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Original article

Contemporary features of predicting the development of luteal insufficiency and related gestational disorders

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Abstract: *The goal* of our study was a comprehensive assessment of obstetric, gynecological, somatic and genetic factors, contributing to high risk of insufficient luteal phase (ILP) and relating gestational disorders to the latter in relevant patients for further optimization of therapeutic and preventive measures.

Material and Methods — A cohort study with a mixed cohort was carried out. The clinical material of the retrospective study was presented based on the results of analyzing 300 cases of patients with verified diagnoses of the threat of spontaneous abortion, miscarriage, and complete spontaneous abortion, who were hospitalized in the period of 2018-2020. As part of a prospective study, we analyzed 66 blood samples of women treated at the State Budgetary Healthcare Institution *Simferopol Clinical Maternity Hospital No.2* in Crimea in 2020. The polymerase chain reaction method in real time mode, with the use of the developed kits, was used for CYP3A5 6986A> G polymorphism.

Results — A comprehensive assessment of obstetric, gynecological, somatic and genetic factors allowed identifying the most informative prognostic markers for the risk of developing luteal phase insufficiency and related gestational disorders, including irregular menstrual cycle, cases of drug-induced abortion, preceding specific infectious diseases (chlamydia, *Ureaplasma urealyticum* infection), gynecological pathology (polycystic ovary syndrome), surgical interventions performed for gynecological pathology (ovarian resection and ovariectomy), as well as single nucleotide polymorphism rs776746 in the CYP3A5 gene.

Conclusion — The identified prognostic criteria make it possible to identify a group of patients with a high risk of miscarriage even before the conception; such patients need more careful and systematic medical monitoring for the timely diagnosis of possible pregnancy complications. Early diagnosing of potential issues would allow clinicians to take preventive measures, along with initiating timely treatment. As a result, the percentage of reproductive losses would go down.

Keywords: luteal phase insufficiency, miscarriage, gestational disorders, menstrual cycle, gynecological pathology, CYP3A5 gene.

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Introduction

The current concept of improving the quality of medical care is focused primarily on predicting individual risks of following specific recommendations for further monitoring and treatment of patients [1]. Various genetic, anatomical, physiological and psychosocial characteristics are studied as predictors of developing the pathologies. The universal goal of such models is to combine predictive factors into the so-called *risk prediction / decision-making model*, which allows improving the efficacy of the healthcare network [2].

Progressive deterioration of the demographic situation in Russia leads to recognition of the reproductive losses' problem as one of the priorities in medical and social fields [3, 4]. According to modern statistical data, about 20% of all clinically diagnosed pregnancies culminate in spontaneous abortion, while 75-80% of miscarriage cases are recorded as early as before 12 weeks of a pregnancy [5, 6].

Insufficiency of the luteal phase of the menstrual cycle (ILP) is among the most common causes of miscarriage. It is manifested by the corpus luteum hypofunction due to insufficient synthesis of progesterone during the luteal phase, which causes the secretory transformation disorder of the endometrium, insufficient for implantation of the ovum and early pregnancy [7]. Currently, according to various authors, 6-30% of fertile women suffer from ILP [8, 9].

Considering its polyetiological nature, ILP remains the subject of numerous discussions among specialists in the field of reproductive endocrinology. Since 1949, after G. Jones [10] first mentioned ILP as a possible major cause of infertility and miscarriage, many studies have been carried out in order to establish its etiopathophysiological mechanisms, as well as to diagnose and treat this medical condition.

Currently, a number of authors consider short menstrual cycles, the use of assisted reproductive technologies, endocrine

disorders, anorexia or obesity in preceding medical history, as well as chronic stress, as etiological factors leading to this pathology [11, 12]. However, the available data are fragmentary and require additional comprehensive study.

Genetic factor is habitually considered among the possible causes of ILP development [13]. Considering that progesterone, like many other hormones, undergoes metabolism with the participation of the cytochrome P450 system, among which isoform CYP3A4/5 play important roles, it is possible to assume that genetically predetermined variability in the activity of these cytochromes may affect progesterone content, and, therefore, the role of the latter in prolonging the pregnancy [14]. Identifying the carriage of these mutations and polymorphic variants is essential and irrefutably important, since prevention and timely correction of the effects of unfavorable gene variants ensure normal pregnancy course.

