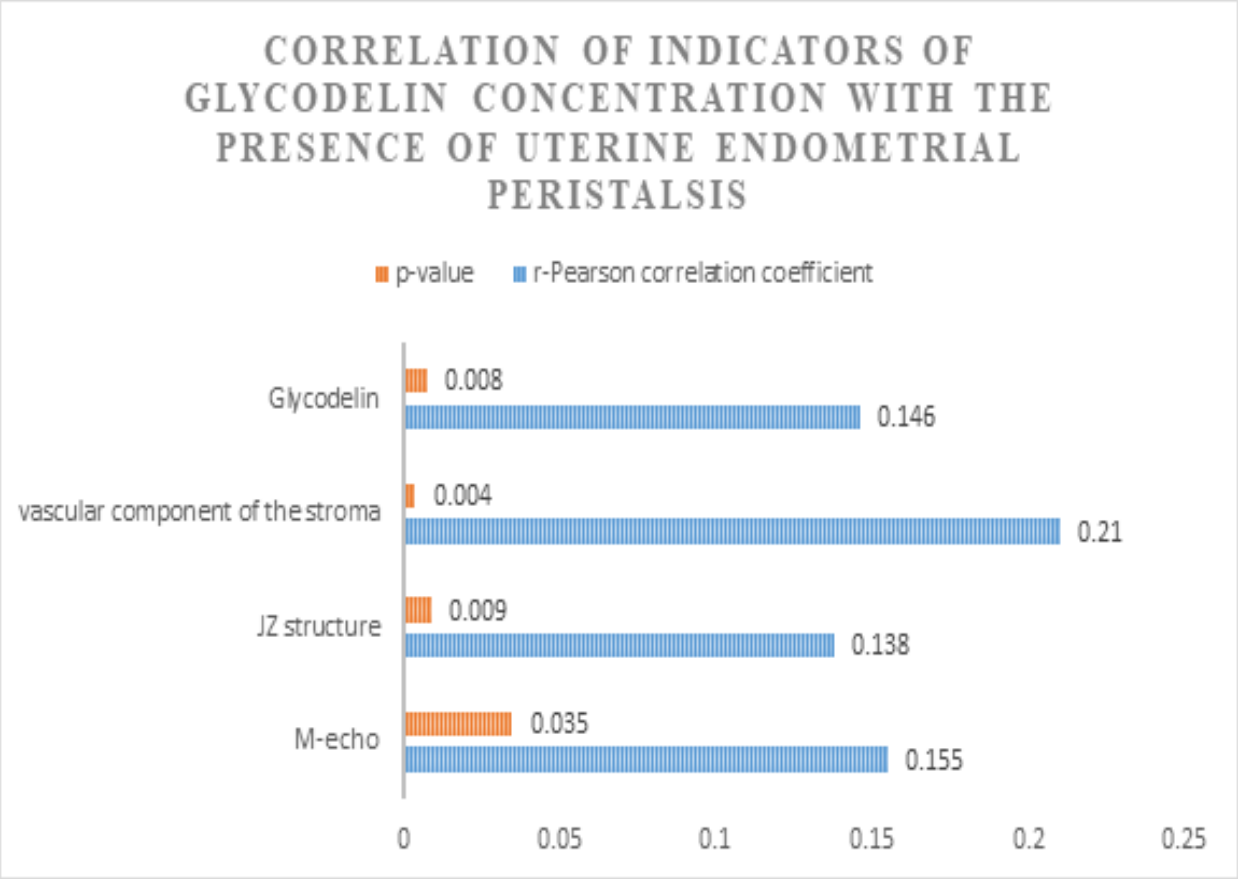

Figure 2: Correlation of indicators of glycodelin concentration with the presence of uterine endometrial peristalsis.

Under our data, PRP therapeutics on the endometrium in patients with reproductive setback at the stage of preconception lead-up after completion of therapy increased the chance of pregnancy (χ^2=5.613; OR=2.430; 95% CI (1.151-5.128); p<0.05) .

Characteristics of the proposed algorithm for the management of patients with non-developing pregnancy

The data obtained in the course of the study showed the diagnostic value of determining serum glycodelin as a marker of the functional state of the endometrium in the intricate of diagnostic measures for impaired endometrial receptivity. In the case of monitoring studies after therapeutic gauge, it is sufficient to determine glycodelin and ultrasound, due to the presence of identified correlations between the concentration of serum glycodelin and ultrasound of semiotics. A second study of the functional condition of the endometrium is justified in the absence of a clinical resalt from therapy and low concentrations of glycodelin in the peripheral blood. Based on the studies, an algorithm for managing patients with non-developing pregnancy was developed Appendix 1.

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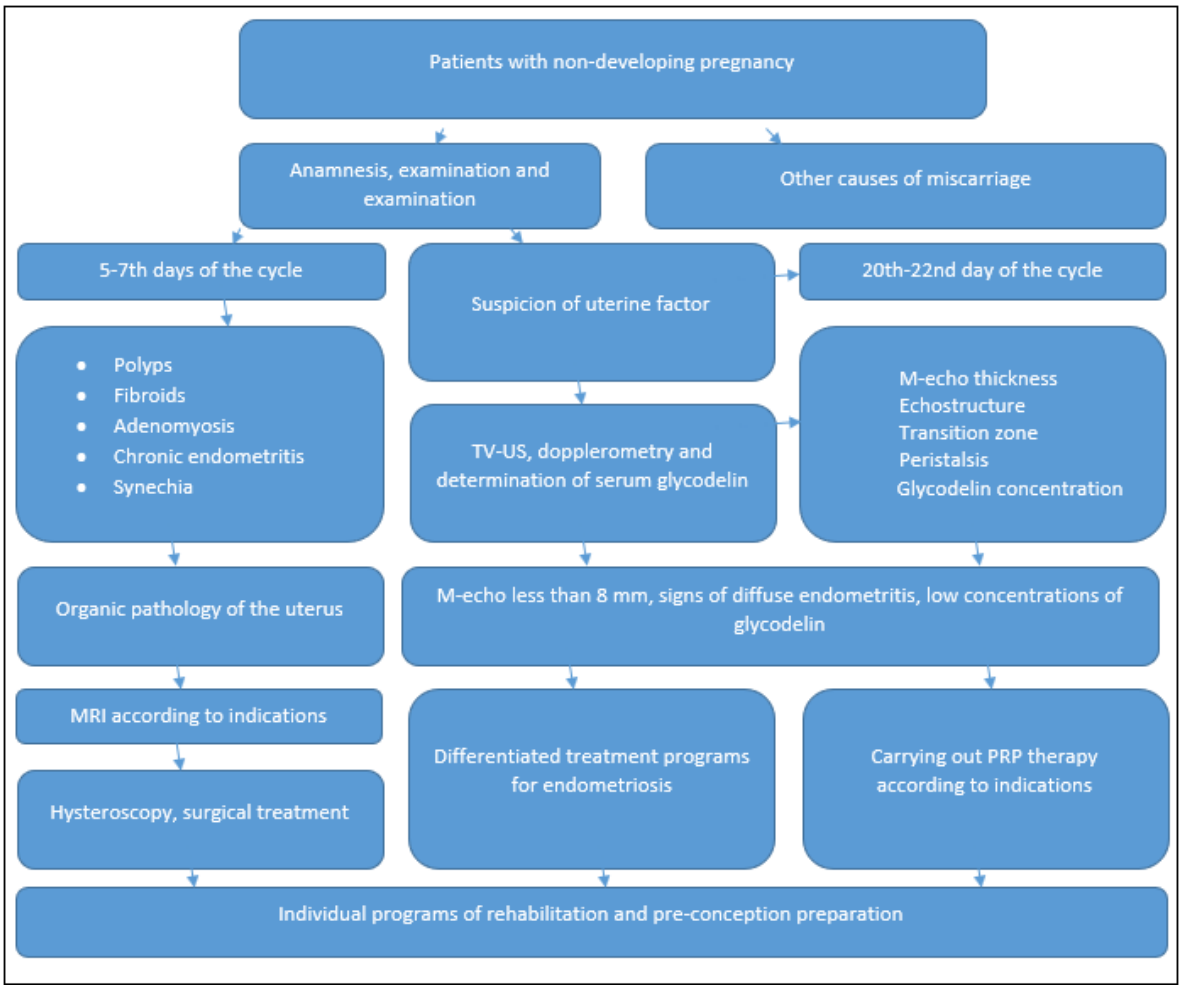

Appendix 1: The proposed scheme of the algorithm for managing patients with non-developing pregnancy.

Conclusion

Evaluation of ultrasound parameters, Doppler characteristics of the uterus and serum glycodelin concentrations in combination with existing diagnostic methods are an objective criterion for diagnosing functional disorders of the endometrium in patients with a history of non-developing pregnancy.

The proposed complex for diagnosing functional disorders of the endometrium will reduce the socio-economic costs of gynecological examination of patients with a history of non-developing pregnancy. The use of the proposed algorithm for managing patients with a history of non-developing pregnancy will reduce the risk of recurrent miscarriages, more effectively correct functional disorders and predict the outcomes of the latter.

Determination of serum glycodelin concentrations makes it possible to reliably determine the degree of functional disorders in patients with a history of non-developing pregnancy. Determination of serum glycodelin concentrations in combination

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with other diagnostic methods is a non-invasive and informative method for determining the functional state of the endometrium.

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