From this prospective, the goal of our study seems quite significant: a comprehensive assessment of obstetric, gynecological, somatic and genetic factors characterizing high risk of ILP and related gestational disorders in relevant patients for further optimization of therapeutic and preventive measures.

Material and Methods

Study design

Study type: cohort study with a mixed cohort (retrospective and prospective).

The clinical material of the retrospective study is presented by the results of analyzing 300 cases of patients who were admitted in 2018-2020 to the gynecological department of the State Budgetary Healthcare Institution, Simferopol Clinical Maternity Hospital No. 2, in Crimea. On the basis of retrospective analysis, we conducted the assessment of clinical and anamnestic factors in women with verified diagnoses of spontaneous abortion threat, miscarriage, and complete spontaneous abortion. The average age of the patients was 28±0.3 years old. According to the design, the patient medical histories were divided into two groups: main group 1 (MG1) (n=174) comprising women with disorders of reproductive system according to the ILP form, and control group 1 (CG1) (n=126) including relatively healthy women with regular ovulatory menstrual cycles and histories of pregnancies that resulted in birth of live full-term babies.

Prospective cohort involved the patients observed at the Simferopol Clinical Maternity Hospital No. 2 in 2020: main group 2 (MG2) (n=31) including women with disorders of reproductive system according to the ILP form and verified diagnoses of spontaneous abortion threat, missed abortion, and complete spontaneous abortion (average age: 31.2±0.7 years old), control group 2 (CG2) (n=35) comprising women with a normally developing pregnancy in history, similar in ages and presence or absence of concomitant diseases (average age: 31.13±0.95 years old).

The study was carried out in accordance with Good Clinical Practice and requirements of the World Medical Association Declaration of Helsinki. The conducted research was approved by the Ethics Committee of S.I. Georgievsky Medical Academy at Vernadsky Crimean Federal University.

Inclusion criteria

For inclusion of women into the main groups we were taking into account the following criteria: 1) the patient age at the time of hospital admission (18-39 years old); 2) the gestational age during this hospitalization (5-15.5 weeks); 3) verified diagnoses of spontaneous abortion threat, miscarriage, or complete spontaneous abortion.

The exclusion criteria were: 1) absence of confirmed diagnoses of spontaneous abortion threat, miscarriage, or complete spontaneous abortion at the time of treatment at a gynecological department; 2) HIV-positive pregnant women, presence of manifested infection of any localization and etiology, or pregnant women with Rh-conflict pregnancy.

Methodology

Deoxyribonucleic acid (DNA) samples taken from 66 prospectively examined patients included in the study were analyzed during the research. For genetic analysis, the peripheral venous blood was taken. Genotyping for polymorphism 6986A> G in the CYP3A5 gene was carried out by the method of polymerase chain reaction in real time using the developed kits (Syntol, Russia).

Statistical analysis

Statistical processing of the results was carried out with using Statistica 10.0 and SPSS 23 software. For quantitative data, arithmetic means (M), standard deviations (SD) and standard errors (m) were used. In the course of comparative analysis, the statistical significance of differences in indicators among the groups was identified by the one-sample t-test. For all cases, the distribution of indicators corresponded to the law of normal distribution. In order to determine the strength and direction of the statistical relationship between quantitative variables, Pearson's correlation analysis was employed. The revealed allele frequencies were compared using the nonparametric $\chi 2$ criteria taking into account Yates's correction. The impact of polymorphic variants on the risk of developing the disease was assessed using the odds ratio (OR), taking into account 95% confidence interval (95% CI). Differences were considered significant at $p<0.05$.

Results

According to the data of the retrospective systemic analysis of anamnestic risk factors for the development of ILP and related gestational disorders, we identified the following features of the menstrual function. The majority of women in MG1 and CG1 had moderate, painless cycles lasting 3-7 days; the average age at menarche was 11-14 years old. At the same time, our attention was drawn to the significantly higher percentage of women in MG with an irregular menstruation in comparison with the patients of CG1: 2.3 times ($p<0.001$) (*Table* 1).

Among the examined patients, 101 (58.0%) and 85 (67.5%) women in MG1 and CG1, respectively, were previously protected from unwanted pregnancies ($p<0.001$). Simultaneously, statistically significant differences in characteristics of the chosen contraception methods were detected among the groups ($p>0.05$) (*Table* 2).

Table 1. Features of menstrual function in patients of retrospective groups; absolute number (%)

Features of the menstrual function		*MG1 (n=174)*
Age at menarche	younger than 11 years old	10 (5.7)
	11-14 years old	155(89.0)
	older than 14 years of age	18 (10.3)
Duration of menses	less than 3 days	16 (9.2)
	3-7 days	118 (67.8)
	more than 3 days	40 (23.0)
Menstrual history	moderate	30 (17.2)
	ample	144 (82.8)
	painful	115 (66.1)
	painless	59 (33.9)
	regular	57 (32.8) ***
	irregular	117 (67.2) ***

*** p<0.001 in relation to the indicators of CG1.

Table 2. Contraception methods in patients of retrospective groups; absolute number (%)

Contraception methods	*MG1 (n=174)*	*CG1 (n=126)*
Oral hormonal contraceptives	64 (63.4)	51 (60.5)
Intrauterine device	28 (27.7)	26 (30.3)
Interrupted intercourse	9 (8.9)	8 (9.2)
Total	101 (100.0)	85 (100.0)

There are no statistically significant differences between the groups (p>0.05).

Table 3. Features of the reproductive potential in patients of retrospective groups; absolute number (%)

Reproductive function parameter		*MG (n=174)*
Infertility		5(2,9)
Types of abortion	Total	70 (40.2) ***
	medicinal	31 (44.2) ***
	surgical	39 (55.7) ***
Pregnancy and childbirth complications	missed miscarriage	14 (8.0)
	threat of spontaneous abortion	111 (63.8)
	spontaneous abortion	49 (28.2)

*** p<0.001 in relation to the indicators of CG1.

Table 4. Infectious diseases of the pelvic organs in patients of retrospective groups; absolute number (%)

Infectious diseases	*MG (n=174)*	*CG (n=126)*
Chlamydia	29 (27.7) **	10 (12.5)
Ureaplasma urealyticum infection	69 (65.7) ***	57 (71.2)
Mycoplasmosis	11 (10.4)	9 (11.3)
Trichomoniasis	11 (10.4)	4 (5.0)
Gonorrhea	5 (4.8) *	–
Total	105 (100.0)	80 (100.0)

* p<0.05 in relation to the indicators of CG1; ** p<0.01 in relation to the indicators of CG1; *** p<0.001 in relation to the indicators of CG1.

Table 5. Gynecological pathology of the pelvic organs in patients of retrospective groups; absolute number (%)

Gynecological pathology	*MG1 (n=174)*	*CG1 (n=126)*
Polycystic ovary syndrome	68 (68.7) *	11 (28.9)
External genital endometriosis	12 (12.1)	13 (35.0)
Cervical erosion	9 (9.1)	4 (11.5)
Uterine myoma	4 (4.0)	5 (13.1)
Endometrial polyp	6 (6.1)	4 (11.5)
Total	99 (100.0)	37 (100.0)

* p<0.05 in relation to the indicators of CG.

During the assessment of the reproductive potential, we discovered that 5 patients in MG (2.9%) and 3 (2.4%) patients in CG1 had primary infertility. All cases were associated with the tuboperitoneal factor and, as a result of using the assisted reproductive technologies, subsequently ended up in pregnancy.

When analyzing the reproductive function, it was revealed that the pregnancy rate in MG1 was 1.8 times smaller than in CG1 (p<0.05). In addition, as a result of studying the patient anamneses, the history of artificial pregnancy termination was revealed: 70 (40.2%) and 21 (16.7%), respectively (p=0.719). Our attention was drawn to 1.9 times higher (p=0.045) number of medical abortions in women from MG1 compared with the patients of the control group.

In the course of our study, burdened obstetric and gynecological history was established in 100.0% of the patients in MG1. At the same time, in the structure of pregnancy and childbirth complications in the patients of the first group, the most frequent were: the diagnosis of spontaneous abortion threat – 111 (63.8%), complete spontaneous abortion – 49 (28.2%), and miscarriage – 14 (8.0%) (*Table* 3).

When studying the presence of preceding sexually transmitted infections, no statistically significant differences in frequencies between the studied groups were found: e.g., 105 (60.3%) cases in MG1 vs. 80 (63.5%) cases in CG1 (p=0.491). At the same time, the proportion of gonorrhea and chlamydia in the structure of infectious pathologies in OM1 patients was 3.1 times (p=0.011) and 2.1 times (p=0.002) greater than of those in CG1, respectively. The dependence of the ILP development on other ailments of infectious origin was not revealed (p>0.5) (*Table* 4).

In the medical histories of patients from MG1, gynecological pathologies were registered in 99 (56.9%) cases, which exceeded this indicator in CG1 by 2.6 times (p<0.001). However, in the structure of morbidity in the first group of women, the syndrome of polycystic ovaries was observed 6.2 times more often compared with the values in the control group (p=0.021). Statistically significant dependence of the ILP development on other considered gynecological diseases was not revealed (p>0.5) (*Table* 5).

Previously, 92 (52.9%) women from MG1, along with 32 (25.4%) women from CG1, underwent surgical intervention for gynecological pathology. Simultaneously, in MG1, in the structure of surgical operations, the frequency of ovarian resection and ovariectomy was statistically significantly higher than of those in CG1 by 2.2 times (p=0.006) and 1.7 times (p=0.004), respectively (*Table* 6).

The correlation analysis showed that the low content of progestogen in the first group was associated with irregular menstrual cycle (r=0.41; p<0.01), cases of drug-induced abortion (r=0.40, p<0.01), preceding specific infectious diseases (chlamydia, *Ureaplasma urealyticum* infection) (r=0.39, p<0.01), gynecological pathologies (polycystic ovary syndrome) (r=0.43, p<0.01), and surgical interventions for gynecological pathology (ovarian resection and ovariectomy) (r=0.41, p<0.01).

In accordance with our tasks, in order to investigate the contribution of the genetic factor into the development of ILP, we carried out a prospective clinical and laboratory examination of patients with obstetric and gynecological profile with reproductive system disorder in the form of ILP and concomitant gestation impairment. In order to assess the type and form of corpus luteum insufficiency, we evaluated the menstrual function, where the

main criterion was duration of the menstrual cycle, and ultrasound examination results (which included indicators of the corpus luteum consistency and secretory transformation of the endometrium), as well as the hormonal profile of the patients. The control group, comparable in age and concomitant pathology, included 35 women.

Evaluation of menstrual function demonstrated that the average cycle duration in patients with impaired gestation caused by ILP was 25.0±3.5 days and was characterized by a shortening of the luteal phase. In the course of a complex hormonal examination on days 5-7 and 21-23 of the menstrual cycle, significant differences in concentration of sex hormones were revealed in the examined patients vs. those in MG2. Thus, in the group of women with impaired gestation, compared with CG2, the pronounced progesterone deficiency was observed: 31.1±3.5 nmol/l versus 52.31±2.7 nmol/l, respectively. According to the ultrasound study, thickness of endometrium in patients with ILP in the luteal phase of the menstrual cycle was slightly reduced, compared with the control group: on average, it was 11.9±0.31 mm.

When studying the anamnesis of prospectively examined patients from MG2, we revealed that the cessation of fetal activity occurred in 45% of women with two or more pregnancies in the anamnesis. The study group was characterized by high incidence of gynecological diseases (70% of women). In 36% of cases, the disease was represented by ovarian cysts, whereas in 13.8% by inflammatory processes of adnexa uteri. In 43% of cases, women had history of extragenital pathology, the most common were the diseases of urinary system (21% of cases) and gastrointestinal tract (9%). Sexually transmitted infections, including chlamydia, *Ureaplasma urealyticum* infection, and mycoplasmosis, were found in 24% of women diagnosed with ILP.

When analyzing the frequency distribution of the AG genotype of the 6986A > G polymorphism of the CYP3A5 gene in the groups of patients in MG2 and CG2, we revealed significant differences among the groups ($\chi2$=6.59, p=0.04). According to our results, the presence of the A/A genotype increases the risk of ILP development by 1.87 times (OR=1.87; 95% CI 1.08-3.23) (*Table* 7).

Table 6. Surgical interventions for gynecological pathology in patients of retrospective groups; absolute number (%)

Surgical intervention	*MG1 (n=174)*	*CG1 (n=126)*
Myomectomy	4 (4.3)	5 (15.6)
Ovarian resection	38 (41.4) **	6 (18.8)
Cystectomy	19 (20.8)	4 (12.5)
Unilateral oophorectomy	11 (11.6) **	1 (3.2)
Endometrial lesion excision	12 (13.1)	9 (28.1)
Cervical erosion cryosurgery	2 (2.2)	3 (9.4)
Removal of endometrial polyp	6 (6.6)	4 (12.5)
Total	92 (100.0)	32 (100.0)

** p<0.01 in relation to the indicators of CG1.

Table 7. Genotype frequencies of the polymorphic marker 6986A> G of the CYP3A5 gene in prospective groups

Gene, polymorphism	*Genotypes*	*Frequency, %* MG2 (n=31)	CG2 (n=35)	*χ2*	*P*	*OR (95% CI)*
CYP3A5 6986A>G	G/G	47.3	45.8			1.06 (0.83–1.36)
	G/A	43.7	49.2	6.59	0.040	0.80 (0.63–1.03)
	A/A	9.0	5.0			1.87 (1.08–3.23)
	G	69.2	70.4	0.36	0.550	0.94 (0.78–1.14)
	A	30.8	29.6			1.06 (0.88–1.28)

Discussion

The hormonal aspect in the physiological course of gestation remains one of the most difficult complications in obstetric and gynecological practice. The changed pace of life in contemporary society, diet, work and rest, as well as idiosyncrasies of sexual behavior lead to maladjustment of the regulatory mechanisms and cause rapid growth of hormonal disorders of the reproductive system, in particular, progesterone deficiency. Insufficient synthesis of progesterone leads to inadequate secretory transformation of endometrium, changes in the function of fallopian tubes, impaired implantation of the fertilized egg, which is clinically manifested by miscarriage, threat of spontaneous abortion, or complete spontaneous abortion [15].

Anamnestic indicators outlined in the course of our study had an anticipated, pathogenetically determined relation to insufficient production of progesterone by the corpus luteum.

Short menstrual cycles, use of assisted reproductive technologies, endocrine disorders, anorexia or obesity in anamnesis, and chronic stress could be mentioned among the traditional causes of gestational disorders [12, 13].

In our study, the group of women with ILP differed from the control group by irregular menstrual cycle, anamnestic data on drug-induced abortion, preceding specific infectious diseases (chlamydia, *Ureaplasma urealyticum* infection), gynecological pathology (polycystic ovary syndrome), and surgical interventions performed for gynecological pathology, in particular ovary resection and oophorectomy.

Currently, sexually transmitted infections play a significant role in the genesis of inflammatory diseases of pelvic organs, with chlamydia and Ureaplasma urealyticum infection accounting for 50-70% of those [16]. Morphological and functional changes in the organs of the reproductive system during inflammation cause pathological afferentation in the parts of the central nervous system that regulate the hypothalamic-pituitary-ovarian system. As a result of such changes, there is a reduction in the endocrine function of the ovaries, which often disrupts the ovulation process [17]. In addition, inflammatory changes in the ovaries inevitably affect their function, leading to a disorder in the production of estrogen and progesterone. The most common consequence of chronic oophoritis is absolute or relative insufficiency of the luteal phase. Lack of adequate responses of the endometrium to hormonal stimulation can be explained in terms of morphological changes in endometrial tissue, as well as by dysfunction of its receptors caused by the inflammation. Hence, the statement about interconnection of preceding specific infectious diseases (chlamydia, *Ureaplasma urealyticum* infection) with an increased risk of progesterone deficiency and related miscarriage becomes quite reasonable.

Pathogenetic conditionality of progesterone deficiency in the context of polycystic ovary syndrome history presents particular interest. It is believed that in this pathology, under the influence of various exogenous or endogenous factors, the pulsating formation of gonadotropin-releasing hormone in the hypothalamus becomes affected, which leads to an increase in the production of luteinizing hormone [18]. In turn, the latter stimulates an increase in the synthesis of androgens in the theca and stromal cells. Androgens undergo aromatization with formation of estrogens. Hyperestrogenism supports chronic anovulation, which, in turn, is accompanied by the reduction in progesterone secretion.

At present, there is no doubt that follicular and luteogenesis disorders of various severity develop after operations on ovaries, but the issue related to the duration and extent of organ function restoration remains controversial. According to the available published data, ovarian resection significantly reduces their functional reserve and is an unfavorable surgery in terms of predicting preservation of reproductive function [19]. In young women, it is recommended to perform ovarian resection solely according to strict indications, giving preference to cystectomy and exfoliation of the formation. In the study by F. Sato, it was shown that the performed oophorectomy in all patients led to decrease in the cyclic secretion of luteinizing hormone, relative hypoestrogenism and progesterone deficiency [20]. These data are consistent with our findings, accordingly allowing us to consider the performed ovarian resection or ovariectomy the predictors of possible luteal phase defect.

The impact of gene polymorphism, metabolizing steroid hormones, has already been the subject of interest in researchers regarding the causes of miscarriage in the first trimester. For example, in the study by A.-H. Karypidis et al., it was revealed that homozygous carriage of a mutation in the gene encoding cytochrome P450 1B1, which is involved in hydroxylation of estradiol, as well as in metabolism of testosterone and progesterone, was significantly associated with miscarriage in the first trimester [21]. At the same time, another group of authors (Saijo Y. et al.) did not reveal such relationship when testing polymorphisms in the CYP1B1, 1A1, and 1A2 genes [22]. In our study, we established a tendency towards higher frequency of occurrence of the genotype, suggesting higher activity of CYP3A5, which may be one of the factors responsible for the decline of progesterone concentration. On the one hand, in the studied group of patients with ILP, there was a higher incidence of severe progesterone deficiency, which could be the confirmation oa our hypothesis. It should be also noted that, if the activity of CYP3A5 is significantly regulated by genetic polymorphism [23], then CYP3A4, which is characterized by similar substrate specificity, is susceptible primarily to external triggering and deactivating effects, and the latter were not investigated in our pilot study.

Consequently, we can conclude that the rs776746 polymorphism in the CYP3A5 gene may contribute to pathogenesis of gestational disorders, but its role is obviously not as substantial as the influence of other factors. To clarify the independent role of CYP3A5 activity, larger studies with a more thorough examination of women are needed.

Conclusion

A comprehensive assessment of obstetric, gynecological, somatic and genetic factors allowed identifying the most informative prognostic markers for the risk of developing luteal phase insufficiency and related gestational disorders, including irregular menstrual cycle, cases of drug-induced abortion, preceding specific infectious diseases (chlamydia, *Ureaplasma urealyticum* infection), gynecological pathology (polycystic ovary syndrome), surgical interventions performed for gynecological pathology (ovarian resection and ovariectomy), as well as single nucleotide polymorphism rs776746 in the CYP3A5 gene.

The developed prognostic criteria make it possible to identify a group of patients with high risk of miscarriage even before the conception. Such patients need more careful and systematic medical monitoring for the timely diagnosis of possible pregnancy complications. Early diagnosing of potential issues would allow clinicians to take preventive measures, along with initiating timely treatment. As a result, the percentage of reproductive losses would go down.

Limitations

The results of this work should be interpreted with some limitations. First, there was a relatively small sample of patients. Another limitation is associated with the fact that we did not characterize the social status of our patients as a potentially significant risk factor for the development of ILP.

Ethical approval

All procedures performed in studies involving human participants were done in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards.

Conflict of interest

We declare that we have no conflicts of interest.

